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**Endoscopic trans-esophageal submucosal tunneling surgery: A new therapeutic approach for diseases around aorta ventralis**

Xiong Y *et al*. A new therapeutic approach for diseases around aorta ventralis

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# Abstract

***AIM***

To assess the efficiency of endoscopic trans-esophageal submucosal tunneling surgery (EESTS) technique around aorta ventralis.

***METHODS***

Nine pigs were assigned to EESTs. The procedures are as follows: First, a long esophageal submucosal tunnel was established. Second, full-thickness myotomy was created. Third, an endoscope was entered into abdominal cavity through muscle incision and the endoscope was around the aorta ventralis. Eventually, around the celiac artery ganglion neurolysis, partial hepatectomy and splenectomy, partial tissue resection in the area of posterior peritoneum, and endoscopic submucosal dissection (ESD) combined with lymph node dissection were performed. The animals were given antibiotics for 5 d and necropsied 7 d after surgery.

***RESULTS***

In all surgeries, one pig died from intraperitoneal hemorrhage after doing partial splenectomy, while the other pigs were alive after successfully operating other surgeries. (1) Surgery of celiac trunk ganglia damage: At necropsy, there is no exudation in the abdominal cavity. (2) Surgery of partial hepatectomy: The wound with partly healing was observed in the left hepatic lobe, and no bleeding and obvious exudation was seen. (3) Surgery of partial splenectomy: Massive hemorrhage was observed on the splenic wound surface. And the metal clips couldn’t stop bleeding. (4) Surgery of retroperitoneum regional organizations resection：Mild tissue adhesion was observed in one abdominal cavity. Another one suffered from severe infection complication. And (5) Surgery of ESD and lymph node dissection：A medium tissue adhesion was observed.

***CONCLUSION***

EESTS was a feasible and safe technique.

**Key words:** Endoscopic trans-esophageal submucosal tunneling surgery; Diseases around aorta ventralis; Endoscopic submucosal tunneling technique; Abdominal surgery; Animal model

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**Core tip:** Endoscopic trans-esophageal submucosal tunneling surgery (EESTS) technique is a new branch of endoscopic tunneling technology for diagnosing and treating of the diseases around aorta ventralis. The objective of our study is to simulate surgeries in a porcine model and to assess the efficiency of this new strategy. The surgeries included around the celiac artery ganglion neurolysis, partial hepatectomy and splenectomy, partial tissue resection in the area of posterior peritoneum, and endoscopic submucosal dissection combined with lymph node dissection. And we confirmed that EESTS was a feasible and safe technique.

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**INTRODUCTION**

Nowadays, surgical procedures are shifting paradigms in minimally invasive surgery, including natural orifice transluminal endoscopic surgery (NOTES)[1].NOTES is a technology of utilizing a flexible endoscope through a natural orifice (*e.g*., mouth, esophagus, gastric, rectum, vagina and urethra) to diagnose diseases and perform surgeries[2].The emergence of endoscopic tunnel technique makes the diseases which used to need surgical or laparoscopic surgical treatments entered into the endoscopic therapy[3]. There is a significant question in scholars’ mind why does endoscopic tunnel technique have such an appropriate curative effect and have some advantages (*e.g.*, fewer complications?) To answer this question, we can explain that the submucosal tunneling technique could well prevent the communication between the intra-luminal and the extra-luminal space by sealing the entry incision of the submucosal tunnel, gas or fluid within the lumen was prevented from entering the extra-luminal space, which could ensure the endoscopic therapy free of perforation[4,5]. In 2000, Kalloo *et al*[6] reported the first NOTES. They performed liver biopsy and examined the peritoneal cavity by using upper gastrointestinal endoscopy entered into the peritoneal cavity in a live swine model. In addition, they successfully confirmed the feasibility and safety of NOTES. In 2006, Rao *et al*[7] made the first attempt of transgastric NOTES in human. Subsequently, a number of scholars used NOTES to simulate a variety of intraperitoneal surgeries including cholecystectomy, colectomy, liver resection, and thyroidectomy in experimental animals[8-11]. A significant and hybrid model of NOTES was proposed for abdominal surgeries using transcutaneous rigid laparoscopes in combination with a flexible endoscope passed through a visceral incision[12,13]. Moreover, it was confirmed that NOTES had been less invasive, relatively safer, earlier rehabilitation, and more cost-effective than either traditional or laparoscopic surgery[14].

