Clinical Analysis of Esophageal Stricture in Patients Treated with Intralesional Triamcinolone Injection after Endoscopic Submucosal Dissection for Superficial Esophageal Cancer

Kazuki Okamoto^a Shigenaga Matsui^a Tomohiro Watanabe^a
Yutaka Asakuma^a Yoriaki Komeda^a Ayana Okamoto^a Ishikawa Rei^a
Masashi Kono^a Mitsunari Yamada^a Tomoyuki Nagai^a Tadaaki Arizumi^a
Kosuke Minaga^a Ken Kamata^a Kentaro Yamao^a Mamoru Takenaka^a
Toshiharu Sakurai^a Naoshi Nishida^a Hiroshi Kashida^a Takaaki Chikugo^b
Masatoshi Kudo^a

Departments of ^aGastroenterology and Hepatology and ^bPathology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan

Keywords

Esophageal stricture · Endoscopic submucosal dissection · Triamcinolone

Abstract

Introduction: Endoscopic submucosal dissection (ESD) has been widely used in the resection of superficial esophageal cancers. Since its use has been extended to cases involving large esophageal tumors occupying nearly the whole or the whole circumference of the lumen, the occurrence of esophageal stricture has increased. Although endoscopic injection of triamcinolone (TA) is widely used for the prevention of postoperative stricture, a significant number of patients still develop stricture after TA injection therapy. **Methods:** We performed a retrospective study to identify the clinical parameters that predispose post-ESD patients to esophageal stricture after TA injection therapy. **Results:** A total of 207 patients who were diagnosed with superficial esophageal

cancer and subsequently underwent ESD were enrolled in this study. Among these patients, 53 patients and 57 lesions bearing mucosal defects covering greater than two-thirds of the esophageal circumference after ESD were treated with TA injection therapy. The rate of esophageal stricture was found to be highest in cases involving mucosal defects that covered more than seven-eighths of the circumference. **Conclusion:** Endoscopic TA injection is not sufficient for preventing esophageal stricture in patients bearing mucosal defects covering more than seven-eighths of the esophageal circumference after ESD.

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Introduction

Endoscopic submucosal dissection (ESD) has now become a standard treatment modality for superficial esophageal cancer [1–3]. ESD has enabled endoscopists

to achieve en bloc resection of large superficial esophageal cancers. Indeed, local recurrence rates are much lower in ESD than in conventional endoscopic mucosal resection (EMR) due to the effectiveness of the en bloc resection [1–3]. Thus, ESD is considered the most useful procedure for resection of superficial esophageal cancer.

As the indications for ESD for esophageal cancer extend to include larger tumors that occupy near or whole circumference, the complication rate associated with the procedure is rising. Esophageal stricture is the most frequent complication associated with ESD [4]. Ono et al. [5] reported that most patients who underwent near- or whole-circumferential ESD developed postoperative esophageal stricture. Severe esophageal stricture can impair quality of life due to the resultant inability to ingest food, and usually requires multiple sessions of endoscopic balloon dilations (EBDs). Hence, there have been many attempts to reduce the incidence of esophageal stricture. Endoscopic intralesional injection of triamcinolone (TA) is widely used for the prevention of esophageal stricture after ESD. Although endoscopic TA injection can cause delayed perforation upon injection into the muscle layer [6, 7], several clinical studies report the safety and efficacy of its use [8, 9]. It should be noted, however, that a significant proportion (10–20%) of patients still develop postoperative esophageal stricture even after treatment with endoscopic TA injection [8, 9]. Therefore, it is important to identify the subgroup of patients at high risk of developing ESD-related esophageal stricture after TA injection.

In this study, we performed a retrospective review of the data from 57 patients treated with near- or whole-circumferential ESD and with TA injection. We report that an extensive circumferential mucosal defect (covering more than 75% of the circumference) was associated with a high risk of developing postoperative esophageal stricture, even after preventive injection of TA.

