Original Article Endoscopic interventional treatment for gastric schwannoma: a single-center experience

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Abstract: Background and aims: Endoscopic Interventional Treatment is of little trauma and less complications in the treatment of gastric schwannoma and leads to faster recovery and fewer days of hospitalization. This study was aimed to investigate the safety and efficacy of endoscopic interventional therapy for gastric schwannoma, including endoscopic submucosal excavation, non-laparoscopic-assisted endoscopic full-thickness resection, endoscopic tunneling submucosal resection, and so on. Methods: Six patients of gastric schwannoma diagnosed by pathology examination were retrospectively analyzed ranging from Oct 2011 to Feb 2014 at Shandong Provincial Hospital affiliated to Shandong University. Five of the six patients accepted endoscopic interventional therapy. Results: Among the five patients, there were four males and one female, aged from 48 to 65 years old (the average age was 58 ± 6.4). The lesions located at the fundus, the fundus-cardia, gastric body or gastric antrum, respectively, with the diameters ranged from 8 to 25 millimeter (the average was 17.1 ± 7.8 mm). All the patients were performed endoscopic interventional therapy successfully. Among five patients, one patient was treated by endoscopic tunneling submucosal resection, two by endoscopic submucosal excavation, and the other two were given endoscopic full-thickness resection. Operation duration was about 43 to 83 minutes (the average was 57.6 ± 16.1 minutes). The mass were completely removed, with limited bleeding. During the operation, perforation and pneumoperitoneum occurred in two patients, who finally recovered by endoscopic and conservative treatment. No bleeding, inflammation or infection occurred in these patients. The average follow-up time was (7.4 ± 4.4) months. Neither recurrence nor metastasis was found during follow-up. Conclusion: Endoscopic interventional therapy is a safe and effective treatment for gastric schwannoma.

Keywords: Gastric schwannoma, endoscopic submucosal dissection, endoscopic submucosal excavation, endoscopic full-thickness resection, endoscopic tunneling submucosal resection

Introduction

Neurinoma, mostly located at brain and spinal cord, is very common in clinic [1]. Neurinoma is also common in other large nerves in the limbs, neck and other parts. Gastric Neurinoma (GN), also known as schwann cell tumors, was first reported by the Pasquazzi in 1966 [2]. It is an uncommon gastrointestinal submucosa tumor. Till now, most of the studies on GN are case reports [3], lack of the imaging investigations. The diagnosis of GN is difficult before operation. Previously the mass was usually removed by surgery. With the developments of endoscopic equipment, instruments and minimally invasive endoscopic techniques, endoscopic submucosal excavation (ESE), endoscopic fullthickness resection (EFR) and submucosal tunelling endoscopic resection (STER), which are based on endoscopic submucosal dissection (ESD), are more and more widely used in clinical practices. Compared with traditional open surgery and laparoscopic surgery, the technologies above are of little trauma and less complications, leading to faster recovery and fewer days of hospitalization. The benign GN is more common than the malignant one, while the benign ones may mutate into malignant [4], hereby once diagnosed as GN, surgical resection should be performed as soon as possible.

In this study, we analyzed six cases of GN retrospectively, which were diagnosed GN by Endoscopic Ultrasonograpy (EUS) firstly and then confirmed by pathology examination in our hospital during the last two years. Among six

Case No.	Age	Gender	Mass diam- eter (mm)	Mass location	Surgery treatment	Surgery time (minutes)	Follow-up time (months)
1	61	male	9.5	Lesser curvature of the stomach body	EFR	62	3
2	48	male	8	Stomach fundus	EFR	43	3
3	56	male	25	Antral	ESE	55	13
4	65	male	23	Stomach fundus-cardia	STER	83	10
5	60	female	20	Stomach fundus	ESE	45	8
6	78	female	40	Lesser curvature of stomach body	Laparoscopic gastric wedge resection	-	_

 Table 1. Baseline characteristics of patients who are diagnosed gastric neurinoma by pathological examination

ESE: endoscopic submucosal excavation; EFR: endoscopic full-thickness resection; STER: submucosal tunelling endoscopic resection.

cases, one patient was given laparoscopic surgery due to the mass was too large to be removed by endoscopy; the other five cases were given routine endoscopic resection.