However, there are several technical challenges in the development of NOTES[14-16].First, it is difficult to close the entrance of natural orifices, which lack of economic and precise suture technique Second, the infection caused by liquid and air from natural orifices to the body cavity would unavoidably occur. Third, it would be lost in body cavity due to the insufficient localization and navigation. Forth, a flexible endoscope couldn’t create a stable operative platform in order to performs a very precise resection of tissues. Eventually, the loss of triangulation is a stubborn problem in either pure NOTES or laparoscopy. These challenges may puzzle endoscopists.

In this study, the authors attempted to put forward a new approach using endoscopic tunneling techniques to perform NOTES, which named endoscopic trans-esophageal submucosal tunneling surgery (EESTS). Additionally, some preliminary studies were performed in a porcine model. The proposed technique can resolve the problem of closing entrance and infection. The aim of this research is to perform some endoscopic surgeries in animals’ body cavity including beside celiac trunk ganglia damage, partial hepatectomy, partial splenectomy, resection of the retroperitoneal organs, endoscopic submucosal dissection (ESD), and lymph node dissection.

**MATERIALS AND METHODS**

***Animals***

Experiments were performed with the contribution of 5 males and 4 females’ porcine corpses at animal laboratory of Pinggu District Hospital (Beijing, China), and approved by the Ethics Committee of the Animal Facility of Chinese PLA General Hospital. All these animals were treated humanely and underwent a 3 d quarantine and acclimation period.

***Preoperative preparation***

All procedures were performed under general anesthesia, using the combination of chloramine hydrochloride (5 mg/kg) and Su Mian Xin II (0.1 mL/kg), as well as endotracheal intubation. All animals received antibiotic prophylaxis with a single dose of intravenous Penicillin (3.2 million units) at 24 h before operating surgery. The pigs were in supine and raised right shoulder positions. Furthermore, the basal body temperature was measured before surgery. All endoscopic instruments were sterile whereas EESTS equipment underwent a high-level disinfection with 25*%* glutaraldehyde solution (Instrunet, Laboratorios Inibsa, Spain).

***Performing EESTS***

These procedures were performed by an experienced endoscopist. A gastroscope (GIF-Q260J, Olympus Medical Systems, Corp., Tokyo, Japan) was inserted through the pig’s mouth which secured with a self-made overtube. The procedure maintained with CO2 insufflation through the endoscope. The vital signs of pigs were closely monitored during the operation.

A submucosal tunnel was made as follows: (1) Rinse repeatedly the esophagus and stomach cavity with saline, rinse with injecting 100 mL metronidazole and retain them for 15 min and then, remove the fluid; (2) the site of interest was the right posterior wall of the cardia and located by injecting 0.5 mL methylene blue (1:2); (3) 10 mL saline with methylene blue (1:10000) was injected to create a submucosal cushion in the right posterior wall at 5 cm above esophagogastric junction; (4) inverted T-shaped incision was created in the mucosal layer of the esophagus with an electric knife (KD-V451M, Olympus Medical Systems, Corp., Tokyo, Japan) and an electrosurgical unit (PSD-30, Olympus Medical Systems, Corp., Tokyo, Japan); (5) the endoscope was introduced into the submucosal space and gently separated the submucosa from the muscularis propria, creating a submucosal tunnel. Look for the dark blue localization spot in the cardia; (6) at the end of the tunnel, a progressive full-thickness incision was created through the muscularispropria with the needle-knife and the endoscope was entered into the abdominal cavity. Once the scope was moved into lesser omental sac, blunt dissection with an electric knife was used to advance the scope until the aorta ventralis was identified; (7) an artificial pneumoperitoneum was created and 20 mL needle was used to puncture exhaust to maintain relatively stable intra-abdominal pressure; and (8) after simulating the abdominal operation, the submucosal space was closed by applying clips at the mucosal entry site.

