Endoscopic Mucosal Resection for Early Esophageal Cancer

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In the United States and Europe, the focus of endoscopic treatment for esophageal cancer has been the palliative management of advanced cancers. In Japan, where cancers of the esophagus and stomach have a high prevalence, the focus has been the early detection of esophageal cancer and the development of endoscopic modalities to curatively treat cancer. Advances in the endoscopic and endosonographic diagnosis of early esophageal cancer have paralleled the development of endoscopic resectional techniques, collectively referred to as endoscopic mucosal resection (EMR). EMIR has achieved a high level of sophistication in Japan, where endoscopists use double-lumen endoscopes, special overtubes, and innovative accessories to achieve complete and safe excision of early esophageal cancer. In appropriately selected patients, EMR offers an attractive alternative to conventional surgical management. Interest for EMR techniques is growing in the United States and Europe as a result of increased awareness of early cancer and the potential for cure endoscopically.

Endoscopic mucosal resection (EMR) refers to removal of a mucosal lesion using a diathermic snare. This technique was first described as a diagnostic method to obtain adequate tissue samples for histopathologic diagnosis by Ottenjann et all in 1973. By using a standard snare for colonic polypectomy, the authors excised large particles of tissue in the upper gastrointestinal tract in 11 patients. The specimens, which included the mucosa and in some cases the submucosa, enabled a histopathologic diagnosis that provided more information than forceps biopsy alone. In 1974, Deyhle et al[2] in Zurich explored the therapeutic potential of EMR for early gastric cancer. The authors removed a 6 mm polypoid, well-differentiated adenocarcinoma in the stomach using a polypectomy snare; histopathologic study revealed that the tumor had been nearly completely excised, except for one focus of penetration into the muscularis mucosa. The patient underwent surgery, and the operative specimen demonstrated no residual tumor or lymph node metastasis. It was not until the mid-1980s that Japanese authors popularized the application of EMR to treat early cancers of the upper gastrointestinal tract. In the United States and Europe, techniques of EMR have begun to receive greater attention. This article describes recent developments in EMR that have made this technique easier and safer for the interventional endoscopist.

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Curative Potential of EMR

EMR should be regarded as a diagnostic procedure that has therapeutic potential. After EMR, the definitive treatment strategy depends on the histopathologic findings of the resected specimen. Factors to consider are the tumor differentiation grade, depth of tumor infiltration, presence or absence of invasion of lymphatics or vessels, and tumor-free resective margins. EMR has curative potential when the cancer is sufficiently superficial in its infiltration depth to allow for complete excision and there is a low risk of lymphatic spread.

Superficial gastrointestinal cancers are commonly referred to as "early" cancers. It is important to note, however, that early cancers are defined as cancers that involve the mucosal or submucosal layers; hence they are not necessarily limited to the mucosal layer of the gastrointestinal wall. This corresponds to a T1-stage cancer according to the 1987 TNM classification. Because the risk of lymphatic spread increases with infiltration depth (see later), a more differentiated classification system is warranted for early cancer. The 1997 revised TNM classification system for esophageal cancer is an improvement over the 1987 classification because it distinguishes between carcinomain-situ (intraepithelial cancer) and T1 stage cancers (invasion into the lamina propria or submucosa).3 A more differentiated classification is offered by the Japanese Society for Esophageal Diseases (Table 1), which distinguishes between intraepithelial invasion (T1-ml), infiltration of the lamina propria (T1-m2), and infiltration of the muscularis mucosae (T1-m3). Furthermore, this classification differentiates between infiltration of the superficial (T1-sml) and deep submucosa (TI-sm2). This classification should be used when defining the infiltration depth of early cancer.

Differentiated staging of the infiltration depth of early cancers such as that provided by the Japanese Society for Esophageal Diseases is important because the risk of lymphatic spread increases with progressive infiltration depth.4 The risk of metastatic spread is practically nil when invasion is limited to the intraepithelial layer, around 10% when the muscularis mucosa is invaded, 20% when the superficial submucosa is invaded, and 40% when the deep submucosa is invaded. Based on these data, Japanese authors consider stage T1-ml and T1-m2 early cancers to be absolute indications for EMR, whereas stage T1-m3 and T1-sml early cancers are relative indications. Stage T1-sm2 cancers are poorly suited for EMR because of the high risk of associated metastatic lymphatic spread.