Material and methods

Patients

The clinical data of six patients who are diagnosed Gastric Neurinoma by pathology examination were collected from Mar 2009 to Dec 2012 in our hospital (**Table 1**). Among six patients, there were 4 males and 2 females, aged from 48 to 78 years old, mean age (61.3 \pm 9.9) years old. The main complains of six patients were upper abdominal discomfort. All of the six patients were given endoscopy examination, and five of them received endoscopic treatment.

The patients with larger mass were given conventional CT scan before operation to have a clear understanding of anatomy structures around the tumor, particularly pay attention to the arteries around the tumor and the tumor protruding into the cavity. Make it clear to the patients the treatments for such disease before surgery. Tell the patients the probable benefits and risks, including possible complications and appropriate treatment measures, as well as the alternative treatment options. All the patients were informed consent.

Methods

All the patients were performed endoscopy first to observe the tumor size, color, shape, texture, activity, relationship with the surrounding tissues, and so on. After that, endoscopic ultrasonography was performed to determine the origin of the tumor and then make an endoscopic ultrasonography diagnosis. The best treatment was chosen according to the location and size

of the lesion. As for the lesion located near the cardia, it is hard to find it, reverse endoscopic techniques are required for the treatment [5]. More closer the lesions near the cardia, more difficult to control the angle of the lens. The mass located in the muscularis propria has greater risk of perforation. Once the perforation occurs, the repair by the endoscopic intervention is almost impossible. Therefore such lesions should be removed by endoscopic tunneling submucosal resection. Typically endoscopic mucosal excavation (ESE) is used for the lesions which are originated from muscularis propria, while no laparoscopic-assisted endoscopic full-thickness resection is a good choice for the lesion originated from deep level without clear boundaries between the mass and the serosa. Of noted, the method could be switched from ESE to EFR during the operation due to the lesion originated from a deeper level.

Materials

All procedures were performed with patients under general anesthesia in the operating room. Intravenous antibiotics were used to prevent infection half an hour before surgery. Second-generation cephalosporin was the first choice. If the patient was allergic to cephalosporins, nitroimidazole, such as tinidazole, can be applied two hours before surgery. A second dose of antibiotics was not necessary unless complications occurred. The operation was performed using a single-channel endoscope (GIF-Q260J, Olympus) and/or a dual-channel endoscope (GIF-2TQ260M, Olympus). Other equipment and accessories included VIO 200s high frequency electric cutting device (ERBE), APC 300 Argon plasma coagulation (ERBE), an endoscopic carbon dioxide regulation unit (Chongqing Jinshan Science and Technology Co., Ltd. JSQB-PI), an endoscopic flushing (Olympus), a transparent cap (NM-200L-0521,

Olympus), an injection needle (SD-230U-20, Olympus), a hook knife (KD-620LR, Olympus), a dual Knife (KD-650L, Olympus), an insulatedtip knife (KD-611L, IT2, Olympus), a flush Knife (DK2618JB-20, Fuji Company), Double helix snare (HX-610-135L, Olympus), hemostatic clips (HX-600-135, Olympus), a hot biopsy forceps (FD-410LR, Olympus).

The procedures of STER

(1) Mark the location of the tumor accurately: In order to avoid losing the target while creating a submucosal tunnel, the lesion was first marked by using argon. The markers should not be too deep to avoid damaging the integrity of the mucous layer.