Materials and Methods

Patients

This was a retrospective study in which we analyzed the clinicopathological factors associated with esophageal stricture after near- or whole-circumferential ESD and endoscopic injection of TA. Between January 2011 and October 2016, a total of 207 patients who were diagnosed with superficial esophageal cancer and subsequently underwent ESD at Kindai University Hospital, Osaka, Japan, were enrolled in this study. Among those 207 patients, ESD was performed in 53 patients for a total of 57 cancerous lesions resulting in mucosal defects covering more than two-thirds of the circumference. Endoscopic injection of TA was performed

Fig. 1. Flow diagram showing the patients enrolled in the study. A total of 207 patients who were diagnosed as having superficial esophageal cancer and underwent ESD at Kindai University Hospital were enrolled in this study. Among these 207 patients and 290 lesions, 53 patients bearing 57 lesions underwent ESD with the extent of more than two-thirds of circumferential mucosal defect and then treated with endoscopic injection of TA for the prevention of esophageal stricture. Among 53 patients and 57 lesions, 14 patients exhibited esophageal stricture that required EBD. The 57 lesions were divided into non-esophageal stricture group ($n = 43$) and esophageal stricture group ($n = 14$).

for the 57 lesions. Ethical permission for this study was obtained from the Review Board at Kindai University, Faculty of Medicine. Patients with a history of chemotherapy or radiotherapy for esophageal cancer were excluded from the study.

Clinical parameters were obtained from the medical records of each patient, including age, sex, location of lesion (cervical, upper, middle, lower), longitudinal diameter of the lesion, endoscopic appearance of the lesion (IIa, IIb, IIc), depth of invasion (EP, LPM, MM, SM1, SM2) [5], ESD procedure time, extent of circumferential mucosal defect after ESD (more than 2/3, more than 3/4), and total dose of TA injection. Esophageal stricture was considered present when the patient complained of dysphagia or when a standard endoscope (GIF-Q260J; Olympus Optical, Tokyo, Japan) could not pass through the post-ESD scar.

Endoscopic Submucosal Dissection

ESD was performed with the patients under conscious sedation by periodic intravenous administration of propofol and pethidine hydrochloride. We used a single-channel upper GI endoscope (GIF-Q260J; Olympus Optical, Tokyo, Japan) with transparent hood and irrigation pump. Carbon dioxide insufflation was used during the procedure. Sodium hyaluronic acid was injected into the submucosal layer to make a submucosal cushion. A flush-knife BT or BTS (DK2620J Fujifilm Medical, Tokyo, Japan) was used to dissect the lesion. The settings of the electrosurgical generator (VIO300 D Erbe Elektromedizin GmbH, Tübingen, Germany) were: soft coagulation (effect 80 W) for marking, endocut I (effect 3, time 2, interval 3) for mucosal incision, swift coagulation (effect 40 W) for submucosal dissection, and soft coagulation (effect

Table 1. Clinical parameters associated with esophageal structure

Clinical parameters	Esophageal stricture 14 cases (14 lesions)	Non-esophageal stricture 39 cases (43 lesions)	<i>p</i> value
Age, years	72.3±9.5	68.3±8.6	0.13 ^b
Male/female	12/2 (85.7, 14.3)	38/5 (88.4, 11.6)	0.55 ^a
Location of lesion			
Cervical	1 (7.1)	0	1.00 ^a
Upper	2 (14.3)	1 (2.3)	0.15 ^a
Middle	9 (64.3)	22 (51.2)	0.54 ^a
Lower	2 (14.3)	20 (46.5)	0.06 ^a
Longitudinal diameter of lesion	55.7±14.0	51.4±19.3	0.45 ^b
Endoscopic appearance			
0-IIa	1 (7.1)	1 (2.3)	0.43 ^a
0-IIb	7 (50)	33 (76.7)	0.09 ^a
0-IIc	6 (42.9)	9 (20.9)	0.16 ^a
Depth of invasion			
EP	4 (28.6)	13 (30.2)	1.00 ^a
LPM	6 (42.9)	20 (46.5)	1.00 ^a
MM	3 (21.4)	5 (11.6)	0.39 ^a
SM1	1 (7.1)	0	1.00 ^a
SM2	0	1 (2.3)	1.00 ^a
ESD procedure time	140.1±58.8	99.2±40.5	0.005 ^b
Circumferential extent (CE)			
3/4 ≤ CE ≤1	11 (78.6)	27 (62.8)	0.34 ^a
7/8 ≤ CE ≤1	10 (71.4)	10 (23.3)	0.003 ^a
Total doses of TA, mg	68±24	44.8±23.2	0.06 ^b

Figures in parentheses indicate percentages. ESD, endoscopic submucosal dissection; TA, triamcinolone.
^a Fisher's exact test. ^b *t* test.

40 W) for bleeding points. Hemostatic forceps were used for preventive occlusions of the vessels. At the end of the procedure, additional coagulation was carefully performed to prevent delayed bleeding.

