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## Retrospective Study

# Ligation-assisted endoscopic submucosal resection following unroofing technique for small esophageal subepithelial lesions originating from the muscularis propria

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## Abstract

### BACKGROUND

The majority of esophageal subepithelial lesions originating from the muscularis propria (SEL-MPs) are benign in nature, although a subset may exhibit malignant characteristics. Conventional endoscopic resection techniques are time-consuming and lack efficacy for small SEL-MPs.

### AIM

To evaluate the efficacy and safety of ligation-assisted endoscopic submucosal resection (ESMR-L) following unroofing technique for small esophageal SEL-MPs.

### METHODS

From January 2021 to September 2023, 17 patients diagnosed with esophageal SEL-MPs underwent ESMR-L following unroofing technique at the endoscopy center of Shenzhen People's Hospital. Details of clinicopathological characteristics and clinical outcomes were collected and analyzed.

### RESULTS

The mean age of the patients was  $50.12 \pm 12.65$  years. The mean size of the tumors

was  $7.47 \pm 2.83$  mm and all cases achieved *en bloc* resection successfully. The average operation time was 12.2 minutes without any complications. Histopathology identified 2 Lesions (11.8%) as gastrointestinal stromal tumors at very low risk, 12 Lesions (70.6%) as leiomyoma and 3 Lesions (17.6%) as smooth muscle proliferation. No recurrence was found during the mean follow-up duration of  $14.18 \pm 9.62$  months.

## CONCLUSION

ESMR-L following roofing technique is an effective and safe technique for management of esophageal SEL-MPs smaller than 20 mm, but it cannot ensure *en bloc* resection and may require further treatment.

**Key Words:** Subepithelial lesions; Muscularis propria; Esophagus; Ligation; Endoscopic submucosal resection

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**Core Tip:** This is a retrospective study to evaluate the efficacy and safety of ligation-assisted endoscopic submucosal resection following unroofing technique for management of esophageal subepithelial lesions originating from the muscularis propria (SEL-MPs) smaller than 20 mm. The technique has numerous advantages, such as simple operation, complete tumor removal, short operation time, less complications, cost effectiveness, *etc.* It is an effective and safe technique for management of esophageal SEL-MPs smaller than 20 mm, but it cannot ensure *en bloc* resection and may require further treatment.

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## INTRODUCTION

Subepithelial lesions (SELs), also known as submucosal tumors within the gastrointestinal (GI) tract, are defined as the tumors originating from the muscularis mucosa, submucosa or muscularis propria (MP). SELs are predominantly located in the stomach, followed by the esophagus, duodenum, and large intestine[1]. They are characterized as rounded protrusions or masses covered with normal overlying mucosa and are commonly detected incidentally during endoscopic examination[2]. The incidence of malignancy is proved to be greater in gastric and esophageal lesions, compared to that in small intestinal and large intestinal lesions. And lesions exceeding 20 mm in diameter exhibit a higher propensity for malignancy compared to the smaller ones[3]. Esophageal SELs constitute less than 1% of all esophageal neoplasms and demonstrate a benign nature in over 90% of cases. While esophageal leiomyomas are typically benign and represent the most common subtype, certain uncommon cases such as GI stromal tumors (GISTs), lymphoepithelioma-like carcinoma, and leiomyosarcoma exhibit malignant features and possess potential for distant metastasis[4-6].

According to American Gastroenterological Association clinical practice, utilization of endoscopic ultrasound (EUS) surveillance is recommended for SELs originating from the MP (SEL-MPs) smaller than 2 cm[2]. However, differentiating potentially malignant esophageal SELs like GISTs from benign lesions through EUS poses a considerable challenge. Although EUS-guided fine needle aspiration serves as a valuable technique to obtain pathological specimens of SELs, its diagnostic accuracy fluctuates according to the size of the target lesion and a range of other variables[7,8]. Therefore, continuous surveillance without resection may pose significant risks and substantial psychological and financial burdens on patients, necessitating the removal of small SEL-MPs in specific circumstances[9].

