

Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study

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Abstract

AIM: To evaluate clinical outcomes and risk factors for endoscopic perforation during endoscopic submucosal dissection (ESD) in a prospective study.

METHODS: We investigated the clinical outcomes and risk factors for the development of perforation in 98 consecutive gastric neoplasms undergoing ESD regarding. Demographic and clinical parameters including patient-, tumor-, and treatment-related factors, clinical parameters, and duration of hospital stay were analyzed for risk factors for perforation. In subgroup analysis, we also compared the clinical outcomes between perforation and "silent" free air without endoscopically visible perforation detected only by computed tomography.

RESULTS: Perforation was identified in 8.2% of patients. All patients were managed conservatively by the administration of antibiotics. The mean procedure time was significantly longer in patients with endoscopic perforation than in those without. According to the receiver-operating characteristic analysis, the resulting cutoff value of the procedure time for perforation was 115 min (87.5% sensitivity, 56.7% specificity). Prolonged procedure time (≥ 115 min) was associated with an increased risk of perforation (odds ratio 9.15; 95%CI: 1.08-77.54; $P = 0.04$). Following ESD, body temperature and C-reactive protein level were significantly higher in patients with perforation than in those without ($P = 0.02$), whereas there was no difference between these patient groups on the starting day of oral intake or of hospitalization. In subgroup analysis, the post-ESD clinical course was not different between endoscopic perforation and silent free air.

CONCLUSION: Only prolonged procedure time (≥ 115 min) was significantly associated with perforation. The clinical outcomes of perforation are favorable and are comparable to those of patients with or without silent free air.

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Key words: Gastric cancer; Endoscopic submucosal dissection; Perforation; Risk factors; Treatment outcome

Core tip: There has been little prospective study on the clinical outcomes of endoscopic perforation in endoscopic submucosal dissection for gastric neoplasia. In the current study, we investigated clinical outcomes of perforation during gastric endoscopic submucosal dissection, and analyzed various demographic and clinical parameters for risk factors. The results clearly demonstrated that prolonged procedure time (≥ 115 min),

but not tumor location, was significantly associated with endoscopic perforation. The clinical outcomes of perforation are favorable and comparable to those with or without silent free air without endoscopic perforation as detected only by computed tomography.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is indicated for early gastric cancer in Japan, and enables *en bloc* resection regardless of lesion size^[1,2]. Besides its positive outcomes, ESD carries controversial risks, such as perforation, bleeding, aspiration pneumonia, and technical difficulties^[1-6]. According to a recent meta-analysis, although ESD had higher *en bloc* and curative resection rates than endoscopic mucosal resection (EMR), operation time was longer, with higher risks of complications compared to EMR^[7].

Previous reports showed that large tumor size, location of the lesion in an upper region of the stomach, and long procedure time are risk factors for perforation following ESD^[8-13]. Although perforation may be the most serious complication in the ESD procedure, most studies have reported recovery from perforation with conservative management such as endoscopic clipping, fasting, nasogastric aspiration, and broad-spectrum antibiotics^[1,14]. However, the previous reports regarding clinical outcomes of perforation during ESD are retrospective analyses^[5,8,9,13-15]. More recently, prospective studies by Onogi *et al*^[16] and our group^[17] found that “transmural air leak” or “silent” free air without endoscopically visible perforation detected only by computed tomography (CT) did not affect the post-ESD clinical course. In contrast, there has been little prospective research regarding clinical outcomes of perforation during the ESD procedure. In this study, we prospectively evaluated clinical outcomes and factors of endoscopic perforation during ESD.

MATERIALS AND METHODS

Patients

Between November 2010 and January 2012, 94 consecutive patients with a total of 98 gastric adenomas or cancers treated with ESD were enrolled in this study. In patients with multiple gastric neoplasms, each of the lesions was treated separately at an interval of at least 1 mo. The indications for ESD for gastric neoplasms, such as intramucosal gastric cancer and adenoma, include in-

tramucosal differentiated tubular adenocarcinoma of any size without ulceration or signs of submucosal invasion and intramucosal differentiated-type adenocarcinoma of less than 3 cm with an ulcer scar. The histology, tumor location, and depth of invasion fulfilled the criteria of the Japanese Research Society for Gastric Cancer^[18]. The histological criteria for the ESD to be considered curative were as follows: (1) margins negative for a lesion; and (2) an intramucosal lesion or minute submucosal invasion (up to 500 μm invasion into the submucosal layer) without any venous or lymphatic invasion^[16].

