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Current Status and Considerations on Endoscopic Diagnosis and Treatment of Subepithelial Microlesions in the Digestive Tract

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Abstract: The detection rate of subepithelial lesions in the digestive tract, especially microlesions (≤ 1 cm in diameter), has significantly increased. Historically, periodic follow-up or surgical resection has been recommended by scholars. Due to the potential risk of malignancy, regular follow-up carries certain risks, while surgical resection, though effective, is highly invasive with a high risk of complications. With the rapid development of endoscopic techniques, more and more subepithelial lesions in the digestive tract have been successfully treated through endoscopic submucosal dissection and endoscopic full-thickness resection. However, these methods require a high level of skill and are associated with significant costs for surgical instruments and materials. Therefore, it is worth exploring whether a simpler and more efficient treatment can transition patients from observation to proactive treatment. A modified technique combining snare, long transparency cap, and Argon Plasma Coagulation under endoscopy has advantages over traditional methods, such as being simpler to perform, less prone to complications, and more cost-effective. This article reviews the current status and considerations of endoscopic treatment for subepithelial lesions in the digestive tract.

Keywords: Subepithelial lesion in the digestive tract; Endoscopic mucosal resection; Endoscopic submucosal dissection; Endoscopic full-thickness resection

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1. Introduction

Subepithelial lesions of the digestive tract include gastrointestinal stromal tumors (GISTs), leiomyomas, lipomas, ectopic pancreas, cysts, polyps, varices, lymphomas, metastases, and extrinsic or compressive lesions. It is often difficult to make an accurate diagnosis based solely on standard gastroscopic observation. Most lesions are discovered incidentally and rarely present clinical symptoms, though large tumors may cause sensations of foreign objects during swallowing or difficulty swallowing. Diagnosis is primarily based on

endoscopy and endoscopic ultrasonography (EUS), with pathological tissue biopsy being the gold standard for confirmation. Previously, for subepithelial microlesions smaller than 1 cm, clinical observation and endoscopic follow-up were the main approaches. However, relying only on clinical presentation and imaging for diagnosis has resulted in a 30% misdiagnosis rate [1-3]. Long-term endoscopic follow-up can have negative psychological and physical impacts on patients.

Currently, an increasing number of experts are using endoscopic submucosal dissection (ESD) or endoscopic full-thickness resection (EFTR) to remove tumors and achieve a final pathological diagnosis [4,5]. On one hand, this removes the lesion and prevents potential malignancy; on the other hand, it provides sufficient biopsy tissue to assess the nature of the lesion. Additionally, it allows for the evaluation of whether the lesion has been completely excised or if residual lesion tissue remains. However, for subepithelial microlesions smaller than 1 cm, ESD and EFTR are time-consuming, technically demanding, and increase healthcare costs. Therefore, it is crucial to explore the safety and efficacy of lesion removal using SCAE and weigh its benefits against the risks of regular follow-up.

2. Common endoscopic treatment methods for subepithelial lesions of the digestive tract

2.1. Endoscopic tumor resection

Endoscopic tumor resection (ETR) is suitable for benign subepithelial lesions with superficial local elevation. After confirming the origin of the lesion via EUS, a snare is used to encircle the base of the lesion, tighten it, and lift it, followed by cutting and coagulation using a high-frequency device. It is essential to strictly control the indications for endoscopic treatment. ETR is considered safe and effective for subepithelial lesions originating from the superficial layers of the digestive tract.

2.2. Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) evolved from snare-based resection techniques. Initially, EMR was used exclusively for mucosal lesions such as gastric polyps, but with advancements in technology and instruments, its indications have expanded to include submucosal lesions. EMR is now suitable for subepithelial lesions with superficial origins and tumor diameters between 1–2 cm. The procedure involves injecting 1:10,000 fructose + epinephrine saline beneath the lesion base, separating the lesion from the muscularis propria, followed by snare resection. For irregularly shaped lesions, piecewise resection (ePMR) can be employed. Lesions in challenging locations (e.g., the lesser curvature of the stomach) can be suctioned using a transparent cap, tied with a rubber band or nylon loop, and then resected. The main complications of EMR are bleeding and perforation, which can be minimized by using EUS to determine the lesion's origin and growth direction prior to surgery. Submucosal injections under EUS guidance also reduce bleeding and perforation risks during EMR [6]. EMR is effective for small, superficial subepithelial lesions, allowing for single-session removal.

