

Endoscopic mucosal resection/endoscopic submucosal dissection for gastric heterotopic pancreas

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Background/aims: To study the features of gastric heterotopic pancreas and to evaluate the feasibility, efficacy, and safety of endoscopic resection for treatment of this condition. **Materials and Methods:** Between August 2007 and December 2010, 60 gastric heterotopic pancreas patients were treated using endoscopic mucosal resection/endoscopic submucosal dissection. The definitive histological diagnosis of heterotopic pancreas was made after the endoscopic treatment. Tumor size, site, layer, complete resection rate, complications, and local recurrence rate were evaluated. **Results:** The mean tumor diameter was 1.4 ± 0.1 (0.4–3.5) cm in the 60 gastric heterotopic pancreas patients during this period. Fourteen cases (23.3%, 14/60) underwent endoscopic mucosal resection, and the en bloc resection rate was 64.3% (9/14). In 3 cases (21.4%, 3/14), arterial bleeding was controlled with hot biopsy forceps or a metal clip during endoscopic mucosal resection. Forty six cases (76.7%, 46/60) underwent endoscopic submucosal dissection procedure, and the en bloc resection rate was 97.8% (45/46). In 6/45 cases (13.3%), arterial bleeding occurred. Pneumoperitoneum developed in 3 cases (6.5%, 3/46) during the operation. The curative resection rate was 98.3% (59/60). There were no recurrences in any cases. **Conclusion:** Endoscopic mucosal resection/endoscopic submucosal dissection is a minimally-invasive technique that allows resection of whole lesions and provides precise histological information, which is particularly suitable for gastric heterotopic pancreas.

Key words: Heterotopic pancreas, gastric, endoscopic resection, endoscopic mucosal resection, endoscopic submucosal dissection

Gastrik heterotropik pankreas olgularında endoskopik mukozal rezeksyon/endoskopik submukozal diseksiyon

Giriş ve Amaç: Bu çalışmada heterotropik pankreas konusu ve bu durumun tedavisinde endoskopik rezeksyon uygulamasının fizibilitesi, etkinliği ve güvenilirliği incelenmiştir. **Gereç ve Yöntem:** Ağustos 2007 ile Aralık 2010 tarihleri arasında, 60 gastrik heterotropik pankreas; hastalarda endoskopik mukozal rezeksyon/endoskopik submukozal diseksiyon kullanılarak tedavi edildi. Heterotropik pankreas tanısı histopatolojik inceleme ertesi kesinleştirildi. Tümör boyutu, yerleşim yeri, derinliği, tam rezeksyon oranı, gelişen komplikasyonlar ve lokal rekürrens sıklığı değerlendirildi. **Bulgular:** Çalışmadaki 60 gastrik heterotropik pankreas hastasının ortalama tümör çapı $1,4 \pm 0,1$ (0,4-3,5) cm idi. Hastalardan 14'üne (%23,3, 14/60) endoskopik mukozal rezeksyon uygulandı ve lezyon bütünlüğü bozulmadan %64,3 (9/14) vakada rezeksyon sağlandı. Bu grup hastaların 3'ünde (%21,4, 3/14) ise, endoskopik mukozal rezeksyon sırasında gelişen arteriyel kanama sıcak biyopsi forsepsi ve klipleme ile kontrol edildi. Hastalardan 46'sında (%76,7, 46/60) endoskopik submukozal diseksiyon uygulandı lezyon bütünlüğü bozulmadan rezeksyon %97,8 (45/46) vakada sağlandı. Bu hastalardan 6'sında (%13,3, 6/45) arteriyel kanama ve 3 hastada (%6,5, 3/46) pnömoperiton gelişti. Küratif rezeksyon oranı %98,3 (59/60) idi. Hiçbir hastada nüks tespit edilmemi. **Sonuç:** Endoskopik mukozal rezeksyon/endoskopik submukozal diseksiyon minimal invaziv olan ve tüm lezyonun çıkartılması sayesinde lezyonun histolojik incelenmesinin doğru yapılmasına olanak veren ve bu nedenlerle midede yerleşen heterotropik pankreas dokusunun rezeksyonunda kullanılabilcek yöntemlerdir.