All patients were admitted on the day before ESD, and were usually discharged 9 d after the procedure. Oral intake was started 3 d after ESD. The hospital stay for patients without any clinical complications was basically 10 d, in line with the clinical protocol at our hospital (Figure 1).

Written informed consent was obtained from all patients prior to the start of the study, and all patients provided written informed consent for publication of individual clinical details. The study design was approved by the ethics committee of Hyogo College of Medicine.

ESD procedure

The ESD procedure was performed under conscious sedation using midazolam and pethidine with or without propofol. ESD was performed using an insulation-tipped diathermic (IT-2) knife (KD-610L; Olympus Medical Systems, Tokyo, Japan) or FlushKnife BT (Fujifilm, Tokyo, Japan) for *en bloc* resection. We marked the normal mucosa about 5 mm outside the tumor edge with a needle knife (KD-1L-1; Olympus Medical Systems). Saline with adrenaline (1:10000 solution in saline) was injected into the submucosa, and the initial incision was made outside the marked line. Next, the diathermic knife was inserted into the initial incision, and the mucosa 5 mm outside the mark was cut circumferentially using a VIO electro-surgical generator (Erbe, Tübingen, Germany). After tumor resection, all visible vessels in the created ulcer were coagulated using coagulation forceps (Olympus Medical Systems) to reduce the risk of delayed bleeding, according to a report by Takizawa and colleagues^[5]. During the ESD procedure, carbon dioxide (CO₂) insufflation was used.

ESD complications

Endoscopic perforation was diagnosed by direct endoscopic observation of the extramural organ or fat through the muscle layer during ESD. When perforation occurred, the perforation site was immediately closed using endoclips (Olympus Medical Systems). However, endoclips sometimes make it difficult to obtain a sufficient resection margin or perform *en bloc* resection. In such cases, it is desirable to apply clips to perforated areas after an incision has been made or an exfoliation performed and after sufficient space for complete resection has been created. All patients with endoscopic perforation were administered antibiotics. In cases with severe pneumoperitoneum such as that caused respiratory failure, de-

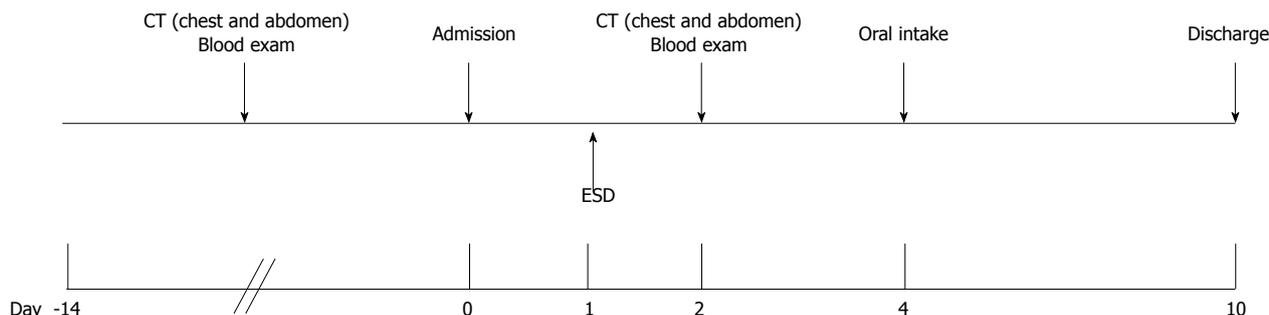


Figure 1 Clinical protocol of endoscopic submucosal dissection. ESD: Endoscopic submucosal dissection; CT: Computed tomography.

creased blood pressure or increased abdominal fullness, after which centesis was performed with an 18-gauge puncture needle to remove air from the abdominal cavity. Patients with this condition received a nasogastric tube for 1 to 2 d. In patients with perforation, oral intake was started once the white blood cell (WBC) count fell to the normal range.