(2) Establish submucosal tunnel: before establishing the tunnel, rinsing the esophageal mucosa by using normal saline to ensure the tunnel clean and free of dirt. A fluid cushion was then made by injecting several milliliters of submucosal injection solution (100 ml saline +2 ml methylene blue +1 ml epinephrine) 5 cm proximal to the submucosal tumor. An inverted T or transverse incision mucosal incision was made with a 650 knife. Fuji flush Knife or hook knife at the esophageal mucosa as the entry point [6]. A submucosal tunnel to the lesion was created with an insulated-tip knife between the submucosal and muscular layers. A little closer to the muscle tissue when separation the submucosal tunnel to avoid damaging the mucous layer and reduce bleeding. Avoid damaging the mucosal surface when establishing the tunnel in order to maintain the integrity of the tunnel.

(3) Resection of tumor: Endoscopic resection of the tumor was performed by ESD skills, with an insulated-tip knife or hook knife, hybrid knife. Complete resection of the lesion without interruption of the lesion capsule is very important. During the endoscopic resection, submucosal injection solution was injected into the surrounding tissue before making a circular excavation around the lesion which helped differentiate the muscularis propria layer from the tumor mass, and facilitated excavation of the tumor from the muscularis propria (MP) layer. A dual-channel electronic gastroscope was used when the lesion was tightly connected to the underlying MP or serosal layer. In these cases, the lesion, including its underlying muscularis propria layer and serosa was resected with an insulated-tip knife or snare.

(4) Closure of mucosal entry site: The full MP layer defect and submucosal tunnel were observed for any remnant tumor and bleeding. After hemostasis with argon plasma coagulation or hot biopsy forceps in the tunnel, the electronic gastroscope was withdrawn through the natural orifice. Most commonly, the mucosal incision site was closed with 4 to 6 hemostatic clips.

The procedures of ESE

The methods of ESE and EFR are both derived from the method of endoscopic submucosal dissection (ESD). They are applicable to remove the gastrointestinal lesions from the muscular propria. If the lesions can't be separated from the serosal adhesions, we can choose EFR for resection.

(1) Mark the location of the lesion: Use argon or coagulation to mark both the oral and anal end of targeted lesion. For the smaller lesions, we can mark the circumferential of the lesions and mark the most obvious place, namely the center of the lesion. We can find the lesions relatively easy, even the mucosa and tumor are upraised after injection.

(2) Submucosal injection: Submucosal injection of mixed solution of saline, indigo carmine, and epinephrine were performed. Make the lesions upraised in order to lift the covering mucosal and submucosal layer seperate from the lesion. If the tumor is small, the situation that the mucosa and tumor relatively offset may occur after injection. In this case, we can perform fenstration to reveal the tumor by using 650 knife, Fuji flush Knife or hook knife before the injection.

(3) Reveal the lesion: the covering mucosa was incised longitudinally using 650 knife, Fuji flush Knife or hook knife to cut the mucosa above the tumor along the marker. Separate the submucosa to reveal the tumor by the skill of ESD. The lesion was gradually exposed by meticulous dissection of submucosal tissue and smooth muscle around the tumor capsule. Then peel the lesion along the tumor by using IT2 or Hook knife. During this procedure repeated submucosa injection is very important, if the tumor can't separate from the surrounding tissue. The submucosa tissue show blue color, the muscle tissue show muscle bundle, while the tumor lumps without any staining after injection. Keep a little distance from the tumor when cutting to avoid damaging the tumor or the tumor capsule.

(4) Peeling lesions: cut the submucosa, after exposing the inherent muscular lesion, stripping the lesion edge to avoid damaging the tumor or the tumor capsule. If necessary, give repeatedly submucosal injection while in the stripping process. After separating most of the tumor, the snare can be put in the root of the lesion and trap the transurethral resection of the lesion completely.

(5) Wound treatment: After complete resection and retrieval of the lesion, electric heating forceps was adopted for hemostasis during operation. The small blood vessels also can be burned by argon. If the injury is serious after the removal of the muscle, the mucosal incision was closed by clips to avoid wound bleeding or perforation after operation.

