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Running title: Risk of stenosis after steroid injection

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Abstract

Background and Aim: Esophageal endoscopic submucosal dissection (ESD) to resect widespread lesions has increased the incidence of strictures, and some patients develop strictures despite receiving prophylactic locoregional triamcinolone injections. This study evaluated the predictive factors for esophageal stricture formation in patients administered prophylactic triamcinolone injections after ESD.

Methods: This was a retrospective observational study. Of 552 consecutive patients who underwent ESD, those who received prophylactic triamcinolone injections immediately after ESD were enrolled. The primary outcome was the predictive factors for esophageal stricture formation in patients administered prophylactic triamcinolone injections.

Results: We evaluated 101 *en bloc* resections involving 144 lesions in 96 patients. Strictures occurred following 17 (16.8%) resections. Wider circumferential mucosal defect (odds ratio [OR] 2.42, 95% confidence interval [CI]: 1.01–5.80; $p = 0.048$) was an independent predictive factor for stricture development. The cut-off value associated with stricture formation was five-sixths of the circumferential mucosal defect. Propensity analysis determined that the frequency of esophageal strictures increased in

patients with circumferential mucosal defects of more than five-sixths compared with those less than five-sixths (OR 5.70, 95% CI: 1.61–20.18; $p = 0.007$).

Conclusions: Resections involving circumferential mucosal defects of more than five-sixths increased the likelihood of stricture formation in patients administered prophylactic locoregional triamcinolone injections after esophageal ESD.

Key words: steroid, stenosis, risk, propensity score, inverse probability of treatment weighting (IPTW)

Introduction

Esophageal cancer has a poor prognosis, and this relates to difficulties associated with early detection.[1,2] New optical imaging techniques, for example, narrow-band imaging endoscopy, have facilitated the detection of early-stage esophageal cancer,[3,4] and curative endoscopic resection has improved the survival rates.[5-8] In addition, *en bloc* resections can be achieved for superficial esophageal neoplasias using endoscopic submucosal dissection (ESD), regardless of the tumor's size.[6-8] However, widespread resection involving over 71% of the circumferential mucosal defect by ESD has led to a high incidence of stricture formation.[9,10] Serious dietary deficiencies caused by refractory esophageal stricture formation reduce the quality of life of patients and necessitate multiple endoscopic balloon dilatation (EBD) sessions that incur high medical costs.

Administering prophylactic oral steroids or locoregional steroid injections is useful for preventing such strictures.[11-16] A single session of triamcinolone injections immediately after ESD may prevent stricture formation without any severe adverse events.[12,14] However, some patients develop strictures despite receiving locoregional triamcinolone injections, and the predictive factors associated with stricture formation in these cases have not yet been determined. A tumor circumferential extent greater than 75% has been reported as a risk factor for refractory stricture development, which was defined as the requirement for more than three sessions of EBD to resolve the stricture, even in cases who have received locoregional triamcinolone injections.[17] While the preoperative circumference was investigated in the aforementioned study, most studies investigating the risk factors associated with stricture formation have evaluated the circumferential mucosal defect after ESD rather than the preoperative

circumference;[9,10] therefore, our study focused on evaluating the circumferential mucosal defect after ESD instead of the preoperative tumor circumference.

The present study aimed to investigate the predictive factors associated with esophageal stricture formation in patients who had been administered a single session of prophylactic locoregional triamcinolone injections immediately after esophageal ESD.

Methods

Patients

This was a retrospective observational study that was conducted at a single center in Japan. A total of 552 consecutive patients and 930 superficial esophageal neoplasias underwent ESD between May 2004 and March 2016 (Figure 1). Patients who received prophylactic locoregional triamcinolone injections immediately after esophageal ESD, were enrolled to participate in this study. Patients who received other prophylactic therapies for stricture formation were excluded. The larger lesions in patients from whom multiple synchronous lesions were resected *en bloc* were considered to be the target lesions.

The ethics committee of the Osaka City University Graduate School of Medicine approved the study's protocol (number 3487).