Data analysis

We evaluated the following demographic and clinical parameters: patient-related factors (age, sex, use of alcohol and tobacco, and body mass index), tumor-related factors (macroscopic type, tumor location, presence or absence of scarring in the tumor, invasion depth, and histology), treatment-related factors (operator’s skill, mean dimension (cm²) of the resected specimen, and procedure time), clinical parameters (body temperature, WBC count, and serum C-reactive protein (CRP) level at one day before and after ESD), and duration of hospital stay. The procedure time was recorded from the start of the marking around the tumor to the removal of the endoscope.

The operator’s skill is thought to affect the total procedure time and the treatment complications of ESD, according to previous reports^[1-6]. Thus, differences in these outcomes between experienced and less-experienced endoscopists should be assessed. Japanese endoscopists receive board certification from the Japan Gastroenterological Endoscopy Society (JGES) after 5 years of training in a JGES-approved educational institution of endoscopy, and must also pass an examination administered by JGES. In the present study, the doctors who were defined as experienced endoscopists had board certification from the JGES and had each performed more than 30 ESD procedures for early gastric cancers^[5,19,20].

Statistical analysis

The data were assessed using the Mann-Whitney *U*-test for comparisons between two independent groups and the χ^2 test or Fisher’s exact test for comparisons between two proportions. Patient-, tumor-, and treatment-related factors were included as potential risk factors for endoscopic perforation in univariate analysis. Risk factors with a *P* value of < 0.05 in univariate analysis were included in the multiple logistic regression model and analyzed using the backward approach. Odds ratios (OR) and 95%CI

were calculated for risk factors. The 95%CI of the OR was used to assess statistical significance at the conventional level of 0.05. Statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, NC, United States).

To identify the ESD procedure time that was associated with the highest diagnostic performance in terms of perforation development, we used receiver operating characteristic (ROC) curve analysis. The ROC curve for procedure time was plotted by using SPSS 11.0 for Windows (SPSS, Chicago, IL, United States). The area under the ROC curve (AUC) was calculated. The point with the largest AUC was defined as the point having the greatest association with perforation. Optimal cutoff points were determined on the basis of maximum values of the Youden index, calculated as [sensitivity + specificity-1], and the minimum values of the square root of [(1 - sensitivity)² + (1 - specificity)²], which indicates the minimum distance from the upper left corner to the point on the ROC curve^[21].

RESULTS

A total of 98 gastric lesions in 94 patients were evaluated, including 6 adenomas and 92 gastric cancers. The mean age of the patients was 70.9 ± 9.1 years (range, 48-87 years), and women accounted for 24.5% (23 of 94) of the patients. The curative *en bloc* resection rate was 88.8% (87 of 98), and endoscopic perforation during ESD occurred in 8.2% (8 lesions).

Factors predicting development of endoscopic perforation

The mean procedure time was significantly longer in patients with perforation than in those without (controls) (*P* = 0.02), but the tumor location and lesion with scar were not associated with perforation (Table 1). Also, the perforation rate did not differ between experienced and less-experienced operators.

The association between endoscopic perforation and procedure time was evaluated using ROC curve analysis (Figure 2). According to this analysis, cutoff points showing optimal performance were chosen by the distance to the ROC curve and the Youden index for the procedure time. The resulting cutoff value of the procedure time