Apart from infiltration depth of the neoplasm, the differentiation grade and lesion size have been found to affect the risk of lymphatic spread. Well-differentiated carcinomas tend to metastasize less than undifferentiated carcinomas. In Kawai's early

TABLE 1. Japanese Society for Esophageal Diseases Classification of Early Cancer

TI-ml: intraepithelial invasion (carcinoma in situ)
Ti-m2: invasion of the lamina propria mucosae
T1-m3: invasion of the muscularis mucosa
T1-sm1: superficial layer of submucosa involved
Ti-sm2: deeper layer of submucosa involved

that were limited to the mucosa had metastasized, compared with none of the well-differentiated mucosal carcinomas. Lymph node metastases also occurred more often in lesions with a diameter greater than 2 cm. Japanese authors consider undifferentiated cancers and cancers larger than 3 cm to be unsuited for EMR.

Use of Vital Dye Staining Before EMR

Early cancers of the esophagus will be missed if the endoscopist does not pay close attention to discrete mucosal abnormalities. The flat type II lesions are particularly difficult to distinguish from the surrounding normal mucosa. Detection of an early cancer can be greatly aided by dye staining. The dyes are applied through a catheter passed through the biopsy channel of the endoscope. Special dye spray catheters have been developed (Olympus PW 6P-1, Tokyo, Japan) for staining, but one can also use a standard endoscopic retrograde cholangiopancreatography (FRCP) cannula.

Lugol's solution (compound iodine solution) is a vital dye that is most commonly used for the detection of early esophageal cancers.6 It is actively absorbed by nonkeratinized, squamous epithelial cells containing glycogen, leaving dysplastic epithelium and squamous cell carcinoma that contains little or no glycogen unstained. Thus, Lugol's solution will highlight dysplastic or neoplastic tissue in the esophagus. Absent staining is not 100% specific for dysplasia or neoplasia, as inflammatory epithelium and columnar epithelium have low or absent glycogen content.

I first inhibit peristalsis with an anticholinergic such as glucagon or Buscopan and then generously spray 1% Lugol's solution over the mucosal surface (10 to 20 mL). One to 2 minutes later, I rinse the surface off with 10 to 20 mL of water and look for areas of lesser or nonstaining. Biopsies are taken from the unstained areas. After 5 minutes, the stain disappears, making the distinction between stained and nonstained areas difficult. It is important to exclude an allergy to iodine before using Lugol's solution.

An alternative dye that I use to highlight an early cancer is indigo carmine. Indigo carmine works differently from Lugol's solution in that it is not a vital dye that is absorbed. Rather, it is a contrast dye that highlights irregularities in the mucosal architecture. Ten to 20 mL of a 0.2% solution is sprayed evenly over the mucosal surface. It is nontoxic and no side effects have been reported.

Marking the Cancer Before EMR

It is advisable to mark the outer margins of a lesion before EMR, particularly if a submucosal injection is performed before EMR. Local injection may obliterate the contours of the lesion and make it difficult to target. I prefer to make four-point markings around the lesion using the tip of the snare (advanced slightly from the sheath) alternative method is to inject small deposits of dye around the lesion, but the dye may dissipate over time.

Resective Techniques

Resective techniques can be broadly divided into three categories: inject-and-cut, lift-and-cut, and suck-and-cut.

Inject-and-Cut

From a technical standpoint, EMR is comparable to snare excision of sessile adenomas in the colon. Very flat adenomas are often difficult to remove using a snare alone. In 1973 Deyhle et al' described submucosal injection with physiological saline as a technique for raising sessile polyps in the colon to facilitate snare excision. The authors performed the technique in the dog model and in seven patients. In dogs, 0.9% saline was injected into the mucosa/submucosa interface, and the raised mucosal tissue was resected using a polypectomy snare. There were no perforations and ulcerative defects completely healed within 1 week. In the seven patients, saline injection enabled removal of sessile polyps in all without complication.

Submucosal injection may improve the safety of EMR by providing a buffer zone for resection. The injected saline separates the lesion in the mucosa/submucosa from the underlying muscularis propria and thereby minimizes the risk of perforation. The absence of visible raising of the tumorcontaining mucosa after saline injection suggests that the tumor is adherent to or invading into the muscularis propria, which contraindicates EMR. Normal saline is most commonly used to perform submucosal injection, but a variety of other agents have been used, including hypertonic saline, hypertonic glucose, glycerol solution, and dyes such as indigo carmine. No substance has been identified to be superior to others.