Outcomes

The primary outcome of this study was the identification of the predictive factors associated with esophageal stricture formation in patients who received a single session of locoregional triamcinolone injections immediately after esophageal ESD. The cut-off value for the circumferential extent of the mucosal defect associated with stricture formation and the incidence of stricture formation associated with this cut-off value were the secondary outcomes.

Endoscopic submucosal dissection procedure

A complete description of the ESD procedure has been reported. [6,15], [18] A bipolar needle knife (B knife; Xemex Co., Tokyo, Japan) and a monopolar needle knife (Flush knife, DK2618JN; Fujifilm Medical, Tokyo, Japan) were the main electrosurgical knives utilized. After the marker dots had been placed, a hyaluronic acid solution was injected into the submucosal layer, then the circumferential mucosal incision and the submucosal dissection were performed. The procedure time was defined as the period from the circumferential incision to the removal of the tumor. The preoperative longitudinal diameter of the lesion was measured endoscopically from the oral to the anal end.

Locoregional triamcinolone injections

The indication for locoregional triamcinolone injections is defined as a patient with a mucosal defect encompassing more than two-thirds of their esophageal circumference, because those with mucosal defects encompassing >71% of the esophageal circumference are at risk of stricture formation.[9] The circumferential mucosal defect was measured as the proportion of the esophageal circumference that was removed, based on its division into 12 equal parts when the esophageal lumen was spread to its maximum width using full insufflation (e.g. 9/12 and 11/12). The measured values were represented as percentages. In addition, patients with mucosal defects that encompass more than half of their esophageal circumference and who have lesions in the cervical esophagus or near a previous ESD scar, receive locoregional triamcinolone injections, because they are considered to be at a high risk of stricture.[17] Patients were administered a single session of triamcinolone acetonide (Kenacort; Bristol-Myers Squibb, Tokyo, Japan) injections into the residual submucosal layer of the resected

region immediately after ESD. Regardless of the sizes of the resected specimens, 40 sequential 0.5 mL (2 mg) injections of triamcinolone acetonide were administered to achieve a total dose of 80 mg.[14]

Follow-up and stricture formation

Endoscopic stricture evaluations were performed every 4 weeks after ESD until scarring was confirmed. The presence of a stricture was confirmed when a standard 9.2-mm diameter upper gastrointestinal endoscope (GIF-Q260; Olympus, Tokyo, Japan) could not be passed through the treatment site. When a patient complained of dysphagia associated with semisolid foods, that is, a dysphagia score of 2, an endoscopic evaluation was performed at that time. [12,19] Dysphagia score is followings: grade 0, can have a normal diet; grade 1, can tolerate some solid foods; grade 2, can tolerate semisolids only; grade 3, can swallow liquids only; and grade 4, complete dysphagia.[19] EBD was repeated when a stricture persisted, either endoscopically or symptomatically.

Statistical analyses

The continuous variables are presented as the means and standard deviations, and the categorical variables are presented as numbers. Regarding the categorical variables, comparisons were using the chi-squared test or Fisher's exact test when necessary, because of the small sample sizes. For the continuous variables, comparisons were using Student's *t*-test. Logistic regression analysis was used to evaluate the simultaneous effects of 12 variables (Table 1) on stricture formation, and the risk factors for stricture formation were estimated by calculating the odds ratios (ORs) and the 95%

confidence intervals (CIs). Preoperative invasion depth of adenocarcinoma was diagnosed limited LPM when no findings suspected SM massive invasion were observed. Generalized estimating equations (GEEs) were used to analyze the repeated measures data.[20] A receiving operating characteristic (ROC) curve was constructed, and the optimal cut-off value for the circumferential extent of the mucosal defect was determined at the inflection point of the ROC curve. Twelve variables that may influence stricture formation were used to generate propensity scores ranging from 0 to 1 using logistic regression. The validity of the model was assessed by estimating the area under the ROC curve using c-statistics. The reliability of the model was evaluated using the Hosmer-Lemeshow test for goodness-of-fit. In addition, the inverse probability of treatment weighting (IPTW) method based on propensity scoring was used.[21-25] We adjusted for the confounding factors by using the estimated propensity scores to assign weights to the data. Analyses involving IPTW linear regressions for stricture formation were performed. The statistical analyses were performed using IBM® SPSS® software, version 23.0 for Windows (IBM Corporation, Armonk, NY, USA). The ROC curve was constructed using R software, version 3.0.2 (R Core Team, Vienna, Austria). All of the statistical tests were two-sided, and a value of $p < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics

Of the 105 patients (162 lesions) who were administered prophylactic locoregional triamcinolone injections, nine patients who received other prophylactic therapies were excluded (Figure 1). Consequently, 101 *en bloc* resections involving 144 lesions in 96 patients were evaluated. Of these, two and three synchronous lesions were resected *en bloc* in 17 and 7 patients, respectively.

Of the 101 *en bloc* resections performed, 17 (16.8%) strictures formed in 17 patients. The longitudinal diameters of the lesions were longer and the circumferences of the mucosal defects were significantly wider in the patients with strictures compared with those without strictures (Table 1). The two groups were similar with respect to all other factors.

We evaluated accuracy of the diagnosis of invasion depth and the positive predictive values of IEN-LPM, MM-SM1, and SM2 were 85.2%, 41.2%, and 100.0%, respectively.

Predictive factors for stricture formation

We evaluated the predictive factors for stricture formation in the patients who were administered a locoregional triamcinolone injections by comparing the resections that were and were not followed by stricture formation (Table 2). A crude logistic regression analysis demonstrated that a longer longitudinal diameter (OR 1.04, 95% CI: 1.00–1.07, $p = 0.03$) and a wider circumferential mucosal defect (OR 2.33, 95% CI: 1.27–4.29; $p = 0.006$) were associated with stricture formation. The multivariate logistic regression

analysis showed that the extent of the circumferential mucosal defect (OR=2.42, 95% CI: 1.01–5.80; $p = 0.048$) was an independent predictive factor for stricture formation.

Cut-off value

The cut-off value for the circumferential extent of the mucosal defect that was associated with stricture formation was 0.833 (five-sixths) (Figure 2), which had a sensitivity of 69.0% and a specificity 64.7%, and the area under the curve 71.2.

Using this cut-off value, we determined that the frequency of esophageal stricture formation increased following resections involving five-sixths or more of the circumferential mucosal defect (29.7%, 11/37) compared with resections involving less than five-sixths the circumferential mucosal defect (9.4%, 6/64) ($p < 0.01$). Logistic regression analysis determined that stricture formation increased in association with resections of five-sixths or more of the circumferential mucosal defect (OR 4.09, 95% CI: 1.36–12.3; $p = 0.012$) (Table 3). The effect of the circumferential extent of the mucosal defect on stricture formation persisted several adjustments (OR 4.88, 95% CI: 1.37–17.4; $p = 0.015$), and following adjustments for all 12 factors (OR 12.13, 95% CI: 2.95–49.96; $p = 0.001$) (Table 3).

Evaluation using the inverse probability of treatment weighting method

A quasi-randomized study can be created by using propensity scoring. The propensity score model was well calibrated (Hosmer-Lemeshow test: $p = 0.22$) and showed good discrimination between the groups (c-statistic = 0.89). After adjusting the model for differences in relation to the baseline risk factors using the IPTW method with the GEEs, we determined that esophageal stricture formation increased in association with

resections involving five-sixths or more of the circumferential mucosal defect (OR 5.70, 95% CI: 1.61–20.18; $p = 0.007$) (Table 3).

Discussion

The findings from this study demonstrated that the extent of the circumferential mucosal defect was an independent predictive factor for stricture formation in patients who were administered a single session of prophylactic locoregional triamcinolone injections immediately after esophageal ESD. In addition, a cut-off value was five-sixths of the circumferential extent of the mucosal defect. After adjusting for differences in the baseline risk factors using the IPTW method, a circumferential mucosal defect of five-sixths or more was associated with a significant increase in stricture formation.

