Circumferential endoscopic mucosal resection in the swine esophagus assisted by a cap attachment

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Background: **The feasibility and safety of piecemeal, circumferential endoscopic mucosal resection of the distal esophagus are unknown. This study assessed this procedure in a porcine model.**
Methods: **Different techniques of endoscopic mucosal resection were tested in Phase I of the study in two animals. During Phase II, 6 pigs underwent piecemeal cap-assisted EMR of the distal esophagus. The mucosa of one half of the circumference of the distal 5 cm of the esophagus was resected. After complete endoscopic re-epithelization, endoscopic mucosal resection was performed on the remaining unresected hemi-circumference. Healing was promoted by daily administration of lansoprazole and documented by weekly endoscopy.**
Observations: **In Phase I, one perforation occurred during initial testing of cap-assisted endoscopic mucosal resection. Subsequent cap-assisted endoscopic mucosal resection led to homogenous and uniform piecemeal resection of mucosa. In Phase II, circumferential cap-assisted endoscopic mucosal resection was performed in 6 pigs without perforation or major bleeding. Complete endoscopic re-epithelization occurred over a mean of 3.6 weeks (range: 3-5). Strictures developed in 3 animals.**
Conclusions: **Piecemeal circumferential cap-assisted endoscopic mucosal resection is safe and feasible in the normal swine esophagus. Proper technique for cap-assisted piecemeal endoscopic mucosal resection is necessary to minimize the risk of perforation. Procedural complications include esophageal stricture formation.**

Barrett's esophagus, a complication of GERD, is associated with an increased risk for the development of esophageal adenocarcinoma.[1-4] Treatment of Barrett's esophagus is controversial. Acid-suppression therapy and fundoplication do not lead to regression of metaplastic epithelium. Endoscopic ablative therapies such as laser photoablation and contact thermal coagulation, combined with acid suppression, have been reported to eliminate metaplastic mucosa.[5] Photodynamic therapy has been used for treatment of dysplasia and superficial cancer associated with Barrett's esophagus.[6] Unfortunately these therapies have common drawbacks such as poor control of the depth of ablation, a risk that underlying

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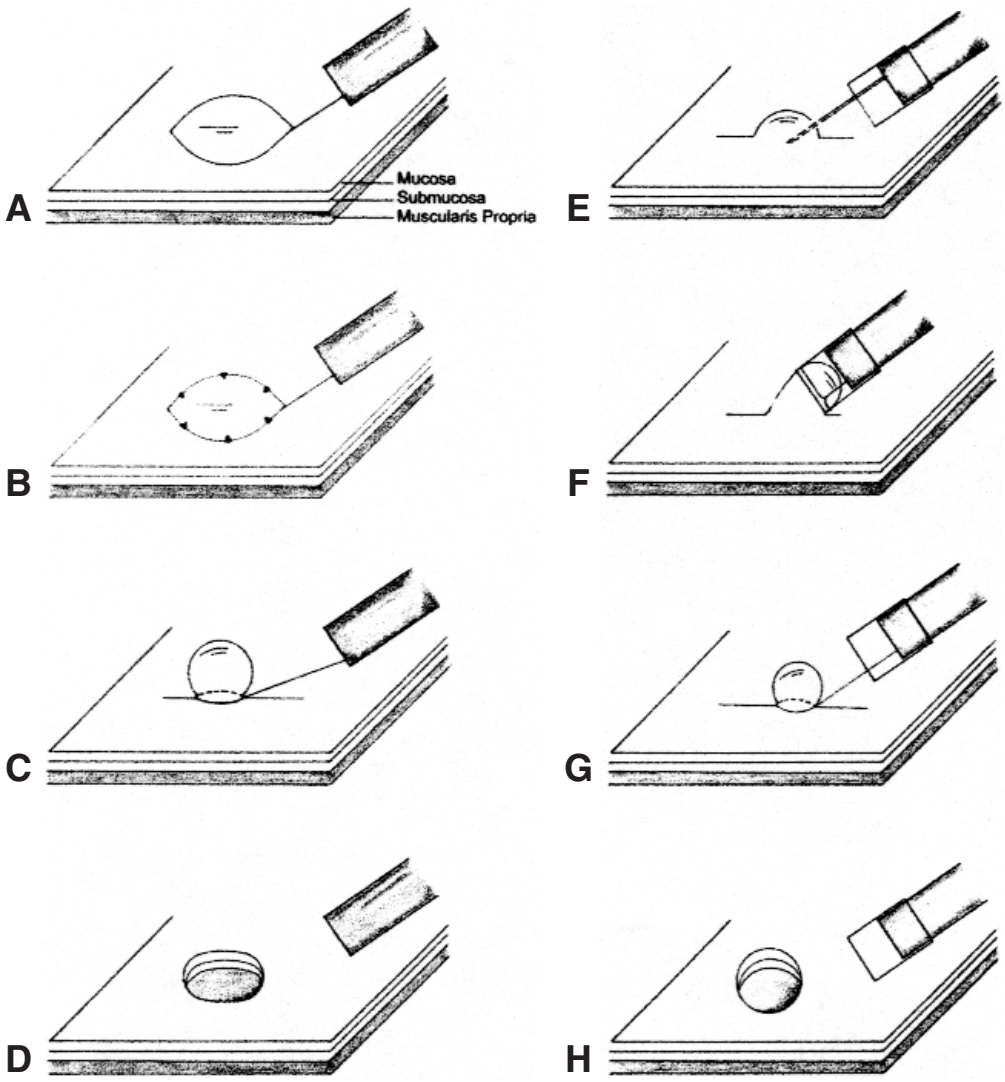