Although submucosal injection is a seemingly straightforward procedure, it can be technically challenging and may have drawbacks. It is important to note lifting of the mucosa during injection, indicating that the injectate is entering the submucosal plane. The needle may need to be maneuvered to and fro to establish the right plane for injection. The injection of saline into the submucosa will elevate a superficial lesion, but this elevation is not always polyp-like. In the esophagus, the saline tends to diffuse quickly along the circumference of the esophageal wall, leaving the lesion relatively unchanged in appearance. Diffusion of the saline into neighboring tissue may result in the flattening of an elevated lesion, which will make snare capture of the lesion more difficult.

A further problem that may be encountered is the alteration of the lesion by the injected saline, which can cause blanching, distort the borders, and even conceal the lesion.

Lift-and-Cut

In 1976 Martin et alb described the lift-and-cut method to biopsy a submucosal lesion using a double-channel endoscope. The authors used a forceps in one channel for lifting and a snare in the other for resection. This technique was initially developed to provide a chronic bleeding ulcer model; however, submucosa was noted on each tissue sample, and the application for large particle biopsy was reported. In the dog model, perforation occurred in 2 of 81 animals, but large samples measuring more than 1.5 cm were obtained in this study (the

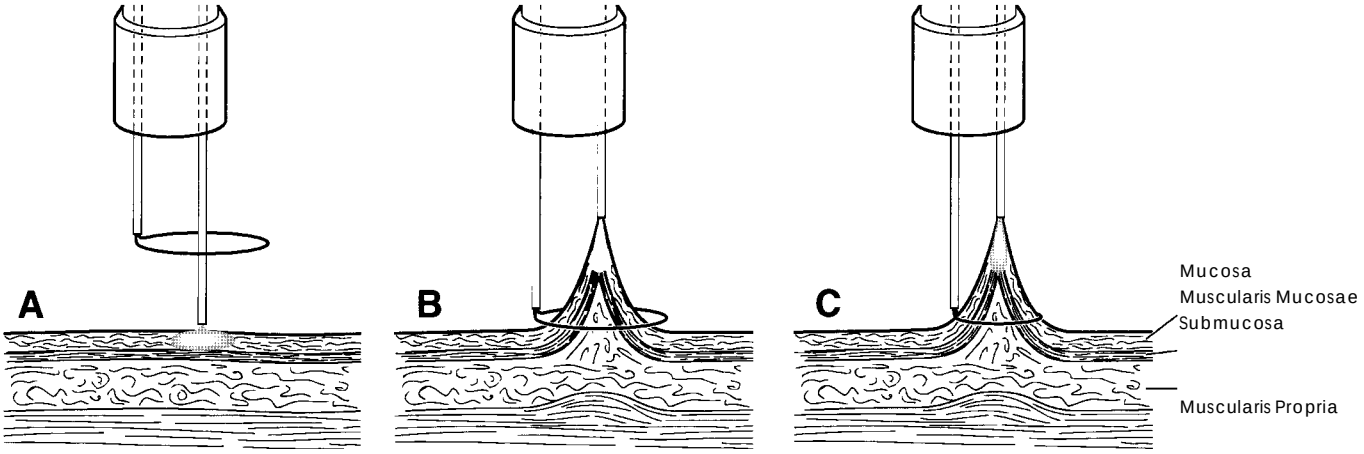

Fig 1. Lift-and-cut technique of EMR using a double-channel endoscope. (A) The double-channel gastroscope is positioned for EMR. A polypectomy snare and a biopsy forceps are introduced through each of the channels. The snare is opened and the forceps is advanced through the open loop. (B) The target mucosa is grasped with the forceps and tented by withdrawing the forceps back into the port. (C) The snare is closed around the pedicle and the tissue is cut with cautery. The resected specimen is retrieved with the forceps for histological examination.

aim was to produce a bleeding ulcer!). The procedure was performed without complication in two patients.

Extending the lift-and-cut technique to perform EMR, Tada et a19 described strip biopsy in the Japanese literature using double-channel echoendoscopes to excise early cancers. The authors first injected approximately 3 to 5 mL of physiological saline into the submucosal layer before using the lift-and-cut technique. The authors reported that the whole mucosal layer and a substantial portion of the submucosal layer could be safely resected to a depth of 2 to 3 mm.