Table 1 Relationship between perforation and various factors

	Control (n = 90)	Perforation (n = 8)	P value
Patient-related factors			
Age (yr)	70.8 ± 9.2	72.4 ± 7.5	NS
Sex, male/female	69/21	6/2	NS
Active alcohol drinking	40/50	4/4	NS
Positive/negative			
Active smoking	16/74	2/6	NS
Positive/negative			
Body mass index (kg/m ²)	23.2 ± 2.9	23.0 ± 3.3	NS
Tumor-related factors			
Macroscopic type: I / II a/ II b/ II c	9/43/2/36	0/5/0/3	NS
Location: Upper/middle/lower	12/48/30	2/6/0	NS
Scar: Positive/negative	9/81	0/8	NS
Depth of invasion: M/SM and beyond	77/13	5/3	NS
Histology: DAC/poorly DAC/adenoma	5/6/1979	7/1/0	NS
Treatment-related factors			
Operator: Experienced/less-experienced	32/58	2/6	NS
Resected dimensions (cm ²)	9.7 ± 6.0	24.0 ± 24.9	NS
Procedure time (min)	122.5 ± 75.6	203.1 ± 114.3	0.02
Clinical parameters			
Body temperature	36.9 ± 0.5	37.3 ± 0.6	NS
White blood cell (/mL)	10566.9 ± 2903.6	9898.8 ± 3149.4	NS
C-reactive protein (mg/dL)	1.5 ± 1.4	2.4 ± 1.3	0.04
Hospital stay (d)	10.5 ± 2.4	10.9 ± 1.5	NS

Data are expressed as mean ± SD. M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; DAC: Differentiated-type adenocarcinoma; Poorly DAC: Poorly differentiated-type adenocarcinoma; NS: Not significant.

for perforation was 115 min (sensitivity, 87.5%; specificity, 56.7%) for patients who underwent gastric ESD.

Based on the ROC curve analysis and optimal cutoff points of the procedure time of gastric ESD determined above, a procedure time of ≥ 115 min was used in the analyses. We analyzed the strength of the association between perforation development and procedure time (≥ 115 min). As a result, procedure time (≥ 115 min) was significantly associated with increased endoscopic perforation (OR = 9.15, 95%CI: 1.08-77.54; P = 0.04).

Clinical course in patients with perforation

Following ESD, only the CRP level was significantly higher in patients with perforation than in those without (P = 0.04) (Table 1). The clinical courses of patients with perforation are summarized in Table 2. Four patients with endoscopic perforation received a nasogastric tube for a mean of 1.3 d. None of the patients with this condition required surgery, and there was no perforation-related mortality. Oral intake was started from a mean of 4.0 d after ESD (range, 3-7 d). Patients with perforation were discharged after a mean stay of 10.9 d (9.9 d after ESD); this did not differ significantly from the average stays of patients without perforation (Table 1).

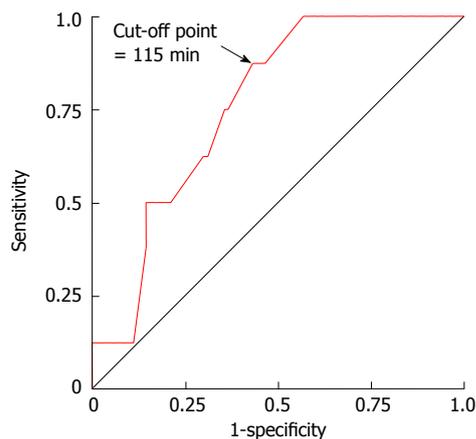


Figure 2 Receiver-operating characteristic curve of perforation development after endoscopic submucosal dissection. The curve is plotted with sensitivity (y-axis) and (1-specificity) (x-axis). The resulting cut-off value of the procedure time for perforation was 115 min (sensitivity, 87.5%; specificity, 56.7%).

Subgroup analysis: Comparison of clinical outcomes between patients with perforation and those with silent free air

All patients underwent plain abdominal CT on the day after ESD. If free air close to the stomach was detected by CT on the day after ESD even though no evidence of endoscopic perforation was seen during ESD and peritonitis, the case was defined as silent free air as reported previously^[17]. We compared the clinical outcomes between patients with perforation and silent free air.

Silent free air was observed in 35.7% (35 lesions) in this period. Body temperature and CRP levels following ESD were significantly higher in patients with endoscopic perforation than in those with silent free air (P = 0.04 and P = 0.03, respectively) (Table 3). Oral intake was started from 3 d after ESD in all patients with silent free air, as scheduled based on the clinical protocol (Figure 1), but no significant difference in the starting day of oral intake was found between these conditions.

