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Endoscopic mucosal resection and endoscopic submucosal dissection in esophageal and gastric cancers

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Abstract

Purpose of review—To summarize the literature to date on endoscopic mucosal removal techniques as applied to the upper gastrointestinal tract, predominantly the stomach and esophagus. This is an area that has rapidly advanced in terms of new procedures and techniques with a large body of outcomes that support their use.

Recent findings—The resection techniques can be divided into two forms, mucosal resection and submucosal dissection. Mucosal resection is typically done with cap techniques and is more suitable for removable of neoplastic lesions that are less than 1.5 cm in size. Submucosal dissection techniques are more difficult, associated with increased complications, and typically reserved for lesions greater than 1.5 cm and less than 3 cm in size. Ideal lesions for mucosal resection are generally flat and are located in areas easily accessible by the endoscope.

Summary—Endoscopic tissue removal methods are capable of removing neoplastic lesions en bloc in the upper gastrointestinal tract. These techniques fulfill cancer treatment guidelines by having histological confirmation of total removal of neoplastic lesions with assessment of the margins of resections. Long-term clinical outcomes of these techniques are emerging and seem promising in terms of disease-free and overall survival.

Keywords

Barrett's esophagus; endoscopic mucosal resection; endoscopic submucosal dissection; endoscopic therapy; esophageal neoplasm; gastric neoplasm

Introduction

This review will encompass two major forms of endoscopic tissue removal that are currently being used for treatment of mucosally based disease in the esophagus and stomach. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are both techniques dedicated to the removal of large volumes of tissue. As opposed to endoscopic biopsies that remove on average 1 mm × 3 mm area of tissue, these techniques remove at least three to four times the amount of tissue. The most common aim of these techniques is to diagnose and treat mucosal-based neoplasia. The rationale for both of these techniques is that en bloc resection with histological examination of the resected specimen will lead to improved diagnosis, improved staging of early neoplasia, and provide information regarding the therapeutic benefit of an endoscopic approach. Both techniques are dependent upon obtaining good mucosal separation from the muscularis propria. However, the method by which tissue is resected constitutes the major difference between these two techniques.

Mucosal resection generally involves the use of a snare to resect the tissue, whereas ESD utilizes a dissecting 'knife'. Because of the use of the snare, inevitably in the EMR techniques, a pseudopolyp must be formed either by suction or by utilizing a submucosal injection and cushion followed by banding. In ESD, fluid must be introduced into the submucosa to define the submucosal space to allow visualization of this area for careful manual dissection. In this article, we will review the indications and complications associated with both of these techniques.

Indications for procedure

EMR and ESD are both targeted toward mucosal lesions [1**]. Therefore, it is not surprising that mucosally based neoplastic lesions such as esophageal squamous cancers, adenocarcinomas associated with Barrett's esophagus, and gastric cancers are the most common targets for this therapy in the upper gastrointestinal tract [2–4]. Less common usages would be for the removal of submucosal lesions such as leiomyomas or GIST [5]. Most of the submucosal lesions are approached with ESD, which allows the endoscopist to carefully dissect the tissue (see Table 1).

Lesions are grossly classified according to the appearance of the lesion (see Fig. 1) [6]. Most often, lesions that are elevated or raised are most amenable to mucosal resection techniques [7]. Lesions that are ulcerated or depressed are less amenable because they have a tendency to invade deeper and to have inflammatory response that makes it difficult to separate the mucosa from the sub-mucosa.

Other factors that determine the indications for resection include the size of the lesion. Generally, lesions that are smaller than 1 cm to perhaps 1.5 cm in diameter are better managed with EMR techniques simply because these are just as effective as submucosal dissection and can remove these lesions en bloc [3]. In lesions larger than this and up to 3–4 cm in size, ESD should be considered. Lesions larger than 4 cm often have deep invasion and high risk of metastatic lesions. The need to do ESD in addition to radiation and chemotherapy to treat an early-staged cancer has not been shown. ESD has been used after chemoradiation to complete removal of tumor in very small case reports with reasonable short-term results [8]. EMR can also be used for this application in smaller lesions especially given the tendency for the submucosal tissue planes to be more difficult to identify after chemo-radiation. In a small cohort of 21 patients, overall survival was 49% at 5 years using EMR as a salvage therapy after chemotherapy and radiation [9].