The procedural steps of the lift-and-cut technique using the double-lumen endoscope are outlined in Fig 1.

The obvious drawback of the lift-and-cut technique is that it requires a double-channel endoscope to enable simultaneous lifting and cutting. Double-channel endoscopes are popular in Japan, but are not commonly used in the United States or Europe. To overcome this drawback, Takechi et also have described an approach using two slim diameter endoscopes inserted alongside one another, whereby one endoscope is used to lift the lesion while the other is used to resect the mucosa at its base. Although innovative, this approach is not practical. I have found that mucosectomy using the doublechannel endoscope requires considerable skill and is fairly blind, as the snare cannot be visualized as it is tightened around the base of the raised lesion. The technique is difficult to perform when the angle of access is tangential such as along the lesser curvature of the body or the posterior wall of the antrum.

Suck-and-Cut

The goal of this technique is to create an artificial polyp from the tumor-bearing mucosa using suction. A decade ago Japanese endoscopists developed a special EMR overtube to achieve this goal. The overtube (Olympus) is transparent and has an outer diameter of 18 mm with an open-circle slip at the tip. The tube contains a small accessory channel for insertion of a snare; the snare exits at the open-circle slit. To achieve effective suction, the tube is equipped with two air-tight valves inside the handle. The procedure is outlined in Table 2.

Using the EMR overtube in the dog model, Inoue and Endo" were able to circumferentially resect the mucosa, leaving the muscularis propria intact without any perforation or bleeding. Reepithelialization occurred within 2 weeks, with mild stenosis occurring in only one dog. The technique was used in 11 patients, enabling almost total circumferential mucosal resection without major complications.

The obvious drawback of the overtube method is the tube itself, which is not approved by the Food and Drug Administration (FDA) for EMR in the United States. Insertion of the 18 mm tube is not easy and quite unpleasant for the patient. Not surprisingly, Japanese authors have sometimes required the use of general anesthesia for tube insertion. No major complications have been reported using the EMR overtube, but the risk of perforation is of concern. Perforations have resulted from the placement of standard overtubes and the Stiegman-Goff band ligation overtube.

A major evolutionary step of the suck-and-cut technique occurred with the recognition that the equipment used for the basic technique of variceal band ligation could be applied for mucosectomy Inoue et al [12] described the use of the transparent cap adapter included in the Stiegmann-Goff Endoscopic Ligator Kit (Bard Interventional Products, Tewks

TABLE 2. Suck-and-Cut EMR Using the Overtube Method

1. With the gastroscope inserted through the EMR overtube to visually guide the procedure, the overtube is positioned in the esophagus so that the lesion is exposed at the open-circle slit of the tube.
2. A snare is passed through the accessory channel of the tube and the snare is opened.
3. A grasping forceps is inserted through the working channel of the gas troscope, and the forceps is passed through the open loop of the snare.
4. The lesion is grasped with the forceps and pulled into the open-circle slit. The snare is then closed around the pseudopedicle created by this maneuver.

bury, MA) to perform EMR. The cap has an outer diameter of 12 mm and is 10 mm long. After submucosal injection, the lesion was sucked into the cap and transected at its base with a minisnare (Olympus SD-7P) that was inserted through the working channel. The authors successfully resected 16 mucosal lesions in the esophagus, stomach, and colon.

Sakai et all' and Fleischer et a1[14] applied both the equipment and the technique of variceal band ligation to achieve EMR. Treating the tumor-bearing mucosa in an analogous fashion to a varix, they aspirated the lesion into the Stiegmann-Goff cap and then applied the rubber band to the base of the tumor-bearing mucosa. Sakai et al[13] used the band ligator in six patients with TIN0 early tumors up to 25 mm without complications. Fleischer et a1[14] used combined submucosal injection and tissue band ligation followed by mucosectomy in the animal model and in five patients with moderate dysplasia or superficial esophageal carcinoma without morbidity

The Stiegmann-Goff cap was recently modified by Inoue et al[15] to facilitate EMR using the snare technique (Fig 2). The Inoue cap adds a circular rim at the tip that captures the opened snare loop. The loop automatically aligns itself along the rim when the loop is opened inside the cap. The modified cap is manufactured by Olympus, with pending FDA approval in the United States. The cap comes in various diameters to accommodate different endoscopes, two shapes (straight and flared), and two designs (straight and oblique distal end). The cap with an oblique distal end is recommended for EMR in the esophagus, because this will accommodate the more tangential approach to the lesion. The technique of EMR using the Inoue cap is detailed in Table 3 and illustrated schematically in Fig 3.

