Original article

Endoscopic mucosal resection using a cap-fitted endoscope improves tissue resection and pathology interpretation: an animal study

JAMES J. FARRELL¹, GREGORY Y. LAUWERS², and WILLIAM R. BRUGGE³

¹Division of Digestive Diseases, UCLA School of Medicine, 200 UCLA Medical Plaza, Suite 365A, Los Angeles, CA 90095, USA

²Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

³Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Background. Endoscopic mucosal resection using a cap-fitted endoscope (EMRC) has been proposed to be significantly better and safer for tissue resection compared with standard snare EMR. However, there are no valid animal or clinical data to support this. We aimed to compare EMRC with standard snare EMR in a porcine model with respect to tissue resected, ease of procedure, and degree of diathermic injury to the resected specimen.

Methods. Gastric EMRs were randomly performed in pigs using a variety of techniques, including EMRC (14mm and 17-mm cap) and the standard snare technique, using a single-channel method without a grasping forceps. Geometric and histological assessment of the resection specimen for size, histological depth, and diathermic injury were performed by a single pathologist, blinded to the endoscopic techniques used.

Results. Thirty-six gastric mucosal resections were randomly performed in three pigs. Use of EMRC resulted in a statistically significant greater resection specimen by weight, size, and histological depth compared with standard EMR ($P < 0.04$). Large-cap EMRC resulted in a statistically significant greater resection weight and size compared to small-cap EMRC ($P < 0.05$). There was a statistically significant greater degree of diathermic injury in the specimens resected using the standard snare EMR technique compared with EMRC ($P < 0.006$). There were no acute complications with either technique.

Conclusion. Gastric EMRC is more technically effective than and as safe and easy as standard snare EMR. Use of the cap, especially the larger cap, is associated with larger and deeper mucosal resection and less diathermic injury compared with the standard snare technique, making the pathologic assessment of depth and margin involvement more reliable. When possible, EMRC should be the EMR method of choice.

Key words EMR · Mucosal resection · Endotherapy · Early esophageal cancer · Early gastric cancer · Cap · Snare

Introduction

Endoscopic mucosal resection (EMR) is an important method of diagnosing and managing precancerous and early cancerous lesions of the esophagus, stomach, and colon [1–3]. It is being increasingly used in North America and Europe. It allows for complete resection of large, sessile lesions confined to the mucosa, as well as lesions with minute submucosal invasion, avoiding the need for surgical resection and its associated increased risk of morbidity and mortality. The additional benefit of retrieving the resected specimen during EMR allows for accurate staging of tumor depth, tissue histology, and assessment of completeness of resection [3,4].

The technique of EMR using “lift and cut” was originally described in the colon in 1973 [5]. However, its refinement for use in the upper gastrointestinal tract, especially for the management of early gastric cancer, was not described until later [6,7]. Saline or a combination of saline and epinephrine solution is injected into the submucosal area beneath the lesion to separate it from the muscularis propria. A tamponade effect provided by the injection also protects the underlying tissue from thermal injury, perforation, and bleeding. The lesion is then ensnared by the placement of a snare at its base and resected whole or piecemeal using electrocautery. However, this technique is often cumbersome and technically difficult to perform. It may be necessary to lift the lesion with a forceps before it can be encircled completely with the snare. These features of this technique make the procedure extremely difficult to perform in certain anatomic locations and may cause it to be time-consuming, requiring the assistance of a skilled assistant [8].

Offprint requests to: J.J. Farrell

Received: May 12, 2005 / Accepted: October 5, 2005

Presented in part at the Annual Scientific Meeting of the American College of Gastroenterology, October 2001, Las Vegas, Nevada.

Endoscopic mucosal resection using a cap-fitted endoscope (EMRC) was first described in 1993 [3,9–14]. EMRC uses a small, translucent plastic device similar to a band-ligation cap, which fits firmly over the tip of the endoscope. The cap has a shallow circumferential lip on the inside in which the snare can be prelooped. The target lesion, similarly to the procedure for standard EMR, is lifted from the underlying tissue, using a submucosal injection of saline. The lesion is suctioned into the cap and the prelooped snare is tightened. The lesion is then resected with the aid of electrocautery. EMRC has many potential benefits. It is easier to target the lesion and so may be useful in anatomically difficult positions. It may also increase the depth of tissue resected and decrease the risk of perforation by suctioning the mucosa away from the muscularis propria and thereby making the procedure safer. Several types of EMRC caps exist, including straight and angled tip. Descriptions of large-scale experience with the EMRC technique has been limited to publications from Japan. In a review of gastric EMR for early gastric cancer, only two of eight large series utilized EMRC [15]. EMRC is approved for use in the United States, but its use has remained limited.