The procedures of EFR

(1) Mark the lesion and separation: EFR procedures began by two cautery markings at both the oral and anal end of targeted lesion. The covering mucosa was incised longitudinally after injection. Then the lesion was gradually exposed by meticulous dissection of submucosal tissue and smooth muscle around the tumor capsule. Separation the tumor from muscularis propria to serosa by using ESD skills, pay attention to maintaining the integrity of the tumor capsule.

(2) Removal of the lesion: Removal the tumor completely along the edge of tumors using Hook knife, IT2 knife or snare. A dual-channel gastroscope was used when the tumor can't be directly stripped due to the location of the lesion. Put forceps into clamp road, grasping the tumor in the gastric cavity to expose the separating space. And put snare or insulatedtip knife into another clamp road for separating until the lesion was completely resected from the stomach.

(3) Wound management and closure: after retrieval of the lesion, electric heating forceps was used for hemostasis or small vascular,

coagulating and cleaning wounds. The simple application of titanium clip to complete wound closure operation after tumor resection is easy if we preserve the excess mucous membranes before separation. The application of titanium clip may be difficult to grip the both sides of the wound mucosa if the lesion is large. In this case, we may perform hit two titanium clips beneath the wound, and then apply a nylon rope lashings titanium clip. After the nylon rope tightened and both sides of the mucosa gather together, then re-apply the titanium clip wound closure is relatively simpler. A dual-channel gastroscope can also be used in which a biopsy channel into the nylon rope inside, another one into the titanium clip releaser. Put titanium clip on the nylon rope clamp the mucosal of wound. After tightening nylon rope, the wound will gather together completely.

(4) Indwelling stomach tube and gastrointestinal decompression: According to patients whether have abdominal pain, bloating, fever, and so on; we decide when to stop gastrointestinal pressure. Under normal condition, EFR operating on gastric submucosal tumor should be routinely indwelling gastrointestinal decompression for 48 hours after surgery.

Histology and immunohistochemistry

The resection specimens were sent for pathological examination after surgery. For the tissue sources which were not confirmed plus immunohistochemical staining, (including S100 protein, CD34, CD117, Dog-1, vimention, SMA, desmin, Ki67, etc). The patients were observed for 48 hours, treated with proton pump inhibitor and parenteral nutrition support. Antibiotics were continue given to the patients for 48 hours after EFR, we may prolong fasting time according to the appropriate surgical time.

Postoperative follow-up

We suggested the patients to reexamination endoscopy 3, 6 and 12 months after surgery, and review endoscopy once a year to observe the wound healing and to observe whether there is residual or recurrent.

Results

Endoscopy findings

Among five patients being performed endoscopic therapy, four cases had submucosal

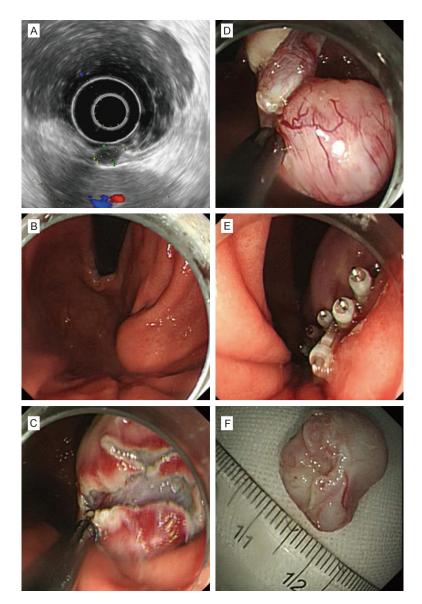


Figure 1. A: An oval hypoechoic mass originated in the stomach muscularis propria by EUS. The edge of the tumor was clear with hypoechoic halo ring. B: Submucosal bump at the fundus. C: The tumor was revealed after the mucosa and submucosa had been cut. D: Peel the tumor. E: Seal the wound with titanium clip. F: The tumor.