Anahtar kelimeler: Heterotopik pankreas, mide, endoskopik rezeksyon, endoskopik mukoza rezeksyonu, endoskopik submukoza diseksiyon

INTRODUCTION

Heterotopic pancreas (HP) is a benign congenital anomaly defined as pancreatic tissue that lacks anatomic or vascular continuity with the pancreas itself (1). This condition is also referred to as pancreatic heterotopia, pancreatic rests, ectopic pancreas, aberrant pancreas, and accessory pancreas. Surgery, laparotomy or laparoscopic, was the traditional radical treatment for HPs (2). However, the trauma might be too large to a certain extent for a benign but potentially malignant disease. Endoscopic resection was another microvasive choice, but reports on HP were limited to the submucosal layer (3,4). The Endoscopic center at the Zhongshan Hospital was one of the largest endoscopic microvasive surgery centers in the world, in which more than 3000 cases of endoscopic submucosal dissection (ESD) were completed (5). From Aug 2007 to Dec 2011, 387 gastric submucosal tumors (SMTs) were removed by ESD and 609 - by EMR; a total of 60 HPs were found. In this study, we retrospectively evaluated these 60 patients to give some useful information regarding the management of HP, including HP involving the muscularis propria which was accepted as a contraindication for endoscopic resection in the past (6,7).

PATIENTS and METHODS

The cases were collected retrospectively by searching the histological diagnosis database of endoscopic resection specimens at the Zhongshan Hospital between Aug 2007 and Dec 2010. There were 60 patients with gastric HP treated by endoscopic mucosal resection (EMR)/ESD. Endoscopic ultrasonography (EUS) was performed preoperatively with a UM-2000 system (Olympus Optical, Tokyo, Japan) to evaluate the origin and size of the tumors (Figure 1 A-B). Informed consent for all procedures, including endoscopic resection, was obtained from each patient. We obtained approval from the institutional review board for this study. All EMR/ESD procedures were performed by four operators (YLQ, ZPH, XMD, ZYS); all of them are surgeons specialized in ESD, and each has done more than 400 cases per year since 2007.

Endoscopic Resection

Standard single accessory-channel endoscope (GIT-H260, Olympus, Japan) and/or dual-channel endoscope (GIF-2T240, Olympus, Japan) were used during the procedures. A short, transparent cap (ND-201-11802, Olympus, Japan) was attac-

hed to the tip of the gastroscope to provide a constant endoscopic view and to apply tension to the connective tissue for dissection. In addition, hook knife (KD-620LR; Olympus, Japan), insulated-tip knife (KD-611L, IT2; Olympus, Japan), and/or hybrid knife (ERBE, Germany) were used to cut the mucosa, to dissect the submucosal layer, and to peel the tumor. The high-frequency generator used was the ERBE Hybridknife System (ERBE, Germany). All the endoscopic procedures were performed under general anesthesia.

EMR Procedures

EMR was performed using a snare after injecting a solution consisting of 100 mL saline + 5 mL 0.2% indigo carmine + 1 mg epinephrine into the submucosal layer. Blended current was used for the resection. After EMR, the area was examined carefully to exclude the presence of any residual tumor. If any residual tumor was observed, additional EMR, hot biopsy, heater probe, or argon plasma coagulation (APC) procedures were performed immediately.

ESD Procedures

ESD was performed as follows (Figure 1 C-J): (i) Marker dots were made around the lesion (ii). Using a 23-gauge disposable needle, several milliliters of the above-mentioned submucosal solution were injected around the lesion to lift it off the muscularis propria layer. However, in case of lesion attached to the muscularis propria layer, only the mucosa was lifted, not the tumor (iii). The mucosa was then incised outside the marker dots using the hook knife /the insulated-tip knife /the hybrid knife (iv). After the mucosal incision, direct dissection of the submucosal layer beneath the tumor under direct vision was performed to obtain the precise specimen, and a complete en bloc resection was achieved (v). In case of lesion involving the muscularis propria layer, the hook knife /the insulated-tip knife /the hybrid knife was used to peel the muscularis propria layer along the edge of the lesion. Finally, the lesion was resected completely from the muscularis propria layer with the knife. Moreover, in the final stage of the ESD procedure, we also used a snare to grasp and remove the undissected, narrowed submucosal tissue, which made the ESD simpler (8). Exposed vessels on the artificial ulcer were coagulated with APC to prevent delayed bleeding (vi). The gastric-wall defect was closed with metallic clips.