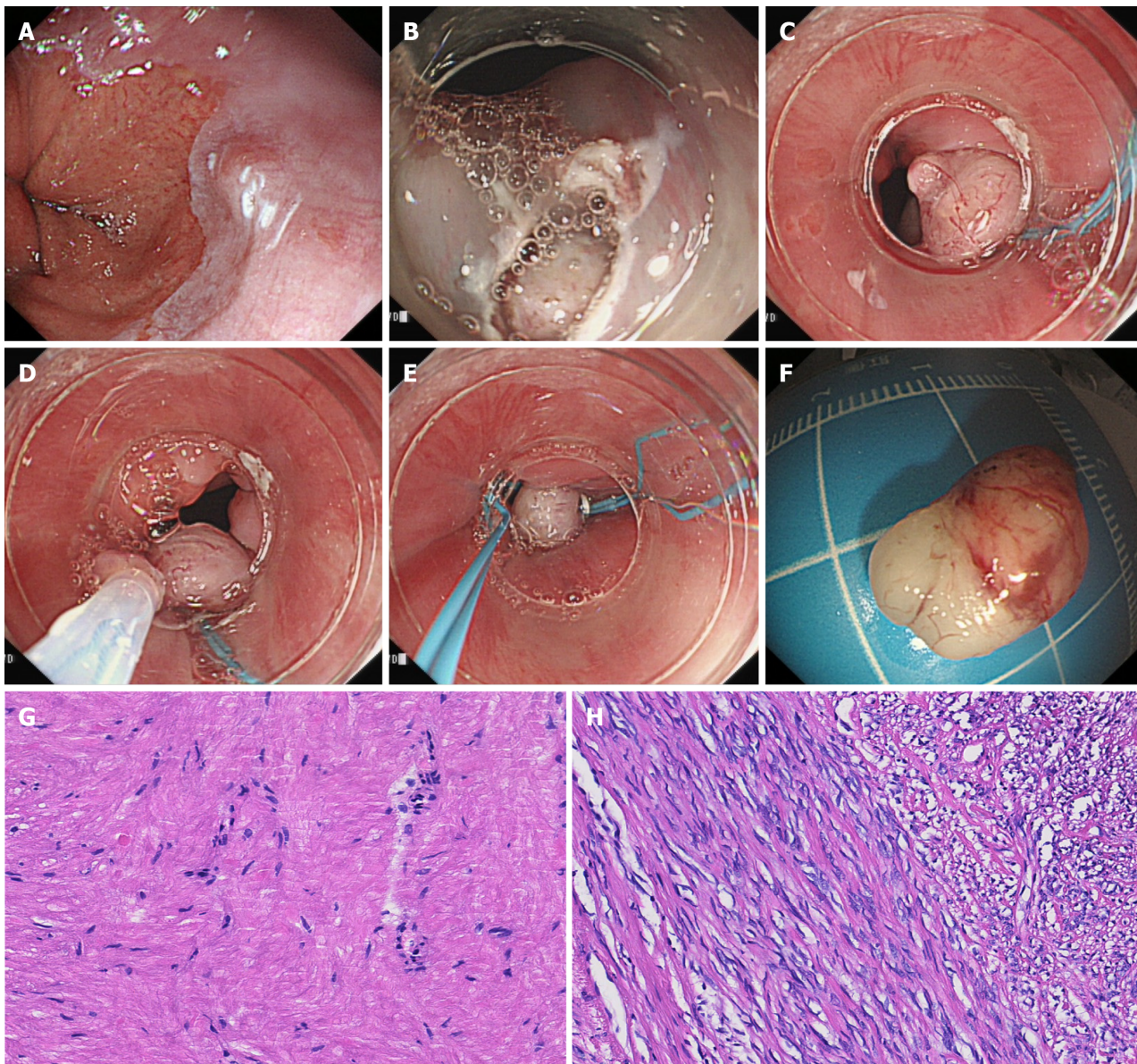
Various conventional endoscopic resection techniques such as endoscopic submucosal excavation (ESE), submucosal tunneling endoscopic resection (STER), endoscopic full-thickness resection, have been demonstrated to be both safe and feasible for the management of esophageal SEL-MPs[1,2,10]. However, these techniques are time-consuming and lack efficacy for small esophageal SEL-MPs. To optimize the technique of endoscopic resection, we present an innovative ligation-assisted endoscopic submucosal resection (ESMR-L) following unroofing technique developed in our center. In this retrospective study, we evaluated the efficacy and safety of ESMR-L for the management of esophageal SEL-MPs smaller than 20 mm.