2.3. Endoscopic submucosal dissection and endoscopic submucosal excavation

With the invention of the IT knife, endoscopic submucosal dissection (ESD) gradually became a standard procedure for the complete resection of lesions, mainly used for early-stage digestive tract cancers. ESD is also suitable for subepithelial lesions larger than 2 cm or with broad bases located in superficial layers (muscularis

mucosae or submucosa). The procedure involves:

(1) Electrocautery marking around the lesion's perimeter.

(2) Submucosal injection of saline + fructose + epinephrine to separate the muscularis propria from the submucosa.

(3) Cutting around the lesion.

(4) Complete dissection of the lesion.

For lesions involving the muscularis propria, careful consideration is needed due to the risk of bleeding and perforation. Some experienced endoscopists have reported successful ESD for lesions originating in the muscularis propria [7]. The perforation rate for ESD is approximately 4%, and the bleeding rate is less than 5% [8]. Foreign reports suggest ESD-related bleeding rates range from 13% to 38% [9]. Some studies have shown that intermittent submucosal injections of various fluids (e.g., glycerin, sodium hyaluronate) during lesion dissection can reduce perforation rates [10]. Zhou *et al.* [11] applied ESD techniques for subepithelial lesion treatment, naming it endoscopic submucosal excavation (ESE). ESE and ESD are fundamentally similar when dissecting submucosal or muscularis propria lesions. Zhang *et al.* [12] reported that the difference between ESE and ESD lies in the resection of lesions involving the muscularis propria: after exposing the lesion, the overlying mucosal and submucosal layers can be removed using a snare, and the muscularis propria tumor is then dissected. To shorten surgery time, a snare can be used to excise the lesion after almost complete dissection. In practice, ESE is just a different name for ESD when treating subepithelial lesions, with no significant differences in techniques, complications, or management between the two.

2.4. Endoscopic full-thickness resection

EFTR, developed from ESD, has recently been applied to treat subepithelial lesions in the digestive tract. EFTR is primarily used for lesions originating from the muscularis propria that are closely adherent to the serosa. The procedure involves:

(1) Submucosal injection of saline, followed by precutting around the tumor to expose it.

(2) Using ESD to separate the muscularis propria from the serosa around the lesion.

(3) Cutting through the serosa along the tumor margins.

(4) Full-thickness resection of the lesion, including the serosa, using tools like the Hook knife, IT knife, or snare under direct endoscopic vision.

(5) Closing the wound with metal clips.

One study [13] reported that EFTR was used to completely resect 20 subepithelial lesions originating from the gastric muscularis propria, with good outcomes. Kantsevoy *et al.* [14] also achieved favorable results with EFTR. The introduction of EFTR has significantly expanded the indications for endoscopic treatment of subepithelial lesions. However, the procedure is technically challenging, and its long-term clinical outcomes require further investigation.

2.5. Combined application technology of snare, long transparency cap, and argon plasma coagulation under endoscope

Combined application technology of snare, long transparency cap, and argon plasma coagulation under endoscope (SCAE) evolved from endoscopic variceal ligation (EVL) and snare polypectomy techniques. Its principle is similar to rubber band ligation for hemorrhoids but utilizes a snare for electrical excision. The

procedure involves:

(1) Attaching a special long transparent cap to the front of the endoscope, equipped with a crescent-shaped electric snare on the cap's exterior. Both the cap and the endoscope are inserted into the digestive tract.