There have been few studies comparing standard snare EMR with EMRC. An animal model study comparing gastric standard snare EMR with standard cap EMRC did not show a significant difference between the two techniques in terms of size of resected specimen or depth of resection [16]. However, EMRC was significantly easier (based on a nonvalidated “ease-of-procedure” score) to perform than standard snare EMR. A single standard cap size (14-mm outer diameter) was used in that study and no pathologic assessment of tissue injury was made. Furthermore, no randomization process was done and the standard EMRs and EMRCs were performed in completely separate sets of animals [16]. One clinical series comparing a variation of EMRC (known as endoscopic aspiration mucosectomy) with standard EMR for the treatment of early gastric mucosal cancer showed a significant increase in the mean longest diameter of the resected specimen with the EMRC compared with standard EMR biopsy, although there was no comparison of the histological depth of the resected specimen [17]. This series was a retrospective review involving several endoscopists without formal prospective evaluation of the resected specimens [18]. Again, no randomization process was employed and two separate patient groups were compared [18].

Our study prospectively compared EMRC (small and large cap) to standard EMR, using a live gastric porcine model. The size of the resected specimen, the degree of tissue injury, the ease of use, and complications were compared.

Methods

A live porcine animal model was used in the study, which was approved by the institutional subcommittee on animal research care of the Massachusetts General Hospital. Three fasting Yorkshire swine (40.0 to 55.0 kg) were used. All procedures were performed under general anesthesia using halothane (1% to 2%) through an endotracheal tube with 100% oxygen as the carrier. An experienced veterinarian assistant administered the anesthesia and carefully monitored the animals during the procedure. Cardiac and respiratory parameters were monitored throughout the procedures. EMRC or standard EMR procedures were performed in each animal, using a randomization process that involved random selection of a sealed envelope which contained information on the type of gastric EMR (standard, small cap, or large cap) and the location (gastric body or antrum).

Under direct endoscopic visualization (Pentax Precision Instruments, Orangeburg, NY, USA), 10 ml of a saline solution (20 ml of saline, 3 ml of methylene blue, and 1 ml of a 1:10000 solution of epinephrine) were injected submucosally to elevate the mucosa and separate it from the underlying muscularis propria. In standard EMR, the previously raised bleb was encircled and tightened using a snare (Acusnare; Wilson Cook, Winston, NC, USA). A grasping forceps was not used to pull the tissue through the open snare. The specimen was then resected electrosurgically with a setting of 25-W cutting mode (Valley Lab, Boulder, CO, USA) and recovered by grasping it with either a snare or forceps while withdrawing the endoscope. EMRC was performed using either a 14-mm (small cap) or a 17-mm (large cap) outer diameter clear straight-tip cap device (D-402-13212; MH 567; Olympus America, Melville, NY, USA) prelooped with a disposable crescent snare (SD-221L-25; Olympus America) and fitted over the tip of the endoscope. This required removal of the endoscope after the initial survey and re-introduction after attachment to the EMRC apparatus. The previously created bleb was suctioned into the cap and resected using an electrical surgical generator set at 25-W cutting mode (Valley Lab) (Fig. 1). Suction was maintained and the specimen was recovered after removal of the endoscope and attached cap.

We assessed each resection with respect to time required for resection, weight, dimensions, and immediate complications. Time was assessed from the initial submucosal injection to the retrieval of the resected specimen and was recorded in minutes. Each resection site was carefully examined for obvious signs of perforation or bleeding for a minimum of 5 min.

The weight (g) and largest diameter (mm) of each individual specimen was measured prior to fixing and

histological evaluation. The recovered resection specimens were examined histologically for the maximum depth and level of tissue removed and the degree of cautery effect. Histological depth was classified as only mucosal, shallow submucosal, and deep submucosal (Fig. