

Original Article

Local steroid injection prevent deformity and stenosis of stomach after large endoscopic submucosal dissection

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Abstract: Background and Aims: Endoscopic submucosal dissection (ESD) involving more than three fourths (75%) of the gastric lumen creates stenosis of the stomach. This study aims to evaluate the capability to prevent the stenosis those cases by local triamcinolone acetonide (TA) injection. Methods: Among 352 patients, 83 patients underwent resection of more than a half (50%) of the circumference. We retrospectively evaluated 83 patients between September 2008 and August 2012 without local steroid injection (non-TA injection, n=43), and between September 2012 and February 2014 with local steroid injection (TA injection group, n=40). TA was locally injected into the post-ESD ulcer floor on days 5 and 12. In each groups, we evaluated passage of the endoscope as a marker for stenosis on post-operative day (POD) 30 after ESD. Results: In non-TA group, resections over 75% of the circumference had stenosis that did not allow for passage of the endoscope. Even though local TA injection was performed, only in 5 patients, resections over 75% of the circumference resulted in stenosis that did not allow for passage of the endoscope ($P=0.001$). Endoscopic balloon dilatation was required 18.6 ± 3.62 times in non-TA group and 5.63 ± 2.86 times in TA group, respectively ($P=0.003$). Conclusions: Although the local injection of TA into the large artificial ulcer following ESD may prevent postoperative gastric stenosis, more than 75% of the circumference resection leads to severe stenosis even in TA injection. Local TA injection to post-ESD large artificial ulcer was new and innovative measurements to reduce severe stenosis.

Keywords: Gastric endoscopic submucosal dissection, resection over three fourth (75%) circumferences, stenosis of the stomach, local triamcinolone acetonide injection

Introduction

Endoscopic submucosal dissection (ESD) for early gastric cancer is a well-established endoscopic therapeutic procedure. In Japan, ESD of the esophagus, stomach, and large intestine are covered by medical insurance [1-8]. There are some reports of local triamcinolone acetonide (TA) injection for early esophageal cancer, and local TA injections are known to prevent esophageal stricture [9, 10]. On the other hand, stenosis is rare after gastric ESD since the gastric lumen is much larger than the esophagus; however, an ESD exceeding 3/4 (75%) of the gastric lumen creates stenosis of the antrum of the stomach, leading to decline of quality of life (QOL) of patients with food passage obstructions. As ESD procedures were almost established in Japan, the number of large ESD exceeding 3/4 (75%) circumference of the gas-

tric lumen has increased and post-large-ESD stenosis has also increased. We previously reported that local TA injections to post artificial ulcer after gastric ESD prevented gastric deformities and severe scars [11]. There are a few reports comparing the relationship between the resection size and post ESD stenosis. Therefore, we investigated whether specific TA injection methods can prevent stenosis and be used as therapy for artificial ulcers after ESD exceeding 3/4 (75%) of the circumference of the gastric lumen.

Method

Three hundred fiftytwo patients were diagnosed between September 2008 and February 2014 with early gastric cancer and histologically well-differentiated adenocarcinoma at Kagawa Rousai Hospital, Ehime Rousai Hospital and

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Table 1. Characteristics of patients

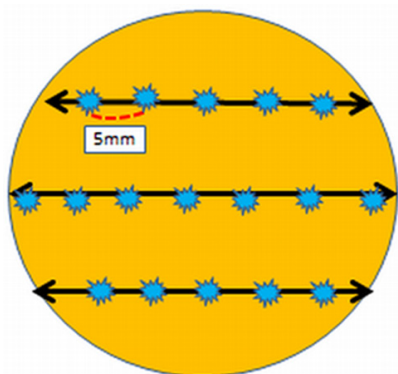
		non-TA group (n=43)	TA group (n=40)	Evaluation
Age	(mean ± SD) (range) (years)	75.4±6.22 (65-82)	73.6±10.59 (59-83)	0.579*; NS
Gender	(M/F)	25/18	22/18	0.712**; NS
Location	(U/M/L)	0/14/29	0/14/26	0.813**; NS
Procedure time of ESD (min)	(mean ± SD) (range)	73.2±30.1 (45-118)	81.2±34.0 (43-124)	0.472*; NS
Specimen size (mm)	(mean ± SD) (range)	62.8±17.9 (42-84)	65.4±15.5 (45-82)	0.528*; NS

TA, Triamcinolone acetonide; SD, Standard Deviation; NS, No Significant; M, Male; F, Female; U, Upper Region of stomach; M, Middle Region of stomach; L, Lower Region of stomach; *Unpaired t-test, ** χ^2 test; chi-squared test.