Figure 1. Schematic diagrams of EMR. **A-D,** Simplified "suck-and-cut" technique: **A,** open monofilament snare; **B,** open barbed snare; **C,** mucosa grasped within closed snare after application of suction; **D,** transected area. **E-H,** EMR with transparent cap: **E,** elevation of mucosa by injection of saline solution; **F,** mucosa suctioned into cap fitted to tip of endoscope and grasped within inserted snare; **G,** mucosa grasped within closed snare; **H,** transected area.

metaplasia may be present, relatively high cost, and the lack of tissue for histopathologic examination.[5]

The applicability of endoscopic mucosal resection (EMR) for the treatment of Barrett's metaplasia in humans has not been studied. However, EMR has been reported to be a therapeutic alternative to surgery for the treatment of early stage esophageal and gastric cancers.[7-10] It has also been used for diagnosis and treatment of high-grade dysplasia and early stage cancer of the esophagus associated with Barrett's esophagus.[11-15]

A variety of EMR techniques have been described since 1973 when Ottenjann et al.[16] demonstrated the technique of "big particle biopsy." Generally, a snare is used to resect a large area of mucosa after elevation from the underlying tissue with saline solution injection, forceps, or suction.

In the "suck-and-cut" technique with a cap, mucosa is separated from underlying tissue by submucosal injection of saline solution or other solution, and suction is applied through the accessory channel of the endoscope. Mucosa is drawn into an attached transparent cap and then excised electrosurgically with a snare. An overtube can be substituted for the cap. An endoscopic variceal ligating device can be used to band mucosa as is done for esophageal varices, and then a snare or a needle knife can be used to resect the banded mucosa. In the simple suction technique, mucosa is drawn through an opened snare positioned over the area to be resected without

using additional devices.[7,17] In the "inject-and-cut" ("strip biopsy") technique, mucosa is separated from the underlying tissue by submucosal injection and resected electrosurgically with snare or needle knife. In the "lift-and-cut" technique, a double channel endoscope is used. Mucosa is lifted with forceps and excised with a snare. Injection of saline solution may be used before lifting.[7,17]

The goal of the present study was to investigate the technical feasibility and safety of circumferential EMR of the distal esophagus in a porcine model by using different techniques. The porcine model was chosen because it closely approximates human GI tract anatomy and histology.[18]

MATERIALS AND METHODS

This study was approved by the Animal Subject Committee of our university (protocol No. 99157). Eight healthy male and female pigs (weight 25 to 30 kg) were used. The animals were fasted (with free access to water) beginning 18 hours before EMR. A mixture of 33 mg/kg of ketamine, 2 mg/kg xylazine, and 0.05 mg/kg atropine was administered intramuscularly. EMR was performed with the animals under general anesthesia, and follow-up procedures were performed with the animals under sedation with a propofol intravenous drip (Diprivan 1%, Zeneca Inc., Wilmington, Del.).