Locoregional steroid injections may prevent stricture formation after esophageal ESD.[11-15] Administering locoregional corticosteroids may inhibit collagen synthesis, fibrosis, and inflammation.[26] Although several methods for administering the steroid injections have been described,[11-15,27] a single session of triamcinolone injections administered immediately after ESD is more straightforward and less expensive, and it may have similar efficacy.

This study has three strengths. First, this is the first study to investigate predictive factors for stricture formation in patients who received a prophylactic locoregional triamcinolone injections after ESD. Stricture formation rate of patients who have

received locoregional triamcinolone injections in the present study (16.8%) was similar to that of previous studies (10–20%).[11-15,28] . A tumor circumferential extent greater than 75% has been reported as a risk factor for refractory stricture development, which was defined as the requirement for more than three sessions of EBD to resolve the stricture, even in cases who have received locoregional triamcinolone injections.[17] Although the preoperative tumor circumference was evaluated in the aforementioned paper, most studies of the risk factors associated with stricture formation have evaluated the circumferential mucosal defect after ESD.[9,10] Changes in the circumferential mucosal defect after ESD compared with the preoperative tumor circumference depend upon the cut margins and the skill of the endoscopist. In addition, the preoperative tumor circumference cannot be evaluated in cases from whom multiple synchronous lesions are resected *en bloc*; hence, it is better to assess the circumferential mucosal defect to evaluate the risk of stricture formation.

This study's second strength relates to the determination of the cut-off value for the circumferential extent of the mucosal defect at the inflection point of the ROC curve. Most studies that have investigated the risk of stricture formation after esophageal ESD, determined the risk by using two-armed categorical data that showed whether the circumference was less than/equal to or greater than 75%.[10,17] After determining the

cut-off value, we determined that a circumferential mucosal defect of five-sixths or more was associated with an increase in stricture formation, and the incidence of strictures was similar to that reported previously.[17] In addition, the number of EBD sessions required to treat the strictures was significantly higher if the resected circumferential mucosal defect was five-sixths or more (0.6 ± 1.4) compared with those required when the resected circumferential mucosal defect was less than five-sixths (0.2 ± 0.6) ($p = 0.04$).

Third, after the cut-off value had been determined, we evaluated the incidence of stricture formation using the IPTW method with propensity scoring.[21,22,24,25] Selection bias can persist in retrospective studies, because the relationship between stricture formation and the circumferential mucosal defect may be affected by confounding factors, including age, gender, and the clinical characteristics.[23] An IPTW method based on propensity scoring, which can be employed without reducing the sample size, was used to assess the sensitivity of the results and to evaluate statistically causal effects that were independent of the confounding effects.

It is difficult to prevent an entire circumferential mucosal defect after ESD despite using several prophylactic therapies,[27,28] and it is an independent risk factor for refractory stricture formation, even in patients who have received locoregional

triamcinolone injections.[17] Given that our study included just one patient who had an entire circumferential mucosal defect, we were unable to evaluate this as a risk factor. Nevertheless, the data from our study showed that a subcircumferential mucosal defect of five-sixths or more was a predictive factor for stricture formation in patients who had received locoregional triamcinolone injections, which excluded the patient with the entire circumferential mucosal defect. A lesion located at the cervical esophagus is considered a risk factor for stricture formation,[17,29] but it was not a predictive factor of stricture formation in our study (2/14, 14.3%). This finding may have been influenced by the small sample size and our indication for steroid injections. The post-CRT status is also considered a risk factor for stricture formation,[17,29] but the findings from the present study did not determine a risk for stricture development (2/11, 18.2%).

Although oral prednisolone can prevent more extensive lesions, it is difficult to prevent strictures in the presence of entire circumferential lesions.[16,27,30,31] Some of the disadvantages associated with oral steroid administration include the long treatment durations, the high total steroid dosages, which lead to systemic adverse events, for example, infections or a worsening of diabetes mellitus, and delays in performing additional surgery or administering CRT because of possible infections in cases with

deeper invasions. Recently, investigators have shown that locoregional steroid injections followed by oral steroids may prevent stricture formation in cases with circumferential mucosal defects that are seven-eighths or more.[29] Hybrid therapy using steroid injections and polyglycolic acid sheets may prevent stricture formation, even in cases with circumferential mucosal defects of five-sixths or more.[32] Therefore, we propose the strategies for the above-mentioned combination prophylactic therapy for circumferential mucosal defects greater than five-sixth of the esophageal circumference. In addition, increasing the total dose of the triamcinolone injection may have the potential to prevent stricture in such cases, because we injected a total amount of 80 mg, regardless of the lesion size. However, a prospective randomized study that compares steroid injections administered alone with the aforementioned combination therapies to patients at a high risk of stricture formation would be beneficial.