bump with hemispherical or oval appearance, while one case shown irregular lobulated. All the mass had smooth mucosa, without ulcers or bleedings. One lesion was at the fundus near cardiac, one at the antrum, one at the gastric body, and two at the fundus. The diameters of the lesions ranging from 2.5 mm to 8 mm by EUS examination. In four cases, the masses originated from the stomach muscularis propria, shown as round or oval hypoechoic appearance, with clear boundary and hypoechoic halo ring (**Figure 1A**). The mass of the remaining one case, also originating from the stomach muscularis propria, had cystic change inside, with unclear boundary and uniform echoes in EUS examination.

Endoscopic treatment outcomes

All the five patients were performed endoscopic interventional therapy successfully. Operation time last about 43 to 83 minutes (the average was 57.6 ± 16.1 minutes). Endoscopic submucosal excavations were used for two cases with the lesions at gastric body. Two patients were performed endoscopic fullthickness resection since the mass grew towards the outside direction and also had close relationship with the serosa (Figure 2). One mass locating at fundus-cardia was removed by endoscopic tunneling submucosal resection (Figure 3).

All the wounds were closed with titanium clips successfully. The lesions located at the lesser curvature of the gastric body need more titanium clips due to the initiative perforation. All the lesions were removed completely, with less bleeding. Pneumoperitoneum occurred in the patients with EFR treatment. However, intraperitoneal gas

could be gradually absorbed after closing the wound completely, and finally disappeared until the patient was fully awake after anesthesia.

Postoperative status and follow-up

No late bleeding, inflammation or infection occurred after the operation. The wound healed well at the third-month, the sixth-month, and the one-year follow ups. The average follow-up time was (7.4 ± 4.4) months. No recurrence or metastasis was found during follow-up.

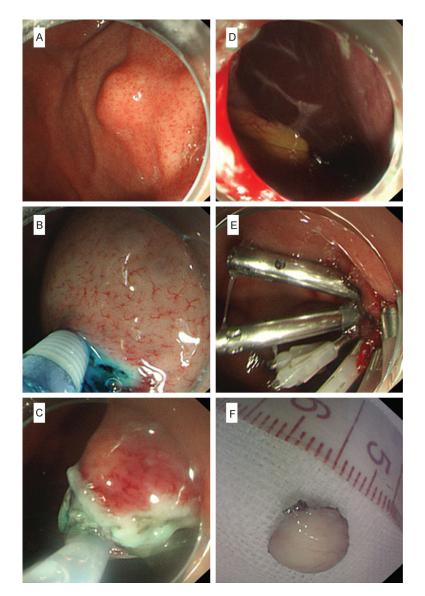


Figure 2. A: Submucosal bump at the gastric fundus. B: Cut the mucosa at the top of the tumor. C: Continue separating the tumor. D: After the tumor removed, the abdominal internal organs (spleen) can be seen due to the perforations. E: Close the wound by titanium clips. F: The tumor.

Pathological results

Gastric schwannoma is mainly composed of spindle cells, which arranged in palisade. Cytoplasm addicted to light red with HE staining, while nucleus may have some atypia with rare mitotic figure. Peripheral lymphocytes and the formation of germinal center has some specificity, interstitial vessels are abundant, scattered lymphocytes. Through immunohistochemistry straining, the tumor has positive expressions of S-100 and GFAP, and negative expressions of CD117, CD34, Dog-1, smooth muscle actin (SMA) and desmin. Therefore, all the patients above were not gastrointestinal stromal tumor patients. Immunoreactivity for Ki-67 was seen focally in all but one case (**Figure 4**).