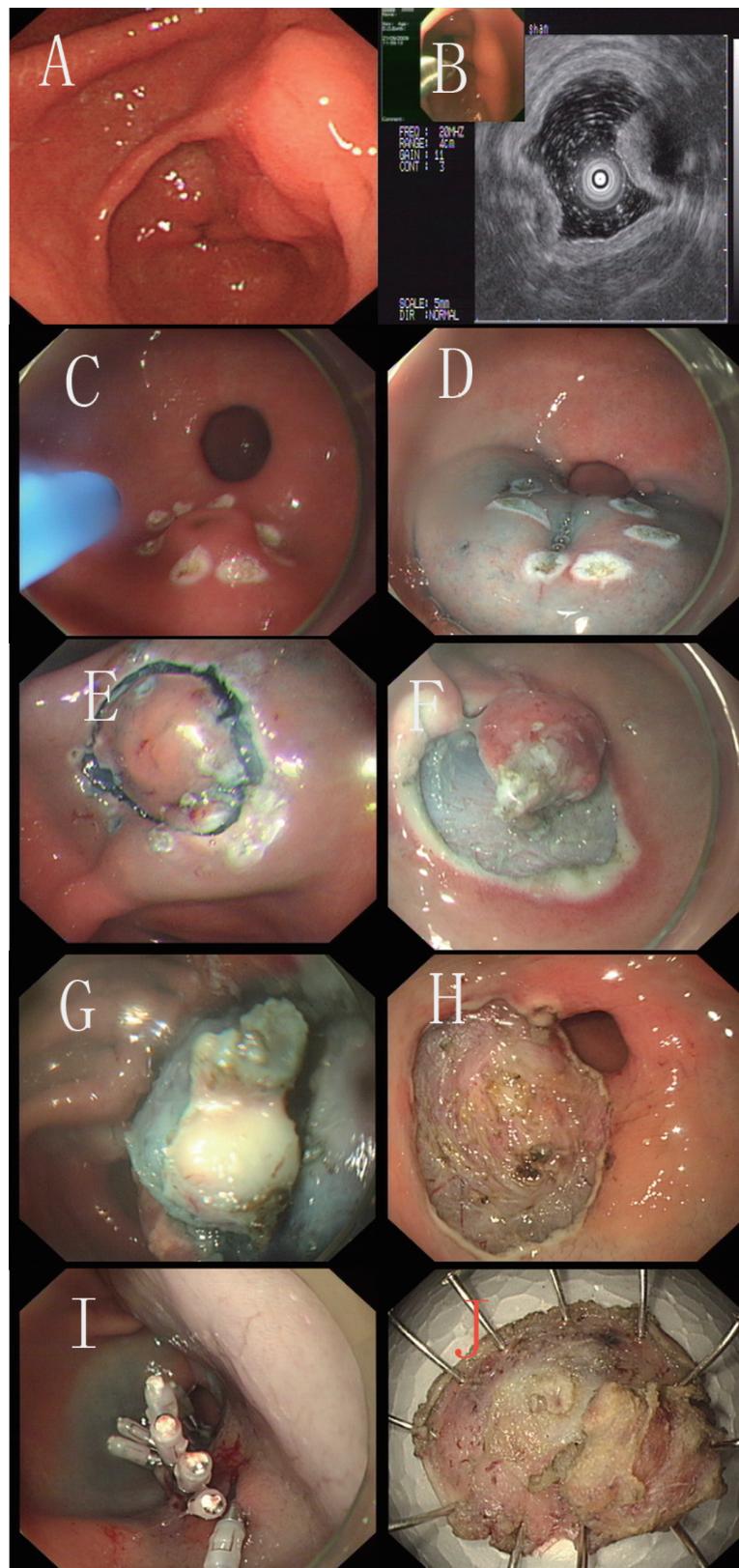


Figure 1. Endoscopic/endoscopic ultrasonography (EUS) view of gastric heterotopic pancreas (HP) and the ESD procedure for the treatment of gastric HPs in the submucosal layer. **(A)** Endoscope image. **(B)** EUS image. **(C)** Marks made near the lesion. **(D)** A solution was injected around the lesion to lift it off the muscularis propria layer. **(E)** The edge of the mucous layer was pre-cut. **(F-G)** Direct dissection of the submucosal layer beneath the tumor under direct vision. **(H)** The wound after stripping. **(I)** Closure of the wound with metal clips. **(J)** The tumor.