After induction of anesthesia and with the animal in a lateral recumbent position, the endoscopy was performed with a single-channel, forward-viewing videoscope (GIF 1T100, Olympus America, Inc., Melville, N.Y.). A small volume of gastric content was suctioned before each procedure for pH measurement (Alkacid Test Paper, Fisher Scientific Company LLC., Tustin, Calif.). EMR was performed in the distal 5 cm of the esophagus. The distal margin of resection was at the point of narrowing of the esophagus at the gastroesophageal junction. The proximal margin was 5 cm proximal to the junction as measured with the endoscope while using the plastic bite block for reference.

Variations of the "suck-and-cut" technique for EMR were tested in 2 animals (Fig. 1) in Phase I.[7,17] These included the following: (1) use of a prototype monofilament snare alone (Olympus); (2) use of a monofilament barbed snare (SD16L, Olympus) alone, and (3) use of a braided crescent snare (SD-221L-25, Olympus) in conjunction with a transparent cap, oblique type with rim (D402-142 12, Olympus) attached to the distal tip of the endoscope. By using the first 2 variations of the "suck-and-cut" technique, the mucosa was aspirated into the snare as it was closed. Submucosal injection of saline solution was not performed. For piecemeal resection, the opened snare was positioned at the edge of the prior resection site. With the third variation the mucosa, after submucosal injection of saline solution, was aspirated into the hollow chamber of the cap as the snare was closed for piecemeal resection; for successive resections, the outer margin of the cap was positioned at the edge of the prior resection.

A 5-cm long, hemi-circumferential segment of the distal esophageal mucosa was resected by using a transparent cap attachment in phase II of the study. Saline solution was injected into the submucosa before EMR to separate the mucosa from the muscularis propria. Blended electrosurgical current from a generator (737-XL, Birtcher, Los Angeles, Calif.) set at a power of 40 to 50 W was used for EMR. Mucosectomy was considered complete if the muscularis propria was visible and there were no bridges or islands of normal mucosa remaining within the 5-cm long hemi-circumferential resected area. Samples of the resected specimens were retrieved (Fig. 2) for histopathologic examination. All endoscopic procedures were recorded on videotape.

Figure 2. Pinned EMR specimen after resection.

After the procedure the animals were recovered and transported to the vivarimn. Buprenorphine 0.005 mL/kg (Buprenex, Reckitt and Coleman Products, Inc., Richmond, Va.) was administered intramuscularly to all animals for control of any possible postprocedural pain. A soft diet was given on the first postoperative day and then a regular diet the following day. Endoscopy and pH measurements were performed at 1-week intervals. When endoscopic evidence of re-epithelization of the resected area was observed, EMR was performed on the unresected half of the circumference of the esophagus, and the animals were followed endoscopically until complete healing was evident.

All animals were given 15 mg of lansoprazole (TAP Pharmaceuticals, Inc., Deerfield, Ill.) daily for the duration of the study by mixing the capsule with food. After completion of the study the animals were used for a further but separate study of EMR. The animals were then euthanized by intravenous administration of a veterinary euthanasia solution (Socumb-6GR, The Butler Company) at a dose of 1 mL/10 lb.

OBSERVATIONS

Phase I

The prototype monofilament snare used alone (variation 1) functioned well for the initial EMR but was unsatisfactory for piecemeal resection. The snare tended to either slip off the mucosa as it was closed, or mucosal bridges were left between EMR sites. Use of the barbed monofilament snare (variation 2) improved anchorage during piecemeal resection, but mucosal bridges were left between EMR sites.

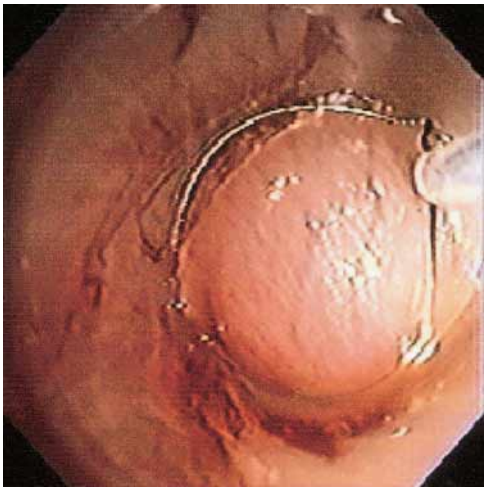

Figure 3. Endoscopic view of second piecemeal resection showing proper positioning of cap and snare over edge of previous resected area at left side of photograph.

Table 1. Complications associated with 43 cap-assisted resections in 8 animals

Perforation	1
Major bleeding	0
Oozing of blood	4
Stricture	3

A perforation (Table 1) occurred during use of the cap attachment to assist piecemeal EMR in the first pig. Saline solution had not been injected before piecemeal EMR and an area of exposed muscularis propria in the previous mucosectomy site was suctioned into the cup and resected. The animal was euthanized after the perforation occurred. In the other animal, saline solution was injected submucosally before each EMR. Additionally, an extra effort was made to avoid aspiration of the exposed muscularis propria into the cap. The snare was positioned to overlap the margins of each prior mucosectomy site after the saline solution–elevated mucosa was gently aspirated to occlude the cap attachment (Fig. 3). In this second pig, mild fever and poor feeding were observed 3 days after the initial procedure. Analgesic medication and antibiotics were administered and the pig recovered in 48 hours. A stricture developed after the second hemi-circumferential resection. Histopathologic examination of samples of EMR specimens documented complete removal of the mucosa with a thick strip of submucosa in all cases (Fig. 4A and B).

Phase II

Two subsequent hemi-circumferential resections in the distal esophagus by cap-assisted EMR were performed in each of 6 pigs without technical difficulty. Histopathologic examinations of randomly

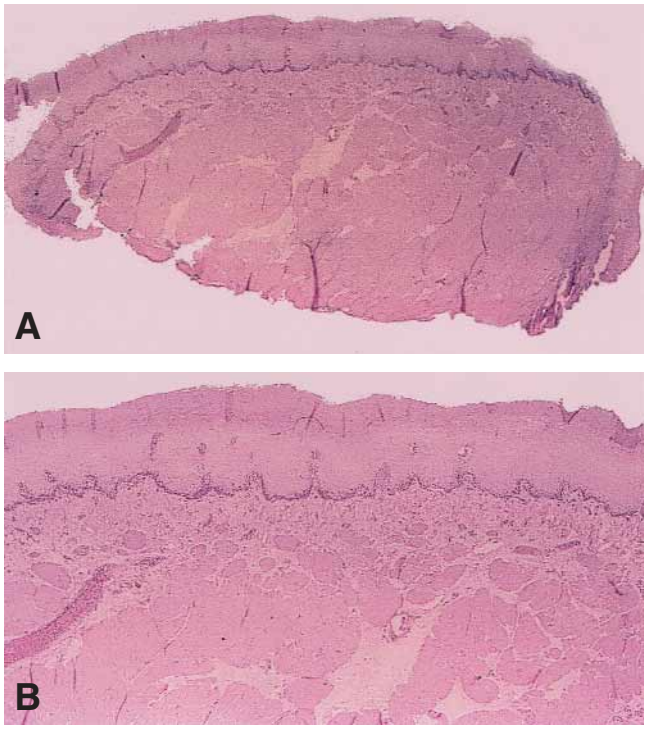

Figure 4. A, Photomicrograph of entire EMR specimen (H&E, orig. mag. ×4). **B,** Photomicrograph showing detail of completely removed mucosa with thick strip of submucosa (H&E, orig. mag. ×10).