***Abdominal operation procedure***

**Surgery of celiac trunk ganglia damage:** At the end of the esophageal tunnel, the endoscope was inserted into the abdominal cavity from the posterior wall of gastric fundus near cardia. The aorta ventralis and its branches were observed in the endoscopic direct status. The abdominal ganglions were unable to find in healthy pigs. Thus, the surgery was simulated by partial removing tissues in the angle formed between the aorta ventralis and the coeliac trunk using thermal biopsy forceps and electric knife (Figure 1A and B)

**Surgery of partial hepatectomy:** The endoscope was inserted into the abdominal cavity. The left hepatic lobe was observed by twisting the body of the endoscope to the right (clockwise) or left (counter-clockwise) direction. Wedge resection of the liver tissues was carried out with an electric knife using a hybrid cutting mode (electro-coagulation was higher than that for cutting). Specimens were collected and stored for diagnostic pathology investigation. The wound was treated with conventional maneuvers (coagulation forceps, Olympus Medical Systems, Corp., Tokyo, Japan) as displayed in Figure 2A and B)

**Surgery of partial splenectomy:** The endoscope was inserted into the area around aorta ventralis. It was attempted to find the left hepatic lobe and then, explore spleen by upward turning the endoscope. Pig’s spleen is in banded shape and spleen tail was relatively unfixed and in free status in the abdominal cavity. Wedge resection of the spleen tissues was done with an electric knife using a hybrid cutting mode. Specimens were collected and stored for diagnostic pathology investigation. The wound was treated with conventional maneuvers (coagulation forceps), as shown in Figure 3A and B.

**Surgery of retroperitoneum regional organizations resection:** The endoscope was inserted into the area around aorta ventralis. The retroperitoneum was observed in the endoscopic direct status and the aorta ventralis was the predetermined structure for identification (Figure 4A and B). Tissues in the retroperitoneum were partially removed using an electric knife, avoiding thick blood vessels (Figure 4C and D). This aimed to simulate surgical removal of the retroperitoneal tumors. Omentum majus was observed when endoscope was reversed continually. Afterwards, some tissues of omentum majus were removed using endoloops (Olympus Medical Systems, Corp., Tokyo, Japan) (Figure 4E and F).

**Surgery of ESD and lymph node dissection:** The endoscope was inserted into the area around aorta ventralis. In the endoscopic direct status, gastric fundus and posterior wall of gastric body were observed. Blunt dissect of omental tissue outside the stomach wall was undertaken with an electric knife. Endoscope exits from esophageal mucosal tunnel and enters into gastric cavity. The simulation of ESD for early gastric carcinoma in posterior gastric body wall was undertaken. After completing submucosal dissection, 0.5 mL methylene blue (1:2) and saline mixtures were used as marker was injected to the intrinsic muscle layer surrounding the wound. The endoscope was inserted into the posterior wall of gastric fundus near cardia in abdominal cavity through the end of the esophageal tunnel. Find Methylene blue marker and then dissect lymph nodes outside the gastric wall. A full-thickness incision was created in the posterior part of gastric body and the opening was enlarged, which the metal clip couldn’t close it. Another endoscope was inserted into the abdominal cavity through this esophageal tunnel. Lateral wall of the perforation was pulled by the tongs from outside gastric wall for alignment and then, this perforation was closed by that endoscope inside gastric cavity using metal clips (Olympus Medical Systems, Corp., Tokyo, Japan).

**Postoperative care and necropsy:** All animals were fasted within 24 h after doing surgery. They were oral administrated glucose (1000 g/d) for 2 d and then, were given regular meals. All animals received intravenous Penicillin (3.2-million units/d) after conducting surgery and monitored for signs of abdominal infection and sepsis during the next 6 d. Necropsy was made for the evidence of ascites and signs of infection, injuries in other organs and tissue adhesion in surgery position. The surgical specimens were stained with HE for pathologic diagnosis.

**RESULTS**

In this study, nine animals weighing 28.5 ± 5.2 kg were examined. In addition, eight animals, in which the surgery was completed, were survived until they were euthanized on 7th day.

***Surgery of celiac trunk ganglia damage***

Two pigs were survived well after finishing the operation without these complications, for example the delayed air leak, severe infection and injuries of other organs. But both had the complication of mild tissue adhesion. The procedure time was 32 min and 28 min*.* The incision size was 5 mm. At necropsy, there is no exudation in the abdominal cavity. In addition, the lesser sac in posterior gastric wall was adhered to adjacent tissue (Figure 1C). The postoperative pathology showed that one was in partly healing and one is in minimal inflammatory reaction.