Inoue has performed more than 170 cases of EMR using the modified cap; he reported one perforation and one severe stenosis (personal communication). Esophageal perforation healed with conservative measures alone.

A drawback of EMR using the cap attachment is the limited aperture diameter of the cap, which measures 12 mm. This

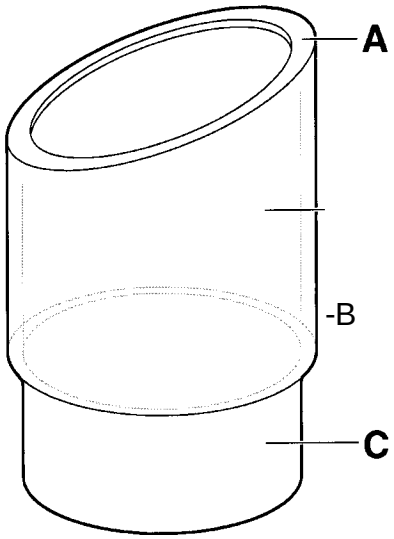

Fig 2. Drawing of the suction cap designed for EMR (Olympus MH-587) with an obliquely cut distal end. The base of the cap has a friction mount (C) that is retrofitted onto the tip of an endoscope. A rim (A) at the tip captures the snare loop as it is opened inside of the body of the cap (B).

TABLE 3. Technique of EMR Using the Inoue Cap

1. The selected cap is attached to the tip of the gastroscope. Although there is a friction mount, the cap may need to be secured to the gastroscope with adhesive tape.
2. Submucosal injection of diluted saline (1:500,000) is performed to lift the lesion.
3. A minisnare is inserted through the gastroscope and prelooped. This is done by positioning the cap against the wall of the esophagus, applying moderate suction to seal off the opening of the cap, and opening the snare within the cap. The opened snare will automatically align itself along the rim of the cap. It is important that the outer sheath of the snare is advanced into the cap, and its tip is positioned at the level of the rim.
4. The target mucosa is sucked into the cap using full-strength suction. Once the mucosa fills the interior of the cap, the snare is closed.
5. The snare is advanced, allowing the cap to be removed from the pseudopolyp. The pedicle is tented away from the wall during applica tion of diathermy to transect the mucosa.
6. The transected lesion is sucked into cap and the gastroscope is with drawn to retrieve the specimen for histological study.

obviously limits the surface area that can be excised (in my experience up to 10 mm). Incomplete excision may result from the limited diameter of the cap, and also from difficulties centralizing the cap over the lesion. Piecemeal excision is problematic, as complete, uniform resection is difficult to achieve. The cap needs to be positioned a safe distance away from a treated area to avoid aspiration of the muscularis propria, sometimes leaving an intervening tissue bridge or island behind.

Simplified Suck-and-Cut Technique in the Esophagus

The techniques described so far require various accessories to facilitate the resection of early cancers with a snare. In my experience, however, flat esophageal lesions in the esophagus can be resected safely with a snare alone. I suck the tumorbearing mucosa into an opened snare and then close the snare while suction is maintained (Table 4, Figs 4 and 5). This technique simplifies EMR to the use of a single accessory-a standard polypectomy snare. Submucosal injection before EMR is optional using this technique.

With the simplified technique, it is important to be able to create enough suction to aspirate the tumor-bearing mucosa into the snare loop. This requires a therapeutic (large-channel) gastroscope. The choice of snare is also important. The sheath should be of small diameter to allow more room in the working channel for suction. A standard-sized snare (approximately 3 cm in span) is recommended so that the entire lesion can be removed (with tumor-free margins) after a single snare resection. Piecemeal resection of a lesion should be avoided because the pathologist will not be able to verify the completeness of the resection. The snare wire should be stiff enough to allow the operator to press it flatly against the mucosa. In this respect, a monofilament wire is preferable to a braided wire. A special snare with barbs (Olympus SD-16 L) to grip the mucosa for EMR is available, but the advantage of this design is not clear.

The type of current recommended for EMR has not been addressed in the literature. Similar to polypectomy in the colon, I have used pure coagulation current for EMR. I have never witnessed bleeding after EMR in the esophagus.