In the treatment of neoplasia, lesions that have high risk of metastasis are not usually felt to be candidates for these resection techniques. These would include the lesions' size, evidence of neural invasion or angiolymphatic invasion, lymphocytic invasion, and evidence of deep sub-mucosal invasion [10,11].

Assessment prior to resection

The current staging of superficial neoplasms includes careful white light endoscopy to visualize the area of neoplasia and to detect whether there is any concurrent disease. There is a need to identify the margins of the neoplasia, which often are only apparent with enhancement. This is often enhanced by using chromoendoscopy with topical contrast agents such as indigo carmine, methylene blue, toluidine blue, acridine orange, and crystal violet [12]. All of these dyes are absorbed by the mucosa with the exception of indigo carmine, which is strictly a contrast dye. The absorptive dyes are less commonly used, as some of these agents, such as acridine orange, will bind to the DNA within cells. This provides good nuclear contrast but may be carcinogenic. Optical methods of providing

contrast include narrow band imaging or autofluorescence imaging which permit visualization of vascular and mucosal patterns [13[•],14].

Endoscopic ultrasound is usually performed to stage the depth of the lesion. This is probably its weakest point in terms of reproducibility and validity. Often endoscopic ultrasound can only stage superficial lesions correctly about 40–60% of the time [15]. The need for endoscopic ultrasound for performance of mucosal resection is limited [16,17]. When performed for staging, it is apparent that high-frequency ultrasound probes are needed to stage early lesions, whereas the echoendoscopes are needed for investigation of lymph node status. However, this is not necessary for low-risk lesions such as lesions smaller than 1 cm without ulceration that lift easily with injection prior to resection. Other imaging techniques such as positron emission tomography (PET) or computed tomography (CT) scans are done to look for meta-static disease. It can be argued that in patients with very superficial cancers, this is not necessary, although it is often part of clinical practice to perform staging imaging studies for all neoplastic lesions.

Techniques of resection: endoscopic mucosal resection

In the United States, the most common way to perform EMR is either using the band ligation technique or cap technique. Both of these techniques involve the use of suction through an endoscope with a friction fitted cap to create a pseudopolyp. The cap technique (Olympus Corporation in Center Valley, Pennsylvania, USA) and band technique (Cook Medical, Indianapolis, Indiana, USA) are the two available devices.

In general, the band ligation device, which is very similar to a variceal banding device, is the most easily applied. This is because it can be done without any preinjection and the technique itself is very similar to variceal ligation. The area of abnormality is identified, suctioned into a cap similarly to variceal banding, and the band is released to capture the area of abnormality (Fig. 2). A hexagonal snare can then be used to remove the area of tissue using a pure coagulation setting. The snare can be applied above the band, below the band, and it can even cut through the band. The tissues are generally retrieved after multiple resections are performed using an endoscopic polyp retrieval basket. As this technique requires that the tissue be easily movable to suction into the cap, it is really best used when the patient is initially evaluated and has not had prior treatment or scarring to the esophagus or stomach. Such scarring can prevent the band from capturing the tissue. After six resections are performed, another device must be deployed if additional resections are needed. The major strengths of this device are ease of use, ability to perform multiple side-by-side resections to piecemeal remove large areas of mucosa, and the ability to maintain a resection snare within the endoscope (if the banding device is used in combination with a therapeutic endoscope). The weaknesses are the lack of ability to localize site of removal of a single resection unless the endoscope is withdrawn, the need to have fairly pliable tissue in order to resect a lesion, and the decreased field of view that occurs with the bands obscuring lateral vision. It is for the latter reason that the author usually recommends preinjection of a dilute epinephrine (1 : 200 000) saline solution to both confirm the pliability of the tissue and decrease any bleeding that may obscure visualization.