## MATERIALS AND METHODS

### Patients

The study was conducted on consecutive patients with esophageal SELs treated by ESMR-L following unroofing technique at the endoscopy center of Shenzhen People's Hospital from January 2021 to September 2023. The inclusion criteria were as follows: (1) Esophageal SELs confirmed by EUS originated from MP layer with intracavitary growth; and





**Figure 1** Ligation-assisted endoscopic submucosal resection after unroofing technique. A: Marking dots around the lesion by snare; B: Unroofing the apical mucosa around the marking dots by snare; C: Aspiring the lesion and ligating the lesions fully with endoloop; D: Cold snaring the lesion above the endoloop; E: Ligating the defect using another endoloop; F: Resected specimen; G: Microscopic appearance with hematoxylin-eosin staining of leiomyoma ( $\times 200$ ); H: Microscopic appearance with hematoxylin-eosin staining of gastrointestinal stromal tumor ( $\times 200$ ).

(2) The diameter of the tumor was smaller than 20 mm.

### Devices

The procedure was performed using a standard single-channel endoscope (GIF-260; Olympus) equipped with a soft, straight, transparent, 14.9 mm diameter cap (D-201-11802; Olympus) attached to the tip. A ligating device (MAJ-339; Olympus) with a detachable 20 mm diameter nylon endoloop was inserted into the accessory channel of the endoscope. Injection needles were used in submucosal injection and snares were used to mark dots and remove tumors.

### Procedure

All procedures were performed by one experienced endoscopist (Dr. Li) in our center under conscious sedation. Before the procedure, all lesions confirmed by EUS were identified as hypoechoic and homogeneous masses originating from esophageal MP layer without any enlarged lymph nodes detected. The procedure of ESMR-L following unroofing technique was briefly described as follows: (1) Marked dots around the lesions by snare; (2) Injected mixture solution submucosally beneath the marking dots; (3) Unroofed the apical mucosa around the marking dots by snare; (4) Aspired the lesions and ligated the lesions fully with endoloop; (5) Resected the lesion by cold snare above the endoloop; and (6) Ligated the defect using another endoloop (Figure 1 and Video 1). After resection, the lesion sites were observed carefully to check whether there were any residual tumors, bleeding, perforations, *etc.* In case of complications occurred during the procedure, hemoclips or alternative devices may be used to manage the wound.

**Table 1** Details of clinicopathological characteristics and clinical outcomes of 17 patients with small esophageal subepithelial tumors originating from the muscularis propria