Table 2. Post-resection observations of both groups

	non-TA group (n=43)	TA group (n=40)	Statistical Evaluation
Number of Patients (50-75%/over 75%) (mean ± SD (%)) (M/L)	23 (8/15)/20 (6/14) (63.4±12.6)	26 (7/19)/14 (7/7) (68.5±12.3)	0.527*; NS
Number of endoscope passage (50-75%) (POD 30) (M/L)	23 (8/15)	26 (7/19)	0.531**; NS
Number of endoscope passage (over 75%) (POD 30) (M/L)	0	9 (7/2)	**0.001
EBD (POD30-90) (50-75%) (mean ± SD) (times)	4.8±5.40	1.6±2.34	**0.043
EBD (POD30-90) (over 75%) (mean ± SD) (times)	18.6±3.62	5.63±2.86	**0.003

TA, Triamcinolone acetonide; SD, Standard Deviation; NS, No Significant; EBD, Endoscopic balloon dilatation; *Unpaired t-test, ** χ^2 test, chi-squared test.



Injections were performed at 5-mm intervals onto 3 straight lines quadrisectioning the maximum diameter of the ulcer.

We injected TA in 0.2-mL (2 mg) aliquots into the each injection site of the artificial ulcer floor (★)

Figure 1. Triamcinolone acetonide local injection. A total of 40 mg of triamcinolone acetonide (TA) was locally injected into the post-endoscopic submucosal dissection ulcer floor (remaining submucosal layer) (every 2 mg TA was injected into the ulcer floor as evenly as possible) on postoperative days 5 and 12 carefully.

Kagawa University Hospital. Of these 352 patients, those undergoing resection of more than 1/2 of the circumference of the gastric lumen were 83 patients who met the expanding indications of ESD according to the Japanese Gastric Cancer Association (JGCA) as follows: mucosal differentiated adenocarcinoma of any size without an ulcer and submucosa 1 (SM1) invaded differentiated adenocarcinoma within a 30-mm diameter. Therefore, all patients were pathologically well-differentiated adenocarcinoma. We retrospectively evaluated 43 patients in the former term between September 2008 and August 2012 without local steroid injection

treatment (non-TA injection group, n=43), and in the latter term between September 2012 and February 2014 with local steroid injection treatment (TA injection group, n=40). In the latter term, we informed patients of the procedure of local TA injection and consented them with written forms (Table 1).

In each groups, we evaluated passage of the endoscope (OLYMPUS GIF TYPE Q260J (OLYMPUS, Tokyo, Japan)) on postoperative day (POD) 30 after ESD. The number of endoscopic balloon dilatation (EBD) (twice per week) from POD 30 to POD 90 to improve endoscope passage. The local TA injection therapy (POD 5 and 12) in the latter term was conducted after approved by the institutional ethics committee of Kagawa University Hospital.

Procedures of local TA injection (POD5, 7) were as follows: A total of 40 mg of TA was locally injected into the post-ESD ulcer floor (every 2 mg TA was injected into the ulcer floor as evenly as possible) on POD 5 and 12 (Figure 1). The total injection dose of TA was determined to be 40 mg because it is one of the standard doses related to the prevention of esophageal steno-

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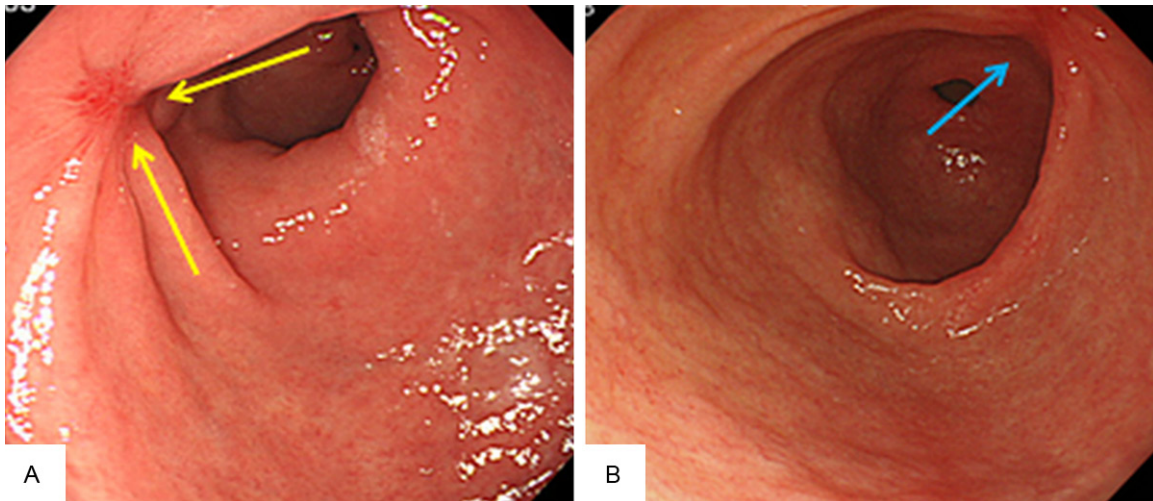