The cap technique was actually developed first and involves using a cap with a lip on the distal end. The targeted lesion is lifted with a submucosal injection of a saline epinephrine solution. This aids in permitting safe removal of the tissue above the muscularis propria. A snare can be positioned around the lip and then tissue suctioned through the opening in the cap and then the snare closed. The most difficult part of this procedure is placement of the snare around the lip of the cap (Fig. 3). Once the snare is closed around the suctioned tissue, the snare is pushed out of the cap and the tissue ‘tugged’ to assess whether the tissue

captured actually is only mucosa or if traction appears to move the entire wall, that there is a possibility that the muscularis propria is also entrapped (Fig. 4). The technique itself requires more experience and is usually more cost-effective when applied in situations where fewer resections are required. In addition, the cap technique is useful when the patient returns for additional mucosal resection, as the cap technique can resect tissues that cannot be suctioned as far into the barrel as required for the banding technique. The tissue is suctioned into the cap and the endoscope is withdrawn. The strengths of this technique are the ability to decrease the cost if only one or two resections are required, the ability to resect tissues that are less flexible, and the ability to retrieve the targeted tissue. The weaknesses are the difficulty in positioning the snare around the tip of the cap, the need to re-intubate the patient should a second resection be required, and both the techniques have been shown to resect approximately the same size of tissue.

Endoscopic submucosal dissection

This technique is also popularized in Japan for en bloc resection of superficial neoplasms. It is really indicated for the large raised or flat lesions of the stomach or esophagus. Generally speaking, the area of interest is first carefully marked using cautery, as once the resection begins, it is difficult to determine the boundaries of the lesion that needs to be removed. After this is done, a viscous fluid is injected submucosally to ensure there is a cushion underneath the lesion to allow dissection. In the United States, the most common viscous fluid is Gonak or hydroxypropylmethyl cellulose. A number of substances have been used in the past including hypertonic saline, 50% glucose, hyaluronic acid, 10% glycerol, sodium alginate solution, and fibrinogen, but most have been replaced with cellulose solutions because of their decreased cost and commercial availability in the United States. It has been reported that hydroxypropylmethyl cellulose can produce inflammation when injected submucosally. The solutions usually have a dye such as indigo carmine added to them to allow the endoscopist to quickly visualize the submucosal space which will be stained blue.

The cutting tools themselves are similar in dimensions to a needle knife but often have more angulated tips or a nonconducting tip to prevent inadvertent puncture of the muscularis propria or a blood vessel. The dissecting knives are used to grab and then cut through the sub-mucosal fibrous tissue. The cutting devices themselves range from triangle tip knife, insulated tip knife, flex knife, fork knife, hook knife, needle knife, and flush knife [18–26] (Fig. 5). All of these knives have been invented by mainly Asian physicians to enable rapid ESD. The variety of available knives often represents improvements in various phases of the dissection. The insulated tip knife and the flex knife were designed to decrease the risk of perforation from the sharp needle knife, which was initially used. The triangle tip knife has a sharp edge to permit better mucosal incision but has a blunt tip as well to permit cautery as well as dissection. The flush knife has a channel in the center that allows flushing of water to enhance visualization in case of bleeding. None of the knives have been clearly shown to be superior to the other and seem to yield similar results in expert hands. ESD can be completed with a single knife, but often for expediency can be completed with a snare after the lesion is incised, circumscribed and dissected free of the submucosal for the most part. Cautery is most commonly applied with an electrocautery unit using a blended current with primary coagulation. Pulsed electrocautery is commonly used to allow greater control.

In the past, it was described that the submucosal dissection had to be performed by first circumferentially cutting around the lesion (Fig. 6). At the current time, a number of experts now incise an area distally and proximally around the lesion, leaving the lateral margins intact to retain more of the viscous fluid. Once the tissue is more than semicircumferentially dissected, it retracts revealing the submucosa. The endoscope has a small flexible dissection cap fitted as shown in Fig. 6, which permits the user to lift the edge of the dissection and insert a cutting knife. The results of this treatment can be seen in Fig. 7, in which a large 4-

cm gastric cardia lesion has been removed. Although this can be done with standard diagnostic endoscopes, for areas such as the cardia, which can be difficult to access, specialty endoscopes have also been created such as the multibending endoscope which can flex at two different points allowing easier access to lesions that must be approached in the retroflexed position [27].