***Surgery of partial hepatectomy***

Two pigs were survived well after doing the operation without these complications of the delayed air leak and the injuries of other organs. But one had the complication of severe infection and medium tissue adhesion. One didn’t have the complication of severe infection, but had the complication of tissue adhesion. The procedure time was 47 min and 39 min*.* The incision size were 10 mm and 15 mm. At necropsy, the wound with partly healing was observed in the left hepatic lobe, and no bleeding and obvious exudation was seen in the abdominal cavity as well (Figure 2C). Furthermore, the lesser sac in posterior gastric wall was adhered to adjacent tissue. The liver tissue, which was excised by an electric knife, was further confirmed by a pathological examination as illustrated in Figure 2D. The postoperative pathology showed that both were in partly healing.

***Surgery of partial splenectomy***

One pig was dead after completing the operation without these complications of the delayed air leak and the injuries of other organs. But this pig had the complication of severe infection and severe tissue adhesion. The procedure time was 92 min*.* The incision size was 15 mm. During the procedure, partial splenectomy was made in spleen tail and massive hemorrhage was observed on the wound surface as well. The wound was repeatedly rinsed with norepinephrine saline (1:20000) and was treated with conventional maneuvers (coagulation forceps) without a proper effect. Then, metal clips were applied to clamp the splenic vessels, and bleeding significantly decreased. The splenic vessels could not be fully clamped, and limited by the small size of metal clips. Consequently, a small amount of bleeding was observed in the splenic wound (Figure 3A and B). After rapid recovery from the anesthesia in 3 h after doing the surgery, the animal’s state was extremely poor and it immediately received antibiotics fluid transfusion. On the second day, the pig died. At necropsy, massive bleeding was seen in abdominal cavity and diffuse blood oozing was observed in the splenic wound, as displayed in Figure 3C. The spleen tissue, which was excised by an electric knife, was further confirmed by a pathological examination (Figure 3D). The postoperative pathology showed that one pig was in intraperitoneal hemorrhage.

***Surgery of retroperitoneum regional organizations resection***

Two pigs were survived well after completing the operation without these complications of the delayed air leak and the injuries of other organs. But one had the complication of severe infection and medium tissue adhesion. One didn’t have the complication of severe infection, but had the complication of mild tissue adhesion. The procedure time were 42 min and 51 min*.* The incision size were 15 mm and 20 mm. At necropsy, mild tissue adhesion was observed between posterior gastric wall and retroperitoneal space in one of the pigs. Besides, another one suffered from severe infection complication. Because of amounts of chyme in stomach and longer operation time, chyme refluxed into the abdominal cavity through the entrance of esophageal tunnel. During this procedure, plenty of saline was used to flush the abdominal cavity without an appropriate effect. The pigs had fever up to 43.2℃. At necropsy, a severe tissue adhesion was observed between posterior gastric wall and retroperitoneal space. The omentum majus tissue, which was excised by an electric knife, was further confirmed by a pathological examination (Figure 4D). The postoperative pathology showed that one was in minimal inflammatory reaction and one is in complete healing.

***Surgery of ESD and lymph node dissection***

Two pigs were employed to simulate the ESD of early gastric carcinoma, and dissection of lymph nodes outside the gastric wall survived well (Figure 5). All animals were survived well after doing the operation without these complications of the delayed air leak and the injuries of other organs. But both had the complication of severe infection and medium tissue adhesion. The procedure time were 57 min and 66 min*.* The incision size of ESD were 25 mm and 20 mm. The incision size of lymph node dissection were both 5 mm. At necropsy, a medium tissue adhesion was observed in the abdominal cavity.

**DISCUSSION**

It is noteworthy that the area around aorta ventralis is difficult to reach in laparoscopic surgery, which made doing the operation to be difficult. However, the endoscope could easily approach to this area, which made it simple and convenient.