Endoscopic TA Injection

TA was diluted with 0.9% NaCl to a final concentration of 10 mg/mL. Then, 0.1- to 0.2-mL aliquots were injected at the base of the artificial ulcer using a 25-gauge, 4-mm needle (TOP Corporation). Effective administration of the steroid into the submucosal layer required dissection at the middle level of the submucosal layer to create enough space for the injection. A potential problem with the injection method is the risk of delayed perforation, which may occur if the steroid is injected into the true muscular layer. Therefore, TA must be injected into the submucosal layer.

Endoscopic Balloon Dilation

EBD was performed every 1–4 weeks after ESD. The dilatation was performed in the outpatient department using CRETM Wire-Guided Esophageal/Pyloric balloon Dilatation Catheters (Boston Scientific, Marlborough, MA, USA). Dilatation therapy was considered successful when the patients reported improvement in dysphagia.

Statistical Analysis

Student's *t* test or Fisher's exact test was used in the univariate analysis. A *p* value less than 0.05 was considered significant. Clinical factors considered significant in the univariate analysis were subjected to multivariate analysis and a *p* value less than 0.05 was considered significant.

Results

Flow Diagrams of the Patients

Esophageal stricture is the most frequent complication in ESD. Endoscopic TA injection is one of the most effective treatments for prevention of ESD-associated esophageal stricture [8, 9]. However, a significant proportion of patients still develop esophageal stricture requiring EBD even after endoscopic TA injection. In this retrospective study, we aimed to identify the risk factors for esophageal stricture in patients who underwent near- or whole-circumferential ESD and were treated with TA injection.

As shown in Figure 1, a total of 207 patients who were diagnosed with superficial esophageal cancer and underwent ESD at Kindai University Hospital were enrolled in this study. Among these 207 patients and 290 lesions, 53 patients bearing 57 lesions, underwent ESD which had resulted in a mucosal defect of greater than two-thirds of the esophageal circumference. These patients were then treated with endoscopic injection of TA for the prevention of esophageal stricture. We performed clinicopathological analysis in these 57 lesions.

Risk Factors for Postoperative Esophageal Stricture in Patients Treated with TA Injection

Among the 53 patients and 57 lesions described above, 14 patients exhibited esophageal stricture requiring EBD. These 57 lesions were divided into 2 groups: the non-esophageal stricture group ($n = 43$) and the esophageal stricture group ($n = 14$). Characteristics of the clinicopathological findings of these lesions are summarized in Table 1. No significant difference was seen in age, sex, tumor location, or depth of tumor invasion for both groups. In contrast, the rate of esophageal stricture was much higher in the cases with a mucosal defect covering more than seven-eighths of the circumference. Total dose of TA injection was higher in the non-esophageal stricture group than in the group with esophageal stricture. We performed multivariate analysis to confirm the results obtained using univariate analysis. As shown in Table 2, a circumferential mucosal defect of more than seven-eighths was identified as an independent risk factor for postoperative esophageal stricture. Conversely, ESD procedure time did not show a significant correlation. Collectively, univariate and multivariate analyses revealed that a mucosal defect covering seven-eighths or more of the circumference was strongly associated with postoperative esophageal stricture in patients treated with TA injection. These data suggest that endoscopic TA injection cannot prevent esophageal stricture in lesions bearing mucosal defects which cover more than seven-eighths of the circumference after ESD.

Case Presentation

Case 1

An 84-year-old man was admitted to Kindai University Hospital for ESD of a superficial esophageal cancer. Lugol's iodine staining revealed a lesion that was almost whole circumferential within the esophageal lumen (Fig. 2a). The patient was treated with ESD, which resulted in a whole-circumferential mucosal defect (Fig. 2b). The patient received endoscopic injection of TA for a to-

Table 2. Risk factors for postoperative esophageal stricture in patients treated with TA injection

	Odds ratio	95% CI	<i>p</i> value
Procedure time	1.01	1.0–1.03	1.01
More than seven-eighths of circumferential mucosal defect	5.83	1.41–24.12	0.01

tal of 80 mg for the prevention of esophageal stricture. Severe esophageal stricture developed 18 days after the procedure (Fig. 2c).

Case 2

A 54-year-old man was admitted to Kindai University Hospital for ESD of a superficial esophageal cancer. Lugol's iodine staining revealed a lesion occupying approximately two-thirds of the circumference of the esophageal lumen (Fig. 3a). The patient was treated with ESD, which resulted in a mucosal defect covering two-thirds of the lumen circumference (Fig. 3b). The patient received endoscopic injection of TA for a total of 40 mg for the prevention of esophageal stricture. Twenty-eight days after ESD, esophageal stricture had not developed (Fig. 3c).