DISCUSSION

Even though ESD is widely accepted and performed worldwide in patients with gastric cancer, perforation is a common and serious complication. In contrast, many retrospective studies show that conservative management by immediate endoscopic closure with endoclips is effective in most patients with perforation^[11,14]. Recently in prospective studies, Onogi *et al.*^[16] and we reported that an “air leak” after gastric ESD, detected only by CT in patients without endoscopically visible perforation, was observed frequently, and this asymptomatic (silent) free air does not affect the post-ESD clinical course. Likewise, the current work, which is based on our recent study^[17], clearly demonstrated that perforation was not associated with clinically significant complications, and showed clinical outcomes similar to those of cases without perfora-

Table 2 Clinical courses after perforation

Age (yr)	Sex	Macroscopic type	Location	Depth of invasion	Scar	Resected dimensions (cm ²)	Procedure time (min)	Nasogastric tube (d)	Beginning of oral intake after ESD (d)	Hospitalization (d)
62	Male	II a	Upper	M	-	69.1	460	1	4	10
63	Male	II c	Middle	M	-	5.5	130	-	3	10
77	Male	II b + II a	Middle	SM	-	18.8	220	1	3	11
71	Male	II a	Middle	M	-	8.2	160	2	3	10
83	Female	II c	Lower	SM	-	56.1	220	-	5	12
72	Female	II a	Middle	M	-	22.0	215	-	3	10
80	Male	II a	Upper	M	-	3.1	100	-	3	10
71	Male	II c	Lower	SM	-	9.4	120	1	7	14

Data are expressed as mean ± SD. M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; ESD: Endoscopic submucosal dissection.

Table 3 Subgroup analysis: Comparison in various factors between perforation and silent free air

	Perforation (n = 8)	Silent free air on CT (n = 35)	P value
Tumor-related factors			
Location: Upper/middle/lower	2/6/0	9/21/5	NS
Scar: Positive/negative	0/6	5/30	NS
Depth of invasion: M/SM and beyond	5/3	5/30	NS
Treatment-related factors			
Operator: Experienced/less-experienced	2/6	16/19	NS
Resected dimensions (cm ²)	24.0 ± 24.9	10.4 ± 7.2	NS
Procedure time (min)	203.1 ± 114.3	145.1 ± 76.5	NS
Clinical parameters			
Body temperature	37.3 ± 0.6	36.8 ± 0.6	0.04
White blood cell (/mm ³)	9898.8 ± 3149.4	10658.0 ± 3119.3	NS
C-reactive protein (mg/dL)	2.4 ± 1.3	1.4 ± 1.0	0.03
Oral intake (d)	3.0	4.0 ± 1.5	NS
Hospital stay (d)	10.9 ± 1.5	10.7 ± 2.1	NS

Data are expressed as mean ± SD. CT: Computed tomography; M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; NS: Not significant.

tion. Therefore, perforations might be considered part of the procedure and not as a complication^[22].

In the current study, a procedure time exceeding 115 min was considered to be a reliable marker associated with perforation development by ROC curve analysis. Thus, prolonged procedure time was a highly significant factor for endoscopic perforation; this finding is consistent with those of other studies^[9,11-13,16]. However, tumor location was not related to perforation. In our previous study^[17], tumor location was also not an independent risk factor for silent free air. Previous studies showed that tumor location (the upper portion of the stomach) was a significant and independent predictor of perforation by multivariate analysis^[8-13,16,17]. A possible explanation for the discrepancy may be the difference in the number of patients with perforation investigated between ours and other studies. Indeed, only 8 of the patients in our study had perforation. In reports from Japan and South Korea, perforation was observed in 1.2% to 6.1% of patients^[8-15]. Our perforation rate (8.2%) was slightly higher than in the other studies. Of the 8 cases with endoscopic

perforation, 6 were treated by less-experienced operators. However, operator skill was not associated with either perforation or silent free air (Tables 1 and 2). This was attributed to the fact that more experienced endoscopists were more likely to perform ESD in patients with larger tumors or tumors with scars than were less-experienced endoscopists. Actually, the features of the lesions, *i.e.*, ulcer scarring, tumor size, and tumor location, in addition to technical skill, may be significant risk factors for perforation, as many reports have pointed out.