Pathologic Evaluation

We defined the resection as en bloc resection; the specimens were sectioned perpendicularly at 2-mm intervals. A complete resection was considered when both the lateral and basal margins were free of tumor cells, and an incomplete resection was considered when the tumor extended into the lateral or basal margins or the margins were indeterminate because of artificial burn effects. Patients with incomplete resections were recommended either for further endoscopic resection until the margins were tumor-free or for surgical intervention. Immunohistochemical staining was used for differential diagnosis.

Follow-Up

The patients were followed up with endoscopy and EUS 1, 2, 6, and 12 months after the last endoscopic resection, and yearly thereafter.

RESULTS

All patient information is summarized in Table 1. The median age of the study subjects was 39 (range: 15–62) years, and 28 of them were women (46,7%). A total of 60 HPs were resected by endoscopy during the study period. The presenting complaint was upper abdominal pain in 16 patients (26,7%), abdominal distension in 8 (13,3%), and black stools in 6 (10%), while the rest of the cases were identified incidentally with endoscopy without specific clinical symptoms.

Endoscopic Features

The lesions were located in the gastric antrum in 51 cases (85%), gastric body in 6 (10%), and in the gastric angle in 3 cases (5%). The lesions were on the greater curvature side in 34 patients (56,7%), posterior wall - in 13 (21,7%), anterior wall - in 5 (8,3%), and on the small curvature in 8 cases (13,3%). Umbilication was found in 23 cases (38,8%) (Figure 1C). The mean maximum size of the lesions was $1,4 \pm 0,10$ (range: 0,4–3,5) cm. EUS revealed involvement of the muscular layer of the mucosa in 2 cases (3,3 %), the submucosal layer in 42 cases (70%), and of the muscularis propria in 16 cases (26,7%). The lesions in 38 patients (63,6%) showed hypoechoic changes on EUS. A medium echo was detected in 4 cases (6,7%), 2 cases (3,3%) were hyperechoic, and 16 cases (26,7%) had a heterogeneous echo.

EMR

Twenty nine cases were planned for EMR proce-

dure. Fifteen cases were converted to ESD procedure because the saline spread into the surrounding normal tissues and the lesions became flattened, which made them impossible to remove by EMR. Fourteen cases (23,3%, 14/60) underwent EMR. The median operation time for successful cases was 12 (range: 7-20) min. The en bloc resection rate, defined as complete detachment without residue, was 64,3% (9/14). In 5 cases, some residual lesions were found after the EMR - the tumor was adhered to the muscularis propria which was not visualized with EUS preoperatively. The residual lesions were wholly resected by hook knife. In 3 cases (21,4%, 3/14), arterial bleeding was controlled with hot biopsy forceps or a metal clip during operation. No perforations or delayed hemorrhage occurred. The median hospital stay was 1 (0-2) day. In cases with small tumor size, after lesion excision and uncomplicated wound closure, the patients were followed up in our Endoscopic center for 2-3 hours and, in the absence of complaints, were discharged home.

ESD

Forty six cases (76,7%, 46/60) underwent ESD procedure. Of those, 15 cases were planned for EMR originally, in 15 cases, the lesion had diameter larger than 1 cm and originated from the submucosal layer, and in 16 cases, the muscularis propria was involved. The median operation time for successful cases was 20 (range: 15-35) min. The en bloc resection rate, defined as complete detachment without residue, was 97,8% (45/46). In one case, the tumor was closely adhered to the muscularis propria and was difficult to remove. Resection of the lesion was as clean as possible, and the wound was treated with APC. In 6 cases (13,3%, 6/45), arterial bleeding was controlled with hot biopsy forceps or a metal clip during operation. Pneumoperitoneum was found in 3 cases (6,5%, 3/46) during the operation. After suturing the wound, abdominal puncture was done to release the air. No patient required conversion to open operation. No delayed bleeding or perforation occurred. The median hospital stay was 2 (1-3) days.

Curative Resection Rate

All lesions were evaluated histopathologically. Except for one case (mentioned in the ESD procedure), no lesion invaded the deep layers and the vertical margins were not affected in the remaining 59 cases. Therefore, the curative resection rate was 98,3% (59/60).