Our study has some limitations. This was a retrospective single center study in small sample size. These limitations may have affected the significance of the other factors, in particular, the cases with lesions located at the cervical esophagus and those previously administered CRT. To resolve these limitations, prospective large-scale multicenter studies should be conducted.

In conclusion, a circumferential mucosal defect of more than five-sixths increases the risk of stricture formation in patients who received a single session of prophylactic locoregional triamcinolone injections immediately after esophageal ESD. Additional or alternative prophylactic therapy would be beneficial for these patients.

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References

1. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med.* 2003; 349: 2241-2252.

2. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008; 58: 71-96.

3. Muto M, Minashi K, Yano T et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J Clin Oncol.* 2010; 28: 1566-1572.

4. Nagami Y, Tominaga K, Machida H et al. Usefulness of non-magnifying narrow-band imaging in screening of early esophageal squamous cell carcinoma: a prospective comparative study using propensity score matching. *Am J Gastroenterol.* 2014; 109: 845-854.

5. Ishihara R, Tanaka H, Iishi H et al. Long-term outcome of esophageal mucosal squamous cell carcinoma without lymphovascular involvement after endoscopic resection. *Cancer.* 2008; 112: 2166-2172.

6. Nagami Y, Machida H, Shiba M et al. Clinical Efficacy of Endoscopic Submucosal Dissection for Adenocarcinomas of the Esophagogastric Junction. *Endosc Int Open.* 2014; 2: E15-20.

7. Nagami Y, Ominami M, Shiba M et al. The five-year survival rate after endoscopic submucosal dissection for superficial esophageal squamous cell neoplasia. *Dig Liver Dis.* 2016, DOI: 10.1016/j.dld.2016.12.009:

8. Ono S, Fujishiro M, Niimi K et al. Long-term outcomes of endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms. *Gastrointest Endosc.* 2009; 70: 860-866.

9. Mizuta H, Nishimori I, Kuratani Y et al. Predictive factors for esophageal stenosis after endoscopic submucosal dissection for superficial esophageal cancer. *Dis Esophagus.* 2009; 22: 626-631.

10. Ono S, Fujishiro M, Niimi K et al. Predictors of postoperative stricture after esophageal endoscopic submucosal dissection for superficial squamous cell neoplasms. *Endoscopy.* 2009; 41: 661-665.

11. Barret M, Beye B, Leblanc S et al. Systematic review: the prevention of oesophageal stricture after endoscopic resection. *Aliment Pharmacol Ther.* 2015; 42: 20-39.

12. Hanaoka N, Ishihara R, Takeuchi Y et al. Intralesional steroid injection to prevent stricture after endoscopic submucosal dissection for esophageal cancer: a controlled prospective study. *Endoscopy.* 2012; 44: 1007-1011.

13. Hashimoto S, Kobayashi M, Takeuchi M et al. The efficacy of endoscopic triamcinolone injection for the prevention of esophageal stricture after endoscopic submucosal dissection. *Gastrointest Endosc.* 2011; 74: 1389-1393.

14. Nagami Y, Shiba M, Ominami M et al. Single locoregional triamcinolone injection immediately after esophageal endoscopic submucosal dissection prevents stricture formation. *Clin Transl Gastroenterol.* 2017; in press:

15. Nagami Y, Shiba M, Tominaga K et al. Locoregional steroid injection prevents stricture formation after endoscopic submucosal dissection for esophageal cancer: a propensity score matching analysis. *Surg Endosc.* 2016; 30: 1441-1449.