selected EMR specimens documented complete removal of the mucosa from the EMR sites. There was no perforation, but self-limiting oozing of blood was observed after 4 EMR procedures (Table 1). Mild fever and poor feeding was evident in 2 animals 3 to 4 days after the initial EMR session. Analgesic medication and antibiotics were administered and both animals recovered fully within 48 hours. Endoscopy 1 week later disclosed normal mucosal healing at the site of the previous EMR. Several new gastric erosions were observed in 1 animal despite treatment with lansoprazole.

Strictures developed in 2 animals after the second hemi-circumferential EMR session. A review of the videotape recordings of the procedures confirmed that the segment treated during the initial hemi-circumferential EMR procedure had healed without stricture formation. The strictures were easily dilated by gently pushing the endoscope through the narrowed segment; no additional equipment was needed for dilation.

Considering all experimental animals (Table 2), a mean of 3.1 (range: 2-5) separate EMRs were needed to achieve complete hemi-circumferential removal of the mucosa (Fig. 5). In total, 43 EMR resections were performed in the 8 animals. Complete re-epithelization of the hemi-circumferential resection was evi-

Table 2. Number of cap-assisted resections and healing time

Animal No.	1st session (No. of EMRs)	Re-ep (wk)	2nd session (No. of EMR)	Re-ep (wk)
Phase 1				
1	1	—	—	—
2*	—	4	5	4
Phase 2				
3	2	3	3	3
4	3	3	2	3
5	3	4	5	4
6	4	4	3	4
7	3	4	2	5
8	4	3	3	3

Re-ep, Re-epithelization.
*First hemi-circumferential resection: EMR with barbed monofilament snare only. Second hemi-circumferential resection with cap attachment only.

dent endoscopically after a mean of 3.6 weeks (range: 3-5 weeks). The gastric pH was less than 2 in all 8 animals before starting treatment with lansoprazole. After initiation of therapy with the proton pump inhibitor, gastric pH was consistently greater than 4 on subsequent evaluations.

DISCUSSION

EMR has been used extensively in Japan for the treatment of early stage cancer of the esophagus and stomach.[7-9] More recently, EMR has been reported to be a therapeutic alternative to surgical esophagectomy for the treatment of high-grade dysplasia (HGD) and early stage cancer of the esophagus associated with Barrett's esophagus.[10-15] However, the application of EMR has been limited to focal areas of metaplastic mucosa. Complete resection of Barrett's mucosa is desirable from both a diagnostic and therapeutic standpoint because of the high risk of unrecognized foci of dysplasia or cancer. In the study of Nijhawan and Wang,[12] biopsies in 11 patients who were thought to have been cured by limited EMR for Barrett's-associated adenocarcinoma revealed residual cancer in 4 patients. Thus, complete resection of Barrett's mucosa may be needed to effect a cure in such patients. Application of EMR to the treatment of circumferential Barrett's mucosa has not been reported.

The goal of the current study was to evaluate the feasibility and safety of circumferential EMR using a piecemeal resection technique in the normal swine esophagus. Variations of the "suck-and-cut" technique of EMR were evaluated in two animals to determine which was best suited for hemi-circumferential esophageal resection. The monofilament snare alone and monofilament barbed snare alone were unsatisfactory for piecemeal resection; the snare either slipped off of the mucosa during closure or mucosal

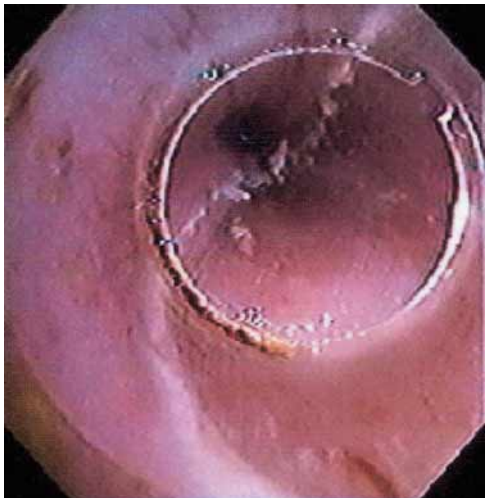

Figure 5. Endoscopic view of esophagus after hemi-circumferential piecemeal cap-assisted mucosal resection (resected area shown on *right side* of photograph).