Discussion

Since Gastric Neurinoma originates from the parietal plexus Schwann cells, it is also called Schwann cell tumors [2]. As a gastrointestinal submucosal lesion, Gastric Neurinoma mainly consists of the nerve ectoderm schwann cells and mesoderm nerve intimal, belong to gastrointestinal mesenchymal tumors [7-9]. It mainly occurs at the neck, limbs, spine and other large neural stem. Gastric Neurinoma rarely occurs in the digestive tract, accounting for only 0.2 percent of gastrointestinal tumors [9-11]. Gastric Neurinoma mainly occurs at the gastric body, followed by gastric antrum and the gastric fundus [7, 8, 18]. The tumors grow slowly and most of them result in no specific clinical symptoms [12]. Abdominal pain, hematemesis [13, 14], melena and other symptoms may appear with the gradual growth of the tumor. As most of the lesions located at the submucosa, the surface of the tumor covered with normal gastrointestinal mucosa, hereby, both Gastric Neurinoma,

gastrointestinal stromal tumor, leiomyosarcoma and other submuscosal tumors are showed bumps in the white endoscopy, resulting in little significance for the endoscopic biopsies [15, 16]. Gastric stromal tumor and leiomyoma are the most common types of gastric submucosal tumors [17, 18]. Gastric stromal tumors originate from Cajal cells, having the possibility of malignant potential [19] and it significantly correlated with the diameter of the tumor [20]. The typical appearance of Gastric Neurinoma under EUS is round or oval hypoechoic homogeneous mass originating from the muscularis propria [21, 22], while its echo is slightly higher com-

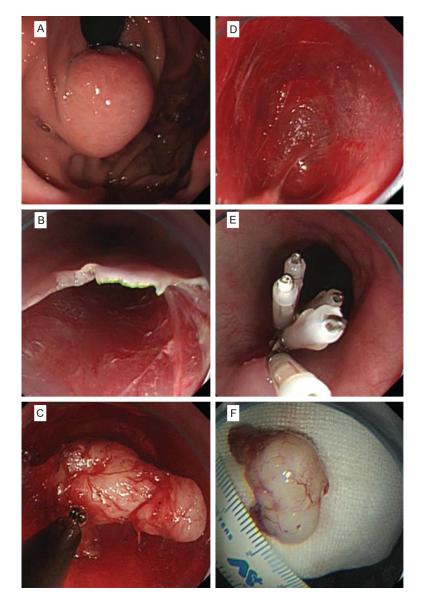


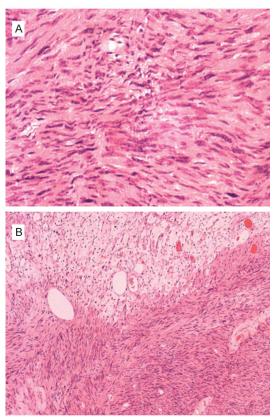
Figure 3. A: Submucosal bump at the fundus-cardia of the stomach. B: The opening tunnel. C: Separating the tumor in the tunnel. D: The tunnel cavity after removing the tumor. E: Close the wound by titanium clips. F: The tumor.

pared with those of other benign and malignant gastrointestinal stromal tumors. Furthermore, the classic Gastric Neurinoma often has regular edge with halo, growing without infiltration. Leaf, cysts or calcification are less common in Gastric Neurinoma. On the contrary, benign gastrointestinal stromal tumors generally have no halo, while cysts are common [7, 16, 21, 23]. The appearances of Gastric Neurinoma and muscle-derived, neurogenic tumors are very similar on CT, MRI and other imaging investigations, resulting in the difficulties in the identification. The diagnosis of Gastric Neurinoma

relies on pathology. The differential diagnosis of gastric tumor is very difficult [20, 24]. Gastric Neurinoma is one of the relatively rare benign mesenchymal tumors of the stomach. With immunohistochemistry, Gastric Neurinoma has positive expressions of S-100 and GFAP, and negative expressions of CD117, CD34, SMA, Dog-1, Desmin which are characteristic maker of gastrointestinal stromal tumor. The important pathological features of Gastric Neurinoma are S-100 (++), CD117 (-), CD34 (-) and Dog-1 (-) [4, 7, 18, 25]. In this study, one case of the tumor at the fundus-cardia was diagnosed as gastric neuroendocrine tumor before surgery. One case of the tumor located at the gastric antrum was diagnosed as gastric leiomyoma. One case at the gastric fundus and one case at the gastric body were diagnosed as gastric stromal tumor. Only two cases were diagnosed as Gastric Neurinoma by EUS before the surgery.