In a previous study was performed by authors, it confirmed some surgical techniques as follows: (1) Supine and raised right shoulder position were chosen as surgical positioning; (2) Methylene blue was injected to preoperative cardiac submucosa in the posterior wall as marker of piercing site; (3) An esophageal submucosal tunnel was established to cardia, as well as creating progressive full-thickness incision through the muscularis propria, and inserting the endoscope into the abdominal cavity. In this study, we inserted the endoscope into the area around aorta ventralis to simulate intraperitoneal surgeries, including celiac trunk ganglia damage, partial hepatectomy, partial splenectomy, resection of the regional organizations in the retroperitoneum, as well as ESD, and lymph node dissection.

In the surgery of celiac trunk ganglia damage, it was revealed that aorta ventralis could be identified as the predetermined structure in retroperitoneal space when endoscope was in the direct status. The abdominal ganglions were scarcely found in healthy pigs. Thus, a part of tissues around the aorta ventralis was removed using thermal biopsy forceps and an electric knife. All animals received accurate postoperative care and survived after doing surgery as well; consequently, the surgery was successful. However, finding and recognizing ganglions around the aorta ventralis was difficult. Thus, it necessitates that endoscopists should increase their knowledge about the anatomy of the abdomen and predetermined structure should be confirmed as well.

In the surgery of partial hepatectomy, the liver tissues with an electric knife using the hybrid cutting mode. No obvious bleeding occurred during the operation and all animals survived well after finishing surgery. The liver tissue was confirmed by a pathological examination. A massive liver resection couldn't be operated because of the restriction to the suitable endoscopic instruments and severe hemorrhage complications of the large vessels’ injuries. Thus, further studies should concentrate on the developments of endoscopic instruments and techniques as well.

In the surgery of partial splenectomy, that surgery was performed in spleen tail and massive hemorrhage was found on the wound surface, while massive bleeding was seen in abdominal cavity, and diffuse blood oozing was observed in the splenic wound. Several conventional maneuvers (coagulation forceps) were applied to stop bleeding, however, that failed. Then, metal clips were used to clamp the splenic vessels, while those metal clips couldn’t fully block the splenic blood supply, which limited to a specification for metal clips (5 mm of arm length and 135° of opening angle). A pig died on the second day after doing the operation. This can be justified as follows: (1) Because of the features of spleen with fragile tissue and rich in blood supply; (2) a traumatic spleen rupture requires emergency total splenectomy by surgeon. Moreover, it is necessary to suture the splenic artery and vein in order to stop bleeding during the operation. Hence, this surgery couldn't be properly undertaken by endoscopic technique.

In the surgery of retroperitoneum regional organizations resection, some tissues were removed in the retroperitoneal space. No obvious complications occurred during the operation, and all animals survived after completing the surgery in one swine model. However, one of the pigs suffered from severe infection, while that survived. Besides, omentum majus tissue was confirmed by a pathological examination.

Regarding developments of endoscopic technology and the improvement of cancer screening systems, the diagnostic rate of early gastric cancer (EGC) was remarkably increased. This led to the increase of survival rate of gastric cancer. Recently, ESD has been preferred in order to treat EGC with strict indications within shallow submucosal (SM1). In addition, the expanded indications within SM1 and deep submucosal (SM2), particularly accompanied with lymph node metastasis (LNM), have been a subject of debate among clinicians[17]. EGC invasion into SM3 is an absolute indication of surgery[17]. Additionally, patients with EGC and LNM should receive lymph node dissection. However, subtotal gastrectomy is difficult to be accepted by the patients because of greater trauma and poor quality of life after operation. Conversely, endoscopic physician couldn’t perform lymphadenectomy. Thus, a hybrid NOTES technique enables minimal surgical resection and would be a new alternative in EGC treatment. Hybrid NOTES utilizes the ESD technique for local excision of early carcinoma, which simultaneously combined with a laparoscopic lymphadenectomy in case of EGC with a risk of LNM[13,17]. Satisfactory results were reported in some studies[13,18]. Although laparoscopic surgery is minimally an invasive treatment, laparoscope is inserted into the abdominal cavity by cutting the abdominal wall.

In the surgery of ESD and lymph node dissection, two endoscopes were utilized instead of a laparoscopy to clear the lymph nodes around the stomach. Moreover, it was confirmed that this surgery is feasible. A new and simple method of perforation closure with two endoscopes was also proposed in the experiment. One endoscope with tongs was used to pull the lateral wall of the perforation from outside gastric wall for alignment, and another endoscope with metal clips was employed to close this perforation.