(2) Positioning the endoscope directly above the lesion, the transparent cap suctions the mucosa and tumor into the cap. The snare is then tightened around the lesion base, ligating it.

(3) Standard snare electrocautery is used to excise the lesion. If residual or suspicious tumor tissue remains, repeated excision is performed.

(4) Argon plasma coagulation (APC) is applied to the wound surface to reduce the risk of microscopic residual tumor, and the specimen is completely retrieved. Metal clips or nylon loops are used to close the wound.

Postoperative management includes fasting, fluid replacement, and the administration of hemostatic agents and proton pump inhibitors. The advantage of SCAE is that no submucosal injection is needed, as the lesion is suctioned directly into the transparent cap for excision.

3. Discussion and Conclusion

Gastrointestinal subepithelial lesions are commonly GISTs [15]. Due to their potential malignancy, complete resection is recommended. The surgical approach varies depending on the size of the lesion: for lesions larger than 3 cm, laparoscopic resection is recommended, while for those smaller than 2 cm, ESD and other endoscopic techniques have been proven to be safe and effective [16].

Before performing endoscopic resection of gastrointestinal subepithelial lesions, it is essential to exclude conditions such as vascular indentations, external compression, or large tumors extending outside the lumen [17,18]. Therefore, EUS examination is crucial to assess the size, growth pattern, and tissue origin of the lesion. For lesions not suitable for endoscopic resection, resection should be promptly abandoned. ESD in the gastric fundus region requires retroflexion of the endoscope, which results in a poor field of view and is heavily influenced by respiration and heartbeat, making it difficult to control the dissection plane. Particularly for small submucosal tumors with a diameter of less than 1 cm, the lesion can easily shift after submucosal injection, causing disorientation during the procedure. Even when the submucosa is accurately dissected, exposing the cutting line is challenging. As a result, more experts are exploring different endoscopic resection techniques for small submucosal tumors in the esophagus and stomach [19]. Sun *et al.* [20] found that using endoscopic rubber band ligation for upper gastrointestinal leiomyomas is safe and effective, but they were unable to retrieve the specimen for pathological diagnosis.

We adopted SCAE for resecting lesions, and in all 13 cases, the lesions were completely resected and pathologically diagnosed. The average procedure time was 20 minutes, significantly shorter than conventional ESD [21,22]. No intraoperative or postoperative massive bleeding occurred. In some cases, minor intraoperative perforations were observed but were promptly identified and securely closed. None of the patients showed signs of peritonitis. Based on our experience with this technique, the following points are noteworthy: (1) After fully suctioning the lesion into the transparent cap, repeatedly pulling and releasing the snare ensures that the lesion is adequately ligated for complete resection while minimizing damage to the surrounding normal tissue. This reduces postoperative mucosal edema and facilitates wound closure. (2) After resection, APC is applied not only to stop bleeding but also to minimize the risk of tumor micro-residuals at the wound margin. (3) During closure

of the defect, slight air inflation should be used, first clamping the distal part of the wound, then sequentially closing the wound with the aid of the previously placed hemostatic clips for traction.

In conclusion, for patients with small subepithelial lesions in the gastrointestinal tract, there is a certain risk associated with relying solely on endoscopic follow-up, as the possibility of malignancy cannot be ruled out. In 2018, expert consensus recommended that institutions with the necessary capabilities should perform endoscopic minimally invasive resection after thorough preoperative evaluation and full communication with the patient. This approach allows for the acquisition of pathological data, preventing misdiagnosis or secondary malignant transformation of the lesion, and spares patients the discomfort and anxiety associated with repeated endoscopic surveillance. The SCAE technique enables complete lesion resection and pathology acquisition without requiring additional equipment or device support, conserving medical resources. SCAE is a simple, safe, effective, and easily implemented procedure. With the continued accumulation of clinical research data and the ongoing refinement of surgical techniques, this approach may present lower risks than long-term follow-up for such patients, offering them more treatment options in the future.

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Disclosure statement

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