Figure 2. Artificial ulcer after endoscopic submucosal dissection (ESD). A: Artificial ulcer after ESD resection of 50% (1/2) of the circumference of the anterior wall of the antrum of the stomach. Artificial ulcer scar at 60 postoperative days without local TA injection revealed severe deformity (yellow arrow). B: Artificial ulcer after ESD resection of 50% (1/2) of the circumference of the posterior wall of the stomach to the antrum. It revealed post-ESD ulcer scar with less deformity at 60 postoperative days after local TA injection (blue arrow).

sis after complete circular resection with ESD. On POD 30, 60 and 90, follow up EGD was performed.

Statistical analysis

Data are presented as the mean \pm SD values. Patient baseline statistics were analyzed using the unpaired t-test or chi-squared test, when appropriate. The procedure time and the specimen size were analyzed using the unpaired t-test. The number of endoscopic passage, remaining residue, bloating and the number of patients requiring EBD were analyzed using chi-squared test. $P < 0.05$ was considered to be significant. The statistical analysis was performed using Graph Pad Prism version 5 for Windows (GraphPad Software, San Diego, CA).

Endoscopic devices

Endoscopes: Two GIF TYPE Q260J (OLYMPUS, Tokyo, Japan).

Incisional knife: Dual knife (KD-650L, OLYMPUS, Tokyo, Japan) and IT knife 2 (KD-611L, OLYMPUS, Tokyo, Japan).

Hemostatic forceps: Coagrasper (FD-410LR, OLYMPUS, Tokyo, Japan).

Incisional device: ERBE VIO300D (Elektromedizin, Tübingen, Germany).

CO₂ insufflation device: UCR (OLYMPUS, Tokyo, Japan).

Results

Among the 83 patients, an average age was 75.4 ± 6.22 years old (range, 65-82) in non-TA group, and 73.6 ± 10.59 years old (59-83) in TA group. There was no significant difference between non-TA and TA group ($P=0.579$). In gender and location, there was no significant difference between non-TA and TA group ($P=0.712$ and $P=0.813$). The procedure times of ESD were 73.2 ± 30.1 in non-TA group and 81.2 ± 34.0 in TA group. There was no significant difference ($P=0.472$). The specimen sizes were 62.8 ± 17.9 in non-TA group and 65.4 ± 15.5 in TA group. There was no significant difference ($P=0.528$) (**Table 1**). **Table 2** showed post ESD results of both groups. Among 83 patients, the number of 50-75% (1/2-3/4) of the circumference was 49 (23 cases in non-TA group, 26 cases in TA group), and over 75% (3/4) of the circumference in 34 cases (20 cases in non-TA group, 14 cases in TA group). In non-TA group, the circumference rate of gastric lumen was $63.4 \pm 12.6\%$ and in TA group, $68.5 \pm 12.3\%$. There was no significant difference between non-TA and TA group ($P=0.527$). In non-TA group, deformity of the stomach was evident in resections 50- 75% of the circumference (**Figure 2A**). However, as the local TA injections in