However, the indication of EESTS seems to be limited at the present time because it contains several limitations. First, tunnel and penetration site could not be created in the same place because of scar healing. Second, various degrees of tissue adhesion and abdominal infection were inevitable regardless of the application of antibiotics before and after operation. Third, a flexible endoscope easily gets lost in abdominal cavity. Sufficient localization and navigation of endoscope would be key points. Forth, instruments, which specially designed for NOTES treatments in the abdominal cavity, were not developed. Furthermore, in this study, an electric knife was used for ESD, thermal biopsy forceps and snare were utilized as well, which limited the operations. Therefore, only a small amount of tissues could be removed. Hemostasis is difficult, and the abdominal vessels could not be fully clipped.

In conclusion, EESTS by submucosal tunneling technique to simulate surgeries around aorta ventralis is a feasible, efficient, and relatively safe in a porcine model. However, the safety of profile has to be improved before adopting in a clinical setting. And developing the new endoscopic instruments suitable for the technique will be one of the future directions.

**ARTICLE HIGHLIGHTS**

***Research background***

Surgical procedures are shifting paradigms in minimally invasive surgery nowadays, including natural orifice transluminal endoscopic surgery (NOTES), which is a technology of utilizing a flexible endoscope through a natural orifice to diagnose diseases and perform surgeries.The emergence of endoscopic tunnel technique makes the diseases which used to need surgical or laparoscopic surgical treatments entered into the endoscopic therapy.

***Research motivation***

We attempted to put forward a new approach using endoscopic tunneling techniques to perform NOTES, which named endoscopic trans-esophageal submucosal tunneling surgery (EESTS).

***Research objectives***

To assess the efficiency of endoscopic trans-esophageal submucosal tunneling surgery technique around aorta ventralis.

***Research methods***

We simulate surgeries in porcine model and to assess the efficiency of this new strategy.

***Research results***

One pig died from intraperitoneal hemorrhage after doing partial splenectomy, while the other pigs were alive after successfully operating all surgeries.

***Research conclusions***

We confirmed that EESTS was feasible and safety.

***Research perspectives***

EESTS by submucosal tunneling technique to simulate surgeries around aorta ventralis is a feasible, efficient, and relatively safe in a porcine model at least. Developing the new endoscopic instruments suitable for the technique will be one of the future directions. However, the safety of profile has to be improved before adopting in a clinical setting.

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Grade E (Poor): 0

figure1

**Figure 1 Surgery of celiac trunk ganglia damage.** A: The aorta ventralis was observed in the endoscopic direct status and the aortic tissue was clamped by thermal biopsy forceps; B: The peritoneal tissue was partially removed by biopsy forceps for simulating ganglion destruction; C: Anatomic structure in posterior gastric wall. The white arrow shows the lesser omental sac, and the two yellow loops show tissue adhesion.

figure2

**Figure 2 Surgery of partial hepatectomy.** A and B: Partial hepatectomy using an electric knife; C: The wound in the left hepatic lobe; D: Hepatic tissue stained by HE (200 ×).

figure3

**Figure 3 Surgery of partial splenectomy.** A: Partial splenectomy using electric knife; B: Wedge resection of spleen and massive bleeding during operation; C: The wound in the spleen tail); D: Spleen tissue stained by HE (200 ×).

figure4

**Figure 4 Surgery of retroperitoneum regional organizations resection.** A: The aorta ventralis was observed in the endoscopic direct status; B: The retroperitoneal space was visible near the aorta ventralis; C and D: Partial resection of tissues in retroperitoneal space using an electric knife; E and F: Partial resection of omentum majus using endoloop; G: Omentum majus tissue stained by HE (200 ×); H: A lot of liquid and chyme in the abdominal cavity.

figure5

**Figure 5 Surgery of endoscopic submucosal dissection and lymph node dissection.** A-D: Simulation of ESD of early gastric carcinoma in pigs; E and F: Methylene blue marker injected to the intrinsic muscle layer surrounding the wound; G and H: Dissection of lymph nodes outside the gastric wall; G: Incision of serosa and muscularis propria; H: Separation of tissues outside gastric wall; I: A close large gastric perforation using two endoscopies. ESD: Endoscopic submucosal dissection.