bridges were left between resected areas. Electrosurgical snare resection with the assistance of a distal cap attachment achieved homogenous and uniform piecemeal removal of the mucosa and this method was therefore used exclusively in the second phase of the study.

One-third of the animals (Phase II) developed a stricture after the second subsequent hemi-circumferential EMR procedure. Strictures were noted during the second week of follow-up. These were easily dilated and did not effect the well-being of the animals, which thrived and gained weight at normal rates. The etiology of stricture formation after the second EMR is unclear, but it is probably related to an overlapping of the hemi-circumferential areas of resection. The hemi-circumferential area that had been previously resected was identified by reference to the position of the endoscope and by visible evidence of scarring. However, the latter can be subtle. Hence, some overlapping of the resected areas may have occurred. Tattooing with India ink and application of hemoclips were tested as methods for marking the margins of the resection, but both were found to be unreliable; the ink spread over a large area and the clips migrated within 1 week of placement.

Cap-assisted EMR resulted in perforation in 1 animal during phase I of the study. This occurred during piecemeal resection and saline solution had not been injected submucosally immediately before a subsequent piecemeal EMR. An area of previously exposed muscularis propria was suctioned into the cap and resected. The technique was subsequently modified to include submucosal injection of saline solution before each EMR. In addition, precautions were taken to avoid aspiration of the exposed muscularis propria

into the cap. The snare was engaged at the margins of the prior mucosectomy site after the saline solution–elevated mucosa was gently aspirated to occlude the cap attachment. No major bleeding was observed during the study. Self-limited oozing of blood occurred after 4 out of a total of 43 resection procedures. There were no other procedure-related complications.

Postprocedure complications included mild fever and poor feeding at 3 to 4 days after the initial EMR session in 3 animals. These animals were treated with analgesic medication and antibiotics and recovered quickly. The etiology of the fever remains unclear. Examination of the animals did not disclose any abnormalities other than mild shivering. A complete biochemistry evaluation including hepatocellular and cholestatic liver enzymes and blood count with differential were within normal limits. Microaspiration, pain, and side effects of lansoprazole were considered in the differential diagnosis.

Measurements of the pH of the gastric contents during the study demonstrated that lansoprazole effectively suppressed gastric acidity. Before treatment with lansoprazole, all animals had a gastric pH of less than 2; during follow-up the pH was consistently greater than 4. It is known that acid refluxes into the distal esophagus in pigs[19] and treatment with lansoprazole or another proton pump inhibitor should be considered in studies of EMR that use the porcine model. Acid suppression may decrease the potential for discomfort after the procedure and lead to faster epithelization.

Histopathologic examination of samples of the EMR specimens documented complete removal of the mucosa in all cases.

In summary, piecemeal circumferential cap-assisted EMR is safe and feasible in the normal swine esophagus when the cap attachment is used in a standardized fashion. The high frequency of stricture formation after the second subsequent hemi-circumferential resection, however, is of concern, and further studies are needed to determine the optimal strategy to prevent this complication after circumferential EMR.

The applicability of circumferential EMR to the treatment of Barrett's metaplasia in humans has not been studied. Chronic inflammatory changes associated with Barrett's esophagus may pose limitations, but the results of EMR for treatment of focal dysplasia and early stage carcinoma associated with Barrett's esophagus are encouraging.[11-15] Therefore, complete removal of metaplastic epithelium with EMR seems to be the logical next step in endoscopic treatment of Barrett's epithelium. The feasibility of this technique for complete removal of the metaplastic epithelium in the human esophagus should be evaluated.

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