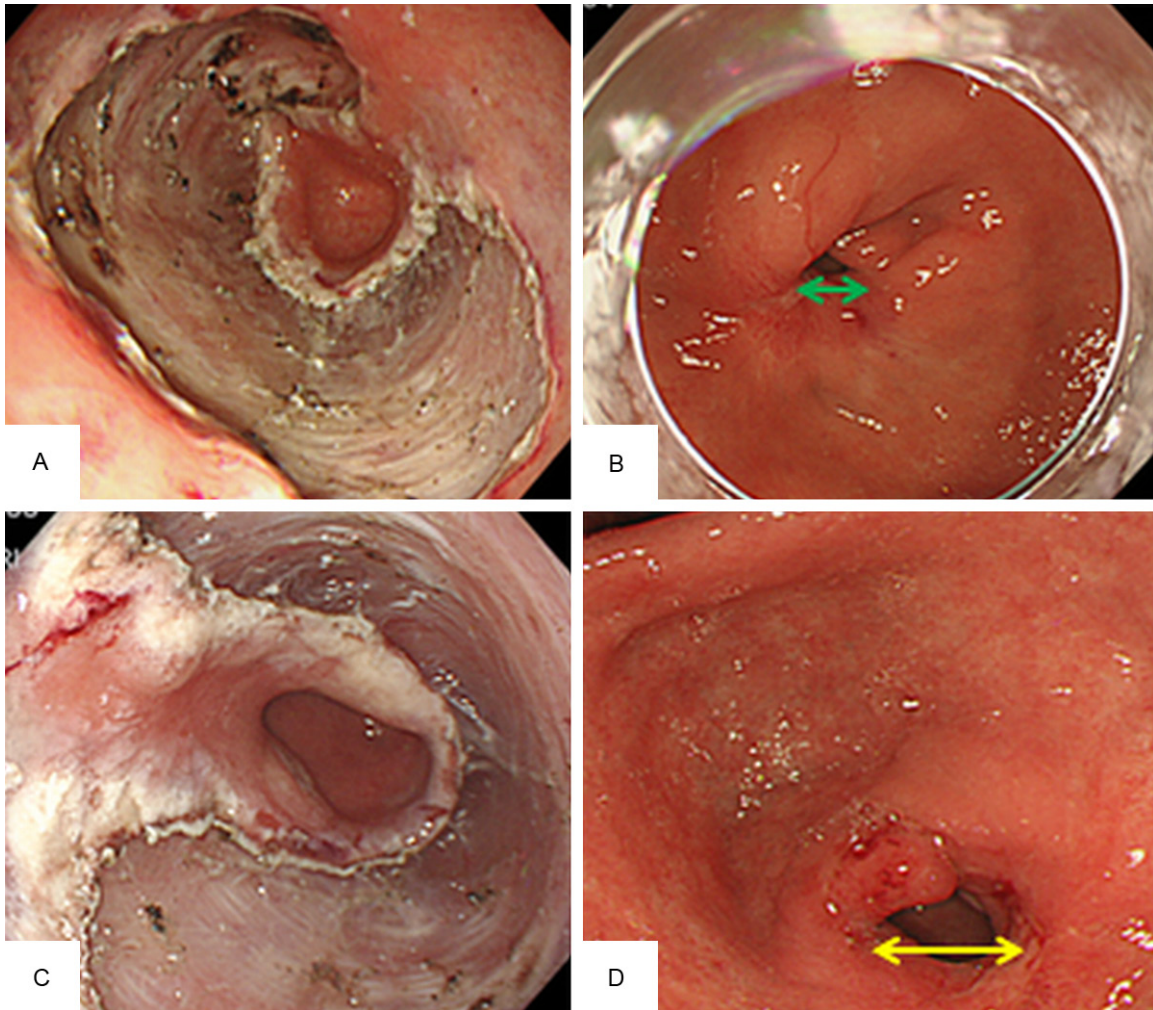


Figure 3. Stricture findings of both groups. A: Artificial ulcer after ESD resection of 75% (3/4) of the circumference of the antrum of the stomach. B: Pinhole stenosis at 60 postoperative days without local TA injection (green arrow). C: Artificial ulcer after ESD resection of 75% (3/4) of the circumference of the antrum of the stomach. D: Post-ESD ulcer scar with mild stricture at 60 postoperative days after local TA injection (yellow arrow). Endoscope was able to pass through the stricture.

the latter term were conducted, gastric deformities were slight in TA group (**Figure 2B**). Resections over 75% of the circumference led to stenosis that did not allow for passage of the endoscope at all in non-TA group on POD 30. In non-TA group, as patient number (over 75%) was 20 (M/L region 6/14), patient in L region developed more severe stenosis (**Figure 3A** and **3B**) (**Table 2**). Even though local TA injection was performed, 5 patients over 75% of the circumference had stenosis that did not allow for passage of the endoscope. In TA group, as patient number (over 75%) was 14 (M/L region 7/7), patient in L region (5 patients) developed more severe stenosis (**Figure 3C** and **3D**) (**Table 2**).