My experience with the simplified suck-and-cut technique is still too limited to recommend it for broader use. Preliminary data in seven patients with early esophageal cancers have

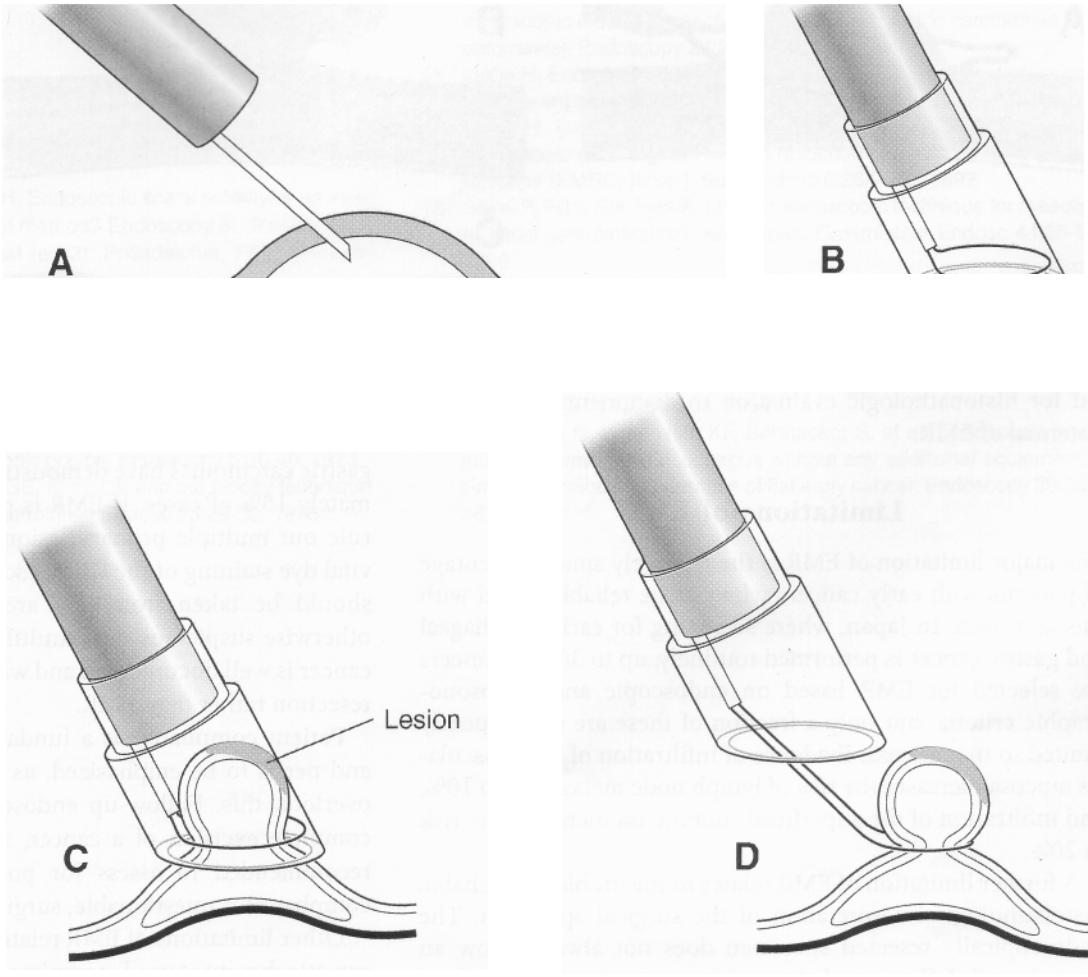

Fig 3. Suck-and-cut technique for EMR using the modified suction cap. (A) The lesion is first injected with saline to lift the lesion from the underlying muscularis propria. (B) The snare is deployed inside of the cap (prelooping). (C) The lesion is sucked into the cap, creating a pseudopedicle. The snare is closed around the base of this pseudopedicle. (D) The lesion is resected with diathermy current.

shown that EMR can be achieved without complication." Complete removal of the cancer was achieved in all cases with .: single treatment.