16. Yamaguchi N, Isomoto H, Nakayama T et al. Usefulness of oral prednisolone in the treatment of esophageal stricture after endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Gastrointest Endosc.* 2011; 73: 1115-1121.

17. Hanaoka N, Ishihara R, Uedo N et al. Refractory strictures despite steroid injection after esophageal endoscopic resection. *Endosc Int Open.* 2016; 4: E354-359.

18. Ominami M, Nagami Y, Shiba M et al. Prediction of Poor Response to Modified Neuroleptanalgesia with Midazolam for Endoscopic Submucosal Dissection for Esophageal Squamous Cell Carcinoma. *Digestion.* 2016; 94: 73-81.

19. Knyrim K, Wagner HJ, Bethge N et al. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. *N Engl J Med.* 1993; 329: 1302-1307.

20. Smith PJ, Hadgu A. Sensitivity and specificity for correlated observations. *Stat Med.* 1992; 11: 1503-1509.

21. Adams TD, Davidson LE, Litwin SE et al. Health benefits of gastric bypass surgery after 6 years. *JAMA.* 2012; 308: 1122-1131.

22. Fukunaga S, Nagami Y, Shiba M et al. Long-term prognosis of expanded-indication differentiated-type early gastric cancer treated with endoscopic submucosal dissection or surgery using propensity score analysis. *Gastrointest Endosc.* 2017; 85: 143-152.

23. Gotoda T, Hatta W. Are randomized control studies needed to evaluate the efficacy of treatment techniques that are clearly minimally invasive and already widely used? *Gastrointest Endosc.* 2017; 85: 153-154.

24. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Stat Med.* 2004; 23: 2937-2960.

25. Wang SJ, Lemieux A, Kalpathy-Cramer J et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol.* 2011; 29: 4627-4632.

26. Ramage JI, Jr., Rumalla A, Baron TH et al. A prospective, randomized, double-blind, placebo-controlled trial of endoscopic steroid injection therapy for recalcitrant esophageal peptic strictures. *Am J Gastroenterol.* 2005; 100: 2419-2425.

27. Miwata T, Oka S, Tanaka S et al. Risk factors for esophageal stenosis after entire circumferential endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *Surg Endosc.* 2015, DOI: 10.1007/s00464-015-4719-3:

28. Takahashi H, Arimura Y, Okahara S et al. A randomized controlled trial of endoscopic steroid injection for prophylaxis of esophageal stenoses after extensive endoscopic submucosal dissection. *BMC Gastroenterol.* 2015; 15: 1.

29. Kadota T, Yano T, Kato T et al. Prophylactic steroid administration for strictures after endoscopic resection of large superficial esophageal squamous cell carcinoma. *Endosc Int Open.* 2016; 4: E1267-E1274.

30. Isomoto H, Yamaguchi N, Nakayama T et al. Management of esophageal stricture after complete circular endoscopic submucosal dissection for superficial esophageal squamous cell carcinoma. *BMC Gastroenterol.* 2011; 11: 46.

31. Sato H, Inoue H, Kobayashi Y et al. Control of severe strictures after circumferential endoscopic submucosal dissection for esophageal carcinoma: oral steroid therapy with balloon dilation or balloon dilation alone. *Gastrointest Endosc.* 2013; 78: 250-257.

32. Nagami Y, Shiba M, Tominaga K et al. Hybrid therapy with locoregional steroid injection and polyglycolic acid sheets to prevent stricture after esophageal endoscopic submucosal dissection. *Endosc Int Open.* 2016; 4: E1017-1022.

Figure legends

Fig. 1. Diagram of the study design. ESD, endoscopic submucosal dissection.