For 50-75% resection of the circumference, EBD was required for 4.8 ± 5.40 times in non-TA group, and 1.6 ± 2.34 times in TA injection group on POD 30 to POD 90, respectively. There was significant difference between non-TA and TA groups ($P=0.043$). For over 75% resection of the circumference, EBD was required 18.6 ± 3.62 times in non-TA group, 5.63 ± 2.86 times in TA injection group on POD 30 to POD 90, respectively. There was significant difference between non-TA and TA group ($P=0.003$).

We experienced only one severe complication related to the local TA injections. A 78-year-old woman underwent ESD for early-phase gastric cancer on the anterior wall of the antrum of the

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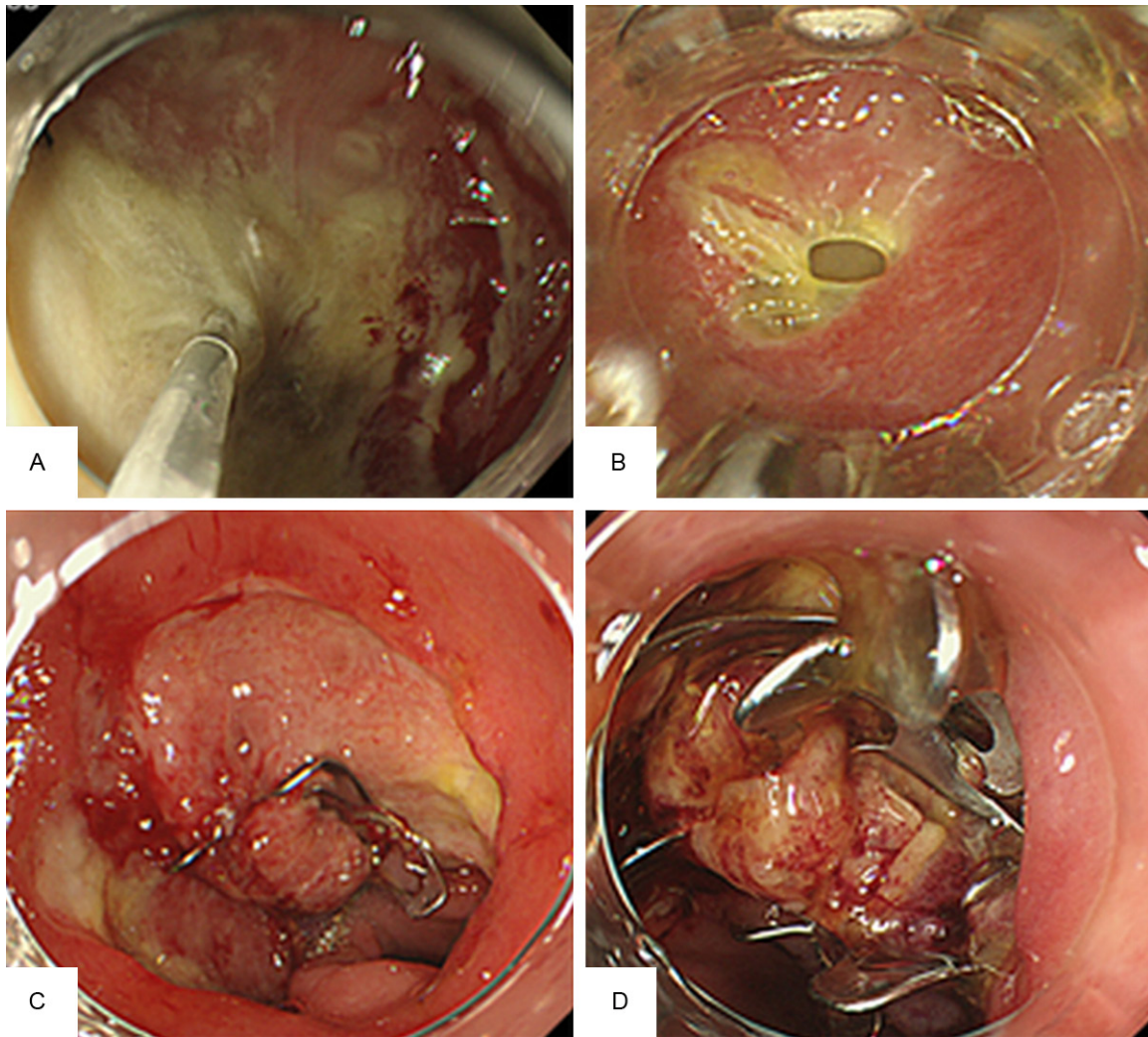