Comparisons of endoscopic submucosal dissection and endoscopic mucosal resection

Although there are no randomized prospective large studies of ESD and EMR for neoplastic lesions, several retrospective cohort studies have been reported. In early gastric cancer, it appears that ESD is significantly more likely to result in higher en bloc resection rates (93 versus 34%) and higher rates of being recurrence free at 5 years (100 versus 83%) [28**]. In retrospective analysis, gastric lesions less than 1.5 cm have a high rate of complete resection with EMR as with ESD. It has been shown in a prospective randomized study of strip biopsy versus ESD that strip biopsy was as effective as ESD in lesions smaller than 1.5 cm [29]. A recent meta-analysis of 15 nonrandomized studies found that ESD was superior to EMR in all size categories including those with lesions less than 1 cm but was associated with a 4.09 odds ratio of perforation and a 2.2 odds ratio of having bleeding [29]. In a recent large series of 1000 gastric cancer patients from multiple centers in Korea, the perforation rates were found to be 1%, with a bleeding complication rate of 16% [30]. These results are substantially higher than EMR complications from our own institution which has a bleeding rate of 2 and a 0% perforation rate in esophageal EMR. A recent innovation with a jet hybrid knife allows injection of more submucosal fluid during dissection, which appears to decrease risk of bleeding and perforation during ESD to levels that occur with EMR, although this was only done in an animal model [3].

Conclusion

EMR and ESD are both techniques designed to remove large areas of tissue. EMR appears to be more appropriate for smaller lesions (<1.5 cm in diameter) and can be completed in less time and with fewer complications than submucosal dissection techniques. ESD is a method to resect larger lesions en bloc to preserve knowledge of neoplastic invasion but is associated with far more significant complications. Both techniques provide increased volumes of tissue to permit better assessment of risk factors for tumor metastasis and establish a definitive diagnosis. EMR can be used to remove larger lesions in a piecemeal fashion but leads to increased recurrence when applied in this way. The instrumentation is different for each of the techniques, with the EMR more likely to be performed with a snare, whereas the ESD requires a cutting device and potentially a different type of endoscope to access more difficult to reach areas.

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Figure 1.
Gross lesion description

Figure 2. Endoscopic mucosal resection with banding cap

This device is similar to a variceal ligation device. The abnormal area of mucosa is banded to create a pseudopolyp and then can be removed with a hexagonal snare.

Figure 3. The cap technique with the snare seen on the left positioned around the lip of the cap, which is friction fitted at the tip of the endoscope
Tissue is suctioned into the cap and the snare closed to remove the captured mucosa.

Figure 4. In the cap technique, after the tissue is captured within the prepositioned snare, the tissue is pushed out of the cap and the reaction of the wall of the gastrointestinal tract to repeated traction is assessed to determine whether the captured tissue represents primarily mucosa or whether there is evidence of whole wall motion, in which case the possibility of entrapment of muscularis propria must be entertained. This is a so-called 'tug sign'.

Figure 5. A variety of endoscopic submucosal dissection knives

From left to right, these include the hook knife, the ceramic tipped or insulated tip knife, the flex knife, the needle knife, and the flush knife.

Figure 6. Endoscopic submucosal dissection is routinely commenced by first beginning to circumscribe the lesion and beginning submucosal dissection
The tissue quickly retracts once the dissection becomes semicircumferential. Shown is the appearance of the tissue through a dissection cap.

Figure 7. Endoscopic submucosal resection of proximal gastric lesion. Approximately a 5-cm lesion was removed through careful dissection using a hook knife
Areas such as the gastric cardia are difficult and should only be attempted by experienced endoscopists.

Table 1

Indications for endoscopic mucosal resection or endoscopic submucosal dissection

	EMR	ESD
Lesion size	<1.5 cm	>1.5 cm
Lesion type	Flat, raised lesions	Flat lesions
Cancer histology	Well differentiated	Well differentiated
Angiolymphatic invasion	None	None
Submucosal lesions	Superficial submucosa	Possible

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.