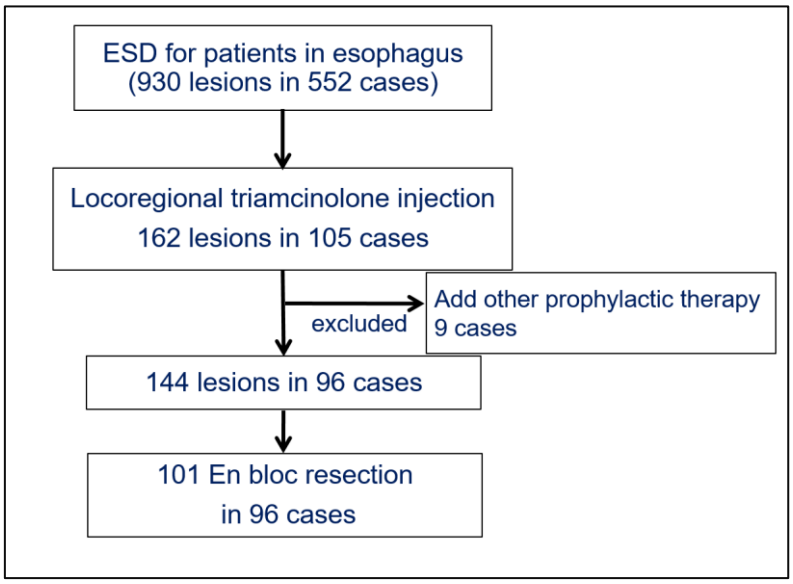

Fig. 2. Cut-off value by ROC curve. The cut-off value of circumferential mucosal defect associated with stricture formation was 0.833 (five-sixth) according to the inflection point of the ROC curve.

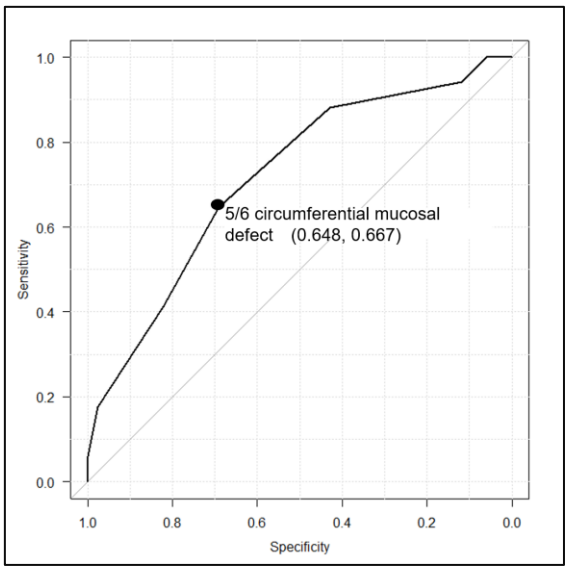

Table 1. Patient characteristics

		Stricture (-)	Stricture (+)	*p* value
Number of cases		84 (83.2%)	17 (16.8%)	
Age, years, mean ± SD		69.9 ± 8.7	69.4 ± 5.3	0.81
Gender	Female	17 (89.5%)	2 (10.5%)	0.52
	Male	67 (81.8%)	15 (18.3%)	
Location	Ce	12 (85.7%)	2 (14.3%)	0.86
	Th	69 (83.1%)	14 (16.9%)	
	Ae	3 (75.0%)	1 (25.0%)	
Macroscopic appearance	Elevated, Flat	28 (84.8%)	5 (15.2%)	0.79
	Depressed	56 (82.4%)	12 (17.6%)	
Longitudinal diameter (mm)		30.9 ± 14.4	38.6 ± 14.4	0.04
Circumferential mucosal defect (%)		74.0 ± 12.0	83.3 ± 11.3	0.004
Preoperative invasion depth	IEN, EP, LPM	68 (84.0%)	13 (16.0%)	0.71
	MM, SM1	13 (76.5%)	4 (23.5%)	
	SM2	3 (100.0%)	0 (0.0%)	
Previous chemoradiotherapy	No	75 (83.3%)	15 (16.7%)	1.00
	Yes	9 (81.8%)	2 (18.2%)	
ESD scar	No	72 (81.8%)	16 (18.2%)	0.69
	Yes	12 (92.3%)	1 (7.7%)	
Endoscopist	Expert	56 (86.2%)	9 (13.8%)	0.41
	Trainee	28 (77.8%)	8 (22.2%)	
Surgical knife	Monopolar	51 (85.0%)	9 (15.0%)	0.60
	Bipolar	33 (80.5%)	8 (19.5%)	
Treatment time (min)		112.2 ± 55.7	121.4 ± 46.5	0.53
Histology	SCC	82 (83.7%)	16 (16.3%)	0.43
	Adenocarcinoma	2 (66.7%)	1 (33.3%)	