Figure 4. Complication of local TA injection. A: On postoperative day 5, TA was injected locally perpendicular to the muscle layer. B: On the second injection (on postoperative day 12), a 2-mm perforation was confirmed. C: The perforation was immediately closed with over-the-scope-clips (OTSCs) (12 mm in diameter; gc version; Ovesco Endoscopy GmbH, Tuebingen, Germany). D: The clip gripper separated further because the artificial ulcer floor had weakened after endoscopic submucosal dissection. Therefore, the perforation was closed with 4 OTSCs while filling greater omentum.

stomach. Since 75% of the circumference of the prepylorus was being resected, a local TA injection was initiated to prevent stenosis. On the POD 5 local TA injection (**Figure 4A**), the injection occurred perpendicular to the muscle layers. Although no abdominal symptoms were reported, a 2-mm perforation was confirmed during the local injection on POD 12 (**Figure 4B**). Over-the-scope clips (OTSCs) (12 mm in diameter; gc version; Ovesco Endoscopy GmbH, Tuebingen, Germany) were immediately used to close the perforation (**Figure 4C**); however, because the artificial ulcer floor is weak after ESD, the clip gripper slipped further. Therefore,

4 OTSCs were used to close the perforation while filling the greater omentum (**Figure 4D**). Computed tomography at the time confirmed free air and the 4 OTSCs at the suture site. Additional maintenance therapy reduced inflammation; after 7 days had passed, no leakage of a continuously administered water-soluble contrast agent (Gastrographin[®]) was observed on contrast images of the upper gastrointestinal tract. However, some delays of passage of the contrast agent were observed at the 4 OTSCs; therefore, to prevent future obstructions, distal gastrectomy and Billroth I method reconstructive surgery were performed.

Discussion

Local TA injections [9] and steroid administration [10] have been reported to prevent post-ESD stenosis for the treatment of early esophageal cancers in narrow-lumen organs such as the esophagus. Although these methods provide some level of prevention from stenosis, no method completely prevents stenosis. These reports suggest that appropriate combinations of local TA injection and steroid administration may provide maximal effects. On the other hand, stenosis occurs less frequently after gastric ESD because the luminal space is larger than that of the esophagus; however, larger lesions are being resected as the technique established, and post-ESD stenosis and passage obstruction for lesions exceeding a certain circumferential size has been confirmed. Our earlier reports demonstrated the preventative effects of local TA injection for post-gastric ESD deformities measured by 2 clips distances [11]. TA has anti-inflammatory effects and prevents keloid-like scarring. Local TA injections suppress the production of cytokines and prostaglandins which leads to the anti-inflammatory effects. TA assists the healing process to suppress inflammatory cell infiltration and fibrosis, and suppression of fibrosis enzyme of collagen [12]. Suppression of these enzymes reduces tissue collagen without fibrotic contractions and scars. Due to the fibrosis-suppressive effects of local TA injections, stenosis prevention and symptom improvement were possible with relatively fewer EBD treatments from POD 30 to 90 even in large ESD resections exceeding 75% of the circumference. In contrast, patients without undergoing TA injection showed pinhole-shaped stenosis requiring repeated EBDs, which in some cases resulted in resistance to EBD therapy and a remarkable declining in patient QOL. In this report, as we retrospectively compared two groups (non-TA injection and TA injection), and there was significant difference in the number of endoscopic passages and EBD especially over 75% (3/4) circumference resection of gastric lumen. Late-onset perforation due to local TA injection for early-phase esophageal cancer has been reported as a serious complication of local TA injections [13]; however, injections made into muscle caused local muscle cell necrosis, and we experienced similar late-onset perforation of the stomach. Therefore, local TA injections after ESD must be performed in the remaining

submucosal layer, and muscle injections must be avoided.

Limitations of this study include the retrospective design of this study and relatively short follow-up. Selection and observer bias may exist and should be considered when interpreting our findings. The follow-up endoscopies were performed after one month of the ESD, which was selected for the investigation on the short- to intermediate-term impact of ESD on gastric stenosis. Long-term data on the post-ESD stenosis and risk of spreading cancer would be interesting. Future prospective, long-term studies therefore are needed.

In conclusion, our methods of local injection of TA to post-ESD large artificial ulcer were innovative measurements to reduce severe stenosis. Local triamcinolone injections prevented both of further strictures and delay stricture. In technical aspect, as TA injections to muscular layer must be avoided to prevent muscle necrosis and perforation, we should have injected TA more carefully into remaining submucosal layer.

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Disclosure of conflict of interest

None.

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