Silent free air was detected in 35.7% of the cases in this study. Jeon *et al*^[14] recently reported a similar study, which compared the clinical outcomes of treatment for macro- and micro-perforations with ESD and determined the short-term prognosis after ESD. Those authors defined micro-perforation as a perforation identified by a pneumoperitoneum seen on plain radiographs after ESD. According to their report, a micro-perforation, resembling the silent free air in our study, was observed in only 0.76% (13 of 1711) of the patients undergoing gastric ESD, an extremely lower incidence than we found in our study. The difference may be attributable to different sensitivities between plain radiograph and CT.

With regards to inflammatory markers after ESD, such as body temperature, WBC level, and CRP level, only CRP level was significantly higher in perforation patients than in controls ($P = 0.04$). All the patients with endoscopic perforation were exposed to antibiotics, and 4 patients received a nasogastric tube. By conservative treatments, these patients with perforation were able to start oral intake from a mean of 4 d following ESD; this time to resume oral intake was not significantly different from that in patients with or without silent free air. Furthermore, the hospital stay did not differ according to the presence or absence of perforation or silent free air. These results indicate that immediate closure of the perforation site, intravenous antibiotic therapy, or brief nasogastric tube replacement may be important for favorable outcomes. In our clinical protocol of ESD, the hospital stay was 10 d, and oral intake was started 3 d after ESD; these may be slightly longer than in other hospitals. It remains possible, therefore, that this longer hospitalization in our protocol affected the present results.

In our series, we used CO₂ insufflation during the ESD procedure. It has been reported that ESD with CO₂

insufflation is safe and reduces both abdominal discomfort and the risk of perforation after ESD^[9,23,24]. Hereafter, ESD with CO₂ insufflation should be performed during lengthy endoscopic treatment procedures to avoid complications during and after ESD.

In the present study, there has been no evidence of peritoneal seeding after endoscopic perforation with short follow-up periods by CT or ultrasonography, and this was consistent with previous results^[10,14]. Similarly, Ikehara *et al*^[25] reported that perforation associated with EMR and ESD does not lead to peritoneal dissemination even in the long term (median 53.6 mo, range 7.0-136.6 mo). Further studies are needed before definitive conclusions can be drawn about the risk of peritoneal seeding after perforation or silent free air^[10].

The limitation of this study is the small number of patients with perforation in a single center, limiting our ability to draw conclusions, as mentioned previously^[8,9,13,14]. Our results do not necessarily mean, therefore, that perforation during ESD can be managed conservatively. Seewald *et al*^[22] previously showed an algorithm for endoscopic management of gastrointestinal perforation. Therefore further studies with larger numbers of patients will be needed to clarify the long-term outcomes of patients with endoscopic perforation.

In conclusion, the current prospective pilot study showed that prolonged procedure time (≥ 115 min) was associated with an increased risk of perforation. However, conservative management of perforation was successful and did not affect the post-ESD clinical course. Therefore, clinical outcomes of endoscopic perforation are favorable and comparable to those with or without silent free air.

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COMMENTS

Background

Endoscopic submucosal dissection (ESD) is indicated for early gastric cancer in Japan, and enables *en bloc* resection regardless of lesion size. Besides its positive outcomes, ESD carries controversial risks, such as perforation, bleeding, aspiration pneumonia, and technical difficulties.

Research frontiers

Even though ESD is widely accepted and performed worldwide in patients with gastric cancer, perforation is a common and serious complication. In contrast, many retrospective studies show that conservative management by immediate endoscopic closure with endoclips is effective in most patients with perforation.

Innovations and breakthroughs

There has been little prospective study on the clinical outcomes of endoscopic perforation in endoscopic submucosal dissection for gastric neoplasia. In the current study, authors investigated clinical outcomes of perforation during gastric endoscopic submucosal dissection, and analyzed various demographic and clinical parameters for risk factors.

Applications

The clinical outcomes of perforation are favorable and comparable to those with or without silent free air without endoscopic perforation as detected only by computed tomography.

Peer review

Generally, this is an interesting and well written prospective study about clinical outcomes and risk factors for perforation in gastric ESD. Authors prospectively investigated 98 consecutive gastric neoplasms undergoing ESD regarding the clinical outcomes and risk factors for development of perforation. They clearly showed that prolonged procedure time was associated with an increased risk of perforation.

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