SD, standard deviation; Ce, cervical esophagus; Th, thoracic esophagus; Ae, abdominal esophagus; IEN, intraepithelial neoplasia; EP, epithelium; LPM, lamina propria mucosae; MM, muscularis mucosae; SM1, submucosal invasion <200μm; SM2, submucosal invasion ≥ 200μm; ESD, endoscopic submucosal dissection; SCC, squamous cell carcinoma.

Table 2. Predictive factors for stricture formation

					GEE Crude-OR		GEE Multiple-adjusted OR	
		n	Cases	%	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Number		101	17	16.8				
Age, years, mean ± SD		101	17	16.8	0.99 (0.95-1.05)	0.74		
Gender	Male	82	15	18.3	1.00			
	Female	19	2	10.5	0.53 (0.11-2.52)	0.42		
Location	Ce	14	2	14.3	1.00		1.00	
	Th	83	14	16.9	1.21 (0.24-6.13)	0.81	0.36 (0.04-2.91)	0.34
	Ae	4	1	25.0	2.00 (0.13-30.5)	0.62	1.06 (0.06-17.5)	0.97
Macroscopic appearance	Elevated, Flat	33	5	15.2	1.00			
	Depressed	68	12	17.6	1.20 (0.39-3.74)	0.75		
Longitudinal diameter		101	17	16.8	1.04 (1.00-1.07)	0.03	1.02 (0.98-1.06)	0.38
Circumferential mucosal defect		101	17	16.8	2.33 (1.27-4.29)	0.006	2.42 (1.01-5.80)	0.048
Preoperative invasion depth	IEN, EP, LPM	81	13	16.0	1.00			
	MM, SM1	17	4	23.5	1.61 (0.46-5.69)	0.46		
	SM2	3	0	0.0	-	-		
Previous chemoradiotherapy	No	90	15	16.7	1.00		1.00	
	Yes	11	2	18.2	1.11 (0.22-5.64)	0.90	1.56 (0.38-6.44)	0.54
ESD scar	No	88	16	18.2	1.00		1.00	

	Yes	13	1	7.7	0.38 (0.05-3.08)	0.36	0.45 (0.03-6.50)	0.56
Endoscopist	Expert	65	9	13.8	1.00			
	Trainee	36	8	22.2	1.78 (0.62-5.69)	0.28		
Surgical knife	Monopolar	60	9	15.0	1.00			
	Bipolar	41	8	19.5	1.37 (0.49-3.89)	0.55		
Treatment time		101	17	16.8	1.00 (0.99-1.01)	0.46		
Histology	SCC	98	16	16.3	1.00			
	Adenocarcinoma	3	1	33.3	2.56 (0.22-30.0)	0.45		

SD; standard deviation; Ce, cervical esophagus; Th, thoracic esophagus; Ae, abdominal esophagus; IEN, intraepithelial neoplasia; EP, epithelium; LPM, lamina propria mucosae; MM, muscularis mucosae; SM1, submucosal invasion <200μm; SM2, submucosal invasion ≥ 200μm; ESD, endoscopic submucosal dissection; SCC, squamous cell carcinoma; GEE, generalized estimating equations; OR, odds ratio; CI, confidence interval.

Table 3. Multivariate and IPTW logistic odds ratio of stricture formation associated with circumferential mucosal defect

	Odds Ratio (95% CI)	*p* value
Unadjusted	4.09 (1.36-12.3)	0.012
Adjusted for location, longitudinal diameter, post CRT, ESD scar	4.88 (1.37-17.4)	0.015
Adjusted for all factors	12.13 (2.95-49.96)	0.001
IPTW	5.70 (1.61-20.18)	0.007

CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; IPTW, inverse probability of treatment weighting.