Case	Sex/age (years)	Location	Size (mm)	Operation time (min)	<i>En bloc</i> resection	Complications	Pathological diagnosis	Follow-up (months)	Recurrence
1	M/54	Lower	12	8	Yes	None	GIST	9	No
2	M/73	Lower	3	14	Yes	None	Leiomyoma	8	No
3	F/66	Lower	5	14	Yes	None	Leiomyoma	8	No
4	F/44	Upper	6	15	Yes	None	Leiomyoma	5	No
5	M/58	Middle	8	22	Yes	None	Leiomyoma	18	No
6	F/57	Lower	6	10	Yes	None	Leiomyoma	3	No
7	M/68	Lower	7	9	Yes	None	Leiomyoma	5	No
8	M/39	Lower	5	12	Yes	None	Smooth muscle proliferation	9	No
9	F/35	Lower	9	9	Yes	None	Leiomyoma	13	No
10	M/26	Lower	13	18	Yes	None	Leiomyoma	15	No
11	F/46	Lower	8	13	Yes	None	Smooth muscle proliferation	17	No
12	M/41	Lower	5	11	Yes	None	Leiomyoma	18	No
13	M/51	Lower	8	13	Yes	None	Leiomyoma	22	No
14	F/42	Lower	10	10	Yes	None	Leiomyoma	33	No
15	M/41	Lower	4	7	Yes	None	Smooth muscle proliferation	34	No
16	F/50	Lower	7	10	Yes	None	Leiomyoma	22	No
17	F/61	Lower	11	13	Yes	None	GIST	2	No

M: Male; F: Female; GIST: Gastrointestinal stromal tumors.

### Pathological evaluation and definition

Pathological evaluation of the resected specimens included histopathologic type, depth of invasion, resection margins, *etc.* The pathological diagnosis was confirmed by experienced pathologists. *En bloc* resection was defined as endoscopic resection of the entire lesions in one piece with tumor-free margins. Complete removal was defined as the gross absence of any tumor remnant after resection.

### Follow up

All patients were recommended to undergo routine endoscopic follow-up 2 months after the procedure. If the pathological diagnosis revealed leiomyomas or other benign tumors, no further surveillance was deemed necessary. Patients diagnosed with GISTs were recommended to undergo annual computed tomography and endoscopic evaluations thereafter. In case of residual tumors and recurrence, further endoscopic or surgical interventions would be performed.

### Statistical analysis

All statistical analyses were performed using statistical product and service solutions software version 25.0 (International Business Machines, Armonk, NY, United States). Continuous variables were expressed as mean  $\pm$  SD and categorical data were displayed as numbers and percentages.

## RESULTS

A total of 17 patients diagnosed with esophageal SEL-MPs underwent ESMR-L following unroofing technique during the study period. The clinicopathological characteristics and clinical outcomes of the patients are presented in **Table 1**, while **Table 2** provides a summary of the information. The mean age of the patients was  $50.12 \pm 12.65$  years (range 26-68 years). The majority of tumors were predominantly located in the distal segment of the esophagus, with an average tumor size measuring  $7.47 \pm 2.83$  mm. *En bloc* resection was achieved in all patients without any complications and the mean operation time was 12.2 minutes (range 7-22 minutes). Pathologically, 2 Lesions (11.8%) were identified as GISTs at very

**Table 2 Summary of clinicopathological characteristics and clinical outcomes, *n* (%)**

Summary of clinicopathological characteristics and clinical outcomes	
Age/year (mean $\pm$ SD)	50.12 $\pm$ 12.65
Gender	
Male	9 (52.9)
Female	8 (47.1)
Tumor size/mm	
> 10	4 (23.5)
< 10	13 (76.5)
Mean size/mm (mean $\pm$ SD)	7.47 $\pm$ 2.83
Mean operation time/min	12.2
<i>En bloc</i> resection	17 (100)
Complications	
Bleeding	0
Perforation	0
Others	0
Pathological diagnosis	
GIST (very low risk)	2 (11.8)
Leiomyoma	12 (70.6)
Others	3 (17.6)
Follow-up duration/month (mean $\pm$ SD)	14.18 $\pm$ 9.62
Recurrence	0

GIST: Gastrointestinal stromal tumors.

low risk and 12 Lesions were diagnosed as leiomyoma. The remaining 3 Lesions exhibited smooth muscle proliferation. The mean follow-up duration was 14.18  $\pm$  9.62 months (range 2-33 months) with no recurrence.