Post-Resection Processing

Because the curative potential of EMR depends on the histopathologic findings of the resected specimen, utmost care should be taken not to traumatize or distort the specimen after EMR. I prefer to use a basket rather than a snare to retrieve the specimen, because a snare may cut into the tissue. The basket should be closed gently around the specimen to avoid crushing artifact. Once the specimen is retrieved from the patient, it is important that it be oriented correctly for histopathologic interpretation. My approach is to pin the specimen to a piece of cardboard with the resected surface facing upwards. The specimen is pinned at four points to prevent shrinkage after it is placed in formaldehyde. One can tattoo the resected surface with India ink.

TABLE 4. Technique of Simplified Suck-and-Cut EMR

1. The lesion is positioned at the 6 o'clock position by rotating the endoscope to optimize access for EMR.
2. The polypectomy snare is inserted through the endoscope working channel and opened.
3. The snare is positioned around the lesion and pressed flatly against the mucosa.
4. Continuous aspiration is applied to draw the lesion into the loop of the snare.

Role of Endosonography Before EMR

As with any esophageal neoplasm, thorough staging with endoscopic ultrasonography (EUS) is essential to determine the most appropriate intervention. This is even more important for small lesions. When there is no evidence of involvement of the submucosa or lymph nodes, EMR may be curative.

Early esophageal cancer, by definition, demonstrates disruption that is limited to the first three layers demonstrable by EUS. Endosonographic staging of early cancer has been improved by the recent development of high frequency catheter probes (miniprobes). Using frequencies of 12 MHz or higher, the miniprobe produces a high resolution image of the wall layers of the esophagus that will depict seven to nine layers. In some instances, the muscularis mucosal layer can be seen.

Although EUS using high frequency miniprobes has made an important contribution to the preoperative staging of early cancer, it is important to recognize that staging is not 100% accurate. Understaging can occur due to micrometastases, and overstaging can occur due to tumor-associated inflammation and tangential imaging. It is difficult to exclude invasion of the submucosa. Because of the limitations of endosonography, it is imperative that the resected specimen be retrieved and submit

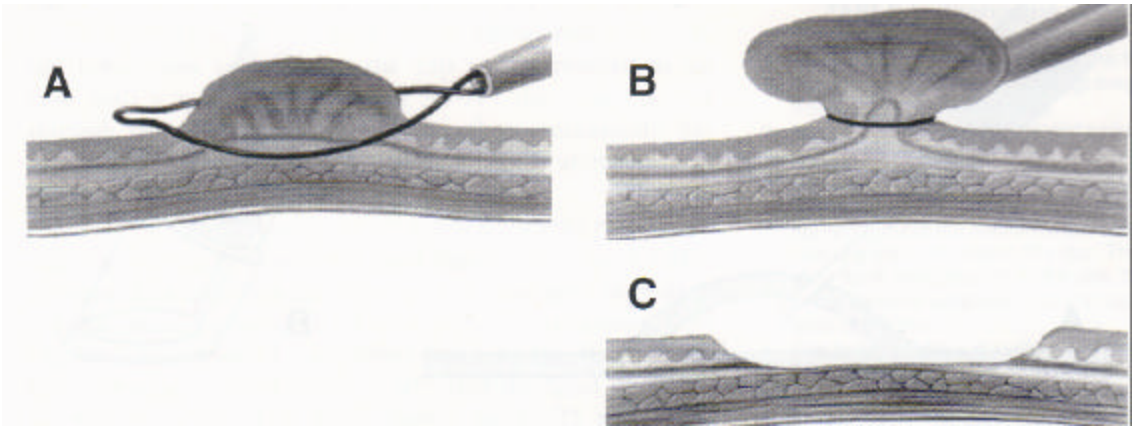

Fig 4. Schematic drawing of EMR using the simplified suck-and-cut technique. (A) The opened polypectomy snare is positioned around the lesion and pressed flatly against the underlying wall. (B) Aspiration is applied and the snare is closed. The lesion is lifted as current is applied to prevent transmural extension of the burn. (C) The muscularis propria layer is exposed after snare excision.

ted for histopathologic evaluation to document the curative potential of EMR.

Limitations of EMR

The major limitation of EMR is the relatively small percentage of patients with early cancers who can be reliably cured with this approach. In Japan, where screening for early esophageal and gastric cancer is performed routinely, up to 30% of cancers are selected for EMR based on endoscopic and endosonographic criteria, but only a fraction of these are subsequently limited to the mucosa. Evidence of infiltration of the muscularis mucosa increases the risk of lymph node metastases to 10%, and infiltration of the superficial submucosa increases the risk to 20%.