Discussion

Esophageal submucosal dissection has been established as a minimally invasive and effective modality for the treatment of superficial esophageal cancer [1–3]. This technique has enabled surgeons to perform en bloc resection of superficial esophageal cancers and to make accurate histological diagnoses, especially in terms of depth of invasion. Thus, judgement regarding successful complete resection is much easier in ESD than in conventional EMR. In fact, local recurrence rates of tumors after ESD are lower than those after EMR due to effective en bloc resections [1–3]. The indications for ESD have been extended to large superficial esophageal cancers that occupy almost the whole circumference of the esophageal lumen. Esophageal stricture is the most frequent complication associated with near- or whole-circumferential ESD for such large superficial esophageal cancers. Since esophageal stricture sometimes worsens quality of life, various preventive methods have been

Fig. 2. Representative case with esophageal stricture after ESD and TA injection. **a** Lugol's iodine staining revealed a lesion which was almost whole-circumferential within the esophageal lumen. **b** ESD resulted in a whole-circumferential mucosal defect. **c** Severe esophageal stricture developed 18 days after the ESD, despite endoscopic TA injection.

Fig. 3. Representative case without esophageal stricture after ESD and TA injection. **a** Lugol's iodine staining revealed a lesion occupying two-thirds of the circumference of esophageal lumen. **b** ESD resulted in a mucosal defect covering two-thirds of the circumference. **c** Esophageal stricture had not developed 28 days after the ESD and endoscopic TA injection.

proposed [4, 7, 10]. Endoscopic injection of TA is widely used in the prevention of esophageal stricture associated with ESD [8, 9]. However, a significant population of patients develop esophageal stricture even after the preventive injection. Therefore, it is important to identify the clinical parameters that predispose ESD treated patients to postoperative esophageal stricture. In this study, we retrospectively analyzed 57 esophageal cancer lesions that occupied greater than two-thirds of the esophageal lumen and that received preventive endoscopic injection of TA. We found that the rate of esophageal stricture was highest in cases when the resulting mucosal defect covered greater than seven-eighths of the esophageal circumference after ESD. Thus, our data suggest that endoscopic TA injection is not sufficient for the prevention of esophageal stricture in cases with mucosal defects covering greater than seven-eighths of the esophageal circumference after ESD.

Since endoscopic TA injection is not sufficiently effective in the prevention of esophageal stricture after near- or whole-circumferential ESD, other preventative strategies need to be considered. Oral prednisolone (30 mg/day) may offer a useful preventive option [11]. However, there are reports linking prednisolone with the development of infectious diseases [12]. Sakaguchi et al. [13] reported the usefulness of polyglycolic acid (PGA) sheets with fibrin glue in the prevention of esophageal stricture after ESD. In line with this, another report showed that the percentage of postoperative stricture after application of PGA sheets was 7.7% in patients with a mucosal defect covering greater than seven-twelfths of the esophageal circumference [14]. Furthermore, Kataoka et al. [15] reported a case in which esophageal stricture was successfully prevented by endoscopic TA injection followed by the application of PGA sheets after a whole-circumferential resection. Therefore, it is important to consider alter-

native strategies including the application of PGA sheets in cases bearing mucosal defects covering greater than seven-eighths of the circumference.

One concern arising from this study is how to optimize TA dosage to most effectively prevent esophageal stricture. TA is injected into the submucosal layer; however, occasionally leakage may occur [10]. Thus, endoscopists often encounter situations in which adequate intralesional distribution of TA is difficult to achieve. In this study, the total dose of TA injected was higher in the patients with esophageal stricture than in those without stricture. However, it remains unknown whether effective doses of TA were actually injected into the submucosal layer in each case. Tracing modalities to confirm adequate distribution of TA would be required to estimate and establish optimal dosage of TA necessary for the prevention of postoperative esophageal stricture.

Conclusion

We have identified a risk factor for esophageal stricture in patients treated with endoscopic injection of TA. Endoscopic TA injection is not sufficient for the prevention of esophageal stricture in patients bearing a mucosal defect covering more than seven-eighths of the circumference after ESD. In such cases, alternative strategies, including the application of PGA sheets with or without TA injection need to be considered to avoid postoperative stricture.

Disclosure Statement

The authors have no conflicts of interest to declare.

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