Table 1. Clinicopathologic features and outcomes of gastric HP in patients undergoing endoscopic treatments

Clinicopathologic features and outcomes	Cases (count)
Patient characteristics (60 patients)	
Males	53,3% (32/60)
Females	46,7% (28/60)
The median age	39 years (range: 15–62 years)
Clinical symptoms (60 patients)	
Abdomen pain and discomfort	26,7% (16/60)
Melena	10% (6/60)
Abdominal distention	13,3% (8/60)
Without clinical symptoms	50% (30/60)
Lesion localization (60 lesions)	
Gastric antrum	85% (51/60)
Gastric body	10% (6/60)
Gastric angle	5% (3/60)
Greater curvature side	56,7% (34/60)
Lesser curvature side	13,3% (8/60)
Anterior wall	8,3% (5/60)
Posterior wall	21,7% (13/60)
Mean size of the tumors	1,4±0,10 (range: 0,4–3,5) cm
≤1 cm	50% (30/60)
>1, ≤2 cm	40% (24/60)
>2 cm	10% (6/60)
Umbilication	
Without umbilication	61,2% (37/60)
With umbilication	38,8% (23/60)
EUS examination (60 cases)	
The muscular layer of the mucosa	3,3% (2/60)
The muscularis propria	26,7% (16/60)
The submucous	70% (42/60)
Hypoecho	63,6% (38/60)
Hyperecho	3,3% (2/60)
Medium	6,7% (4/60)
Heterogeneous	26,7% (16/60)
Treatment and Complication	
EMR treatment	23,3% (14/60)
En bloc resection rate	64,3% (9/14)
Complication	21,4% (3/14)
Arterial bleeding	21,4% (3/14)
ESD treatment	76,7% (46/60)
En bloc resection rate	97,8% (45/46)
Complication	18,8%, (8/45)
Arterial bleeding	13,3%, (6/45)
Pneumoperitoneum	6,5% (3/46)
The curative resection rate	98,3% (59/60)
Recurrence	0

Local Recurrence

In all successful cases, 27 (45%) wounds had healed at 1-month follow-up and the remaining 33 had

completely recovered at 2-month follow-up. During the median 27-month (range: 14–54 months) follow-up period, there were no recurrences in any ca-

ses. The patients reported good quality of life, and no reflux, weight loss, poor appetite, intestinal adhesions, or other complications that usually occur after conventional open surgery.

DISCUSSION

HP occurs in 2% of the general population and is more common in males than in females (9); however, the factors leading to the development of HPs remain unknown (10). The stomach is the most common location for HP, representing 25-38% of all cases. Gastric HP is discovered in the antrum in 95% of patients. It may occur on either the posterior or the anterior wall, and is more common along the greater curvature (11). The involvement of the submucosal layer occurs in 73% of cases, the muscularis propria is involved in 17%, and subserosal layer involvement occurs in 10% of cases (12). In some cases, HP stretches through several or all of the layers of the stomach (10). In our cases, 85% of the lesions were found in the antrum and 70% were located in the submucosa.

HP is most often detected as an incidental finding during routine upper endoscopy, but it may become clinically evident depending on the size, location, and pathological changes (7). Patients can also present with upper gastrointestinal bleeding, gastric ulceration, and gastric outlet obstruction. In rare cases, symptoms may occur due to the irritative effect of the hormones and enzymes secreted by the HP at a particular site (7). In our study, the most common complaint was upper abdominal pain (26.7%), and 50% of patients reported no discomfort.

Historically, the diagnosis of HP has often been made based on histological examination of surgical specimens. The preoperative imaging studies (ultrasonography, EUS, and computed tomography) lack suitable specificity (7). The classic endoscopic appearance is that of a small, well-circumscribed submucosal protrusion covered with normal mucosa. Tumors larger than 5 mm often show central umbilication, which is believed to be the site of a draining duct. Central umbilication, however, is not a definitive indicator of HP, and it is difficult to differentiate HP from leiomyoma, which is the most common submucosal tumor of the stomach (13). Biopsy of the gastric mucosa of endoscopically suspected HP rarely reveals the heterotopic pancreatic tissue because the specimens contain only mucosa and HP are submucosal lesions (2).