A further limitation of EMR relates to the problem of reliable histopathologic interpretation of the surgical specimen. The endoscopically resected specimen does not always allow an unequivocal definition of the resection margins and depth of invasion. The epithelial tumor is often fragile, and the resective technique and the application of diathermy easily traumatize the mucosa. Completeness of tumor excision may be impossible to document, especially if a lesion has been resected piecemeal. Ambiguity regarding the completeness of resection and infiltration depth leaves lingering concern that an RO resection was not achieved.

The possibility of multifocality of an early cancer should always be considered before performing EMR. Esophageal and gastric carcinomas have demonstrated multifocality in approximately 15% of cases. If EMR is performed, it is imperative to rule out multiple primary lesions. It is advisable to perform vital dye staining of the entire esophagus before EMR. Biopsies should be taken from any areas that appear irregular or otherwise suspicious. The multifocal development of Barren's cancer is well documented and would argue in favor of surgical resection rather than EMR.

Patient compliance is a fundamental prerequisite for EMR and needs to be emphasized, as enthusiasts for EMR tend to overlook this. Follow-up endoscopy is mandatory to ensure complete excision of a cancer, and follow-up in intervals is recommended to assess for possible recurrence. If patient compliance is questionable, surgical removal is preferable.

Other limitations of EMR relate to technical problems. If the cap attachment is used, complete excision may not be possible, as discussed previously. Failure of the lesion to draw into the cap (or the snare) with aspiration should alert the endoscopist to the possibility of adherence to the muscularis propria.

Finally, it must be remembered that reports on EMR are primarily from Japan where a high volume of this procedure is performed and a high level of expertise has been achieved to execute these techniques effectively and safely. EMR in the

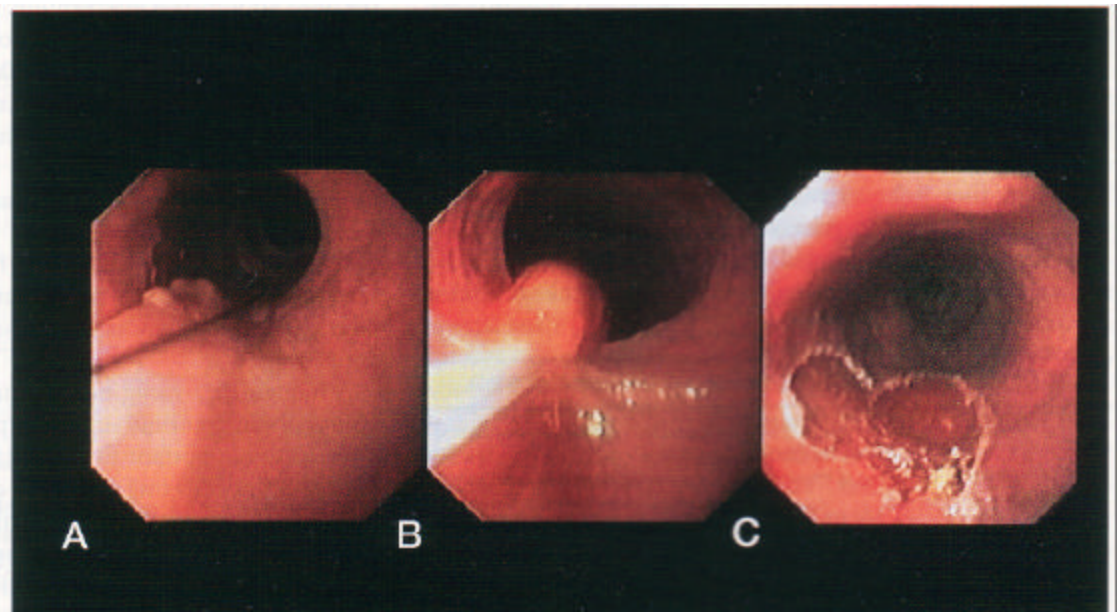

Fig 5. Endoscopic images showing EMR of a flat early carcinoma in the esophagus using the simplified suck-and-cut technique. (A) The opened snare is positioned around the lesion and pressed flatly against the underlying wall (left image). (B) As the snare is closed, suction is applied to draw the mucosa and submucosa into the snare (center image). (C) Appearance after EMR showing the exposed muscularis propria layer (right image).

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