As for gastric schwannoma, benign lesions are more common than malignant ones, while the benign ones may turn malignant according to the lesion growth, intraoperative conditions and postoper-

ative follow-ups. Hereby, the gastric schwannoma should be removed as soon as possible, which not only contributes to obtain a complete sample for pathology and guide further treatment, but also relieves mental stress of patients to the greater degree. With the developments of endoscopic equipments, instruments, and minimally invasive endoscopic techniques, ESMR, ESE, EFR, STER are widely applied in clinic. Most of gastric submucosal cancers can be resected with these technologies above, due to simplicity, less invasion, less cost and faster recovery [5, 19, 26, 27]. $400 \times$



 $100 \times$

Figure 4. A: Schwannoma cells are fusiform, arranged in fence-like, swirling (×400 magnification microscope). B: Visible Antoni A area and Antoni B area, rare verocay bodies (×100 magnification microscope).

Gastric schwannoma mainly occurs in the gastric body, followed by gastric antrum and fundus [7, 8]. Except for the lesions at fundus-cardia, ESE and EFR can be applied to resect the lesions in the stomach without severe complications during the operation and postoperation [28, 29]. The difference between ESE and EFR is that active perforation is made during EFR to remove the lesion involving serous layer. Therefore, during the procedure of EFR, it is very important to completely suction the residual liquids in the stomach before cutting out the lesion. What's more, the specimen should be promptly removed to avoid falling into peritoneal cavity which may lead to tumor metastasis. Both the tumor and the envelope should be kept intact carefully during the procedure. Blind operation should be avoided when the perforation occurs during EFR. As the perforation

occurs, the surgeon should keep calm, even more carefully separate the tumor, stop the bleeding thoroughly after the tumor removed, and finally completely close the wound. After the operation, the patient was required fasting for a few days, given proton pump inhibitor, parenteral nutrition, and decompression treatment. None of the five patients have postoperative gastrointestinal bleeding or peritoneal infection. During the treatment of the lesions located at fundus - cardia, reverse endoscopic technique is typically applied [30]. The lesion locate in the muscularis propria, it is difficult to control the angle of the lens. Risks of perforation in the muscularis propria is great, once the perforation occurs, the repair the wound by the endoscopic method would be very difficult. So we treat those lesions by using endoscopic tunneling submucosal resection. Endoscopic surgery in this position has been considered forbidden [31]. Innovation of STER is to use the tunnel space between gastrointestinal mucosa and muscularis propria to resect the tumor completely, as well as maximize the retention of gastrointestinal mucosa, and thus remarkably reduce the incidence of gastrointestinal fistula [32, 33]. For the Gastric Neurinoma at the fundus-cardia, submucosal tunnel was established 5 cm from the straight-line distance near the port side of the tumor. After the removal of the tumor, the tunnel opening would be closed and hereby the digestive tract could be kept impact. Without gas or digestive liquids flowing into the abdominal cavity, no complications of abdominal infection occurred. The patients could be discharged 3-5 days after operation. No recurrence or metastasis was found during follow-up by clinical or telephone follow-up. Based on endoscopic mucosal dissection, Endoscopic interventional therapies, including endoscopic mucosal excavation, no laparoscopic-assisted endoscopic full-thickness resection, endoscopic tunneling submucosal resection, are safe and effective treatments for gastric schwannoma. Notably, full-thickness excision is typically applied to the mass involving the deeper level, and the integrity of the tumor and the envelope thus should be paid much attention to avoid part of the tumor falling into peritoneal cavity.

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Disclosure of conflict of interest

None.

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