Endoscopic ultrasound is a more sensitive method for detecting and characterizing small submucosal HP. On EUS, HP often appears as a solid submucosal mass of low echogenicity compared to the hyperechoic submucosa, and it is isoechoic to the hypoechoic muscularis propria layer (14). In our patient group, however, only 63.6% (38/60) were hypoechoic. Goto et al. (15) reported a case of esophageal HP diagnosed by EUS-guided fine-needle aspiration (FNA); the sensitivity of this method is 80-100% (9). The risk of tumor metastasis through the channel of needle could be increased if a gastric SMT, suspicious of HP, is a gastrointestinal stromal tumor (GIST) (16). Moreover, adhesions and inflammation may develop following bite-on-bite biopsies and EUS-FNA, which makes the ESD difficult if the SMTs need to be treated.

When HP causes symptoms, the lesion should be resected, but the management of asymptomatic HP is under debate. In the majority of HP cases, surgical resections have been reported, which has led to the impression that the rate of HP-associated disease, especially cancer (17), is very low, and post-operative complications after routine procedures affect the patient's quality of life, so it is suggested to follow up only (7). However, based on the following reasons, we believe that treatment of asymptomatic HP is also necessary (1). It is difficult to obtain a definitive diagnosis of HP preoperatively (2). Although HPs are usually described as entirely benign lesions, malignant transformation has been identified in several reports (3). Additionally, even asymptomatic benign tumors can cause the development of complications such as obstruction or bleeding due to tumor growth. The previous debate is built on the traditional radical treatment for HP, such as surgery, laparotomy or laparoscopic. EMR/ESD is a minimally invasive technique that offers the possibility of localized treatment of HP with relatively few complications and low mortality.

A few reports describe the use of EMR for HP resection. Khashab et al. (7) reported the use of ligation-assisted EMR for gastric HP. Ryu et al. (18) presented 8 cases of HP that were initially planned for EMR. But in 4 cases (50%), saline spread into the surrounding normal tissues during EMR procedure, the lesions became flattened and impossible to remove by EMR, thus ESD was performed.

The indications to choose EMR or ESD were depending on the size, originating layer, and endos-

copists' technique, in our clinical practice. If the lesion diameter is not larger than 1 cm and preoperative EUS reveals no adherence to the muscularis propria, we commonly plan an EMR procedure. Due to the anatomic features, HP may involve several layers of the stomach, such as submucosa and muscularis propria. The lesions may "disappear" after the injection of saline, which may be a sign that the lesion is attached to the muscularis propria; Thus, ESD will be the best choice. As shown in our data, more than 50% (15/19) of the cases planned for EMR were converted to ESD during the operation. Moreover, EMR technique seemed to have a high rate of lesion residual - about 37% (5/14) had residual lesions after EMR resection and needed further resection using ESD.

Complication rate of EMR/ESD for HP was low. The main complication was bleeding during operation, which can be the reason for fail and conversion to surgery. Due to the anatomic features, gastric HP has some nourishing arteries originating from the muscularis propria. The pressure of these arterial is high to some extent, which cannot be controlled during EMR and needs special coagulation with hot biopsy forceps. In our data, bleeding during EMR (23.3%) was higher than during ESD (13.3%).

Pneumoperitoneum was not a rare phenomenon in the procedure of ESD for SMTs originating from the muscularis propria layer. We think it is not a problem since abdominal puncture can let the air escape and no further operation is needed. In the present study, only 3 cases (6.5%, 3/46) were found have pneumoperitoneum during operation.

In another study, we demonstrate a new endoscopic treatment technique, called submucosal tunneling endoscopic resection (STER), in the management of SMTs originating from the muscularis propria layer (19). The advantage of this new method is the maintenance of GI tract mucosal integrity while achieving an en bloc resection of SMTs. This method will possibly reduce the risk of postoperative GI tract leakage and secondary infection. We often use this method in the esophagus, which do not have serosa and there is only a sparse connective tissue outside the muscle layer. But we noticed that STER can also be successfully used in gastric SMTs (20).

In conclusion, EMR/ESD offer an effective localized treatment for gastric HP with relatively low complication and mortality rates. If the lesions were SMTs originating from the muscularis propria layer, ESD was the first choice rather than EMR. STER is a safe, easy, and feasible new method for providing accurate histopathologic evaluation as well as radical treatments of SMTs from the MP layer. However, large, prospective, multi-centered studies are required to further corroborate these results.

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