## DISCUSSION

The incidence of esophageal SELs remains uncommonly rare. Although the patients are typically asymptomatic, a recent study revealed that esophageal SELs exhibit pathological consequences on esophageal motility, primarily manifesting as ineffective esophageal motility disorder[11]. A considerable proportion of patients in China have requested the removal of small esophageal SEL-MPs because of the follow-up anxiety, fear, cost, uncertain malignant potential, *etc.* However, long procedure time and increased adverse events limited the application of conventional endoscopic resection techniques on small esophageal SEL-MPs[1,2,10].

In recent years, more and more innovative endoscopic techniques are springing up with the rapid development of GI endoscopy. Ko *et al*[12] reported a novel 3D-printed tailored cap for removal of small esophageal SELs. Although the 3D-printed tailored caps demonstrated high *en bloc* resection rates and efficient procedure time, their individual customization for each patient resulted in an augmented treatment cost. Liu *et al*[13] introduced a novel technique, known as endoscopic muscularis dissection, derived from endoscopic submucosal dissection, for removal of upper GI SEL-MPs. Although it was proven to be feasible and minimally invasive, the blunt dissection in the MP layer posed challenges and necessitated skilled endoscopists, ultimately resulting in a heightened risk of perforation. Guo *et al*[14] developed the ligation-assisted endoscopic enucleation technique for treating small esophageal SEL-MPs (less than 12 mm) with a mean procedure time of 12.5  $\pm$  4.6 minutes. However, complete dissection of the spherical tumors posed a challenge and entailed a certain risk of intraoperative hemorrhage.

Inspired by ESMR-L of gastric SEL-MPs with a detached ligation device after apical mucosal incision[15] reported in our center, we had developed a similar ESMR-L following unroofing technique for esophageal SEL-MPs smaller than 20 mm. Our study demonstrated that ESMR-L following unroofing technique had following advantages: (1) Simple operation. Irrespective of the position of the SELs, the ligation device effectively generated negative pressure to aspirate the lesion into the transparent cap and subsequently released the endoloop, inducing a polypoid configuration with a pseudo-stalk that facilitated resection by cold snare; (2) Complete removal. Although there was a possibility of



incomplete resection, the utilization of double-ligation ensured complete removal of the tumors. This was further confirmed by pathological examination, and even in cases where residual tumor existed, it would eventually undergo necrosis and be shed over time due to the “loop-and-let-go” effect[16,17]; (3) Short operation time. Lu *et al*[18] reported the mean operation time of ESE and STER for esophageal or cardial SEL-MPs was 65.9 minutes and 84.4 minutes respectively. The mean operation time in our study was found to be 12.2 minutes, significantly shorter than that achieved using conventional techniques; (4) Less complications. The utilization of double ligation and cold snare in the ESMR-L technique significantly mitigated the risk of bleeding and perforation. The patients included in our study did not experience any postoperative complications. Relevant studies have previously indicated that conventional techniques were associated with elevated rates of adverse events, whereas in Ye *et al*'s study on the treatment of small esophageal SEL-MPs using endoscopic excavation technique, there were still 4 cases (8.9%) that experienced perforation[19]; and (5) Cost effectiveness. Endoscopic unroofing technique by snaring had been proved safe and effective for partial mucosal resection[20,21]. Additionally, it eliminated the need for a hook knife and reduced patients' cost.

There were also several limitations in our study. For instance, achieving *en bloc* resection of all tumors using this technique seemed unattainable. Instead, complete removal, defined as “gross” absence of any remnant tumor in our study, could theoretically be achieved in all cases. Therefore, long-term follow-up and further treatments should always be considered in case of incomplete resection and malignant SELs. Additionally, it is important to note that our study was conducted at a single center with a small sample size. Hence, multi-center prospective randomized controlled trials with larger sample sizes are necessary to assess the clinical feasibility and value of this technique.

## CONCLUSION

ESMR-L following unroofing technique is an effective and safe technique for management of esophageal SEL-MPs smaller than 20 mm. However, it cannot ensure *en bloc* resection and may require further treatment.

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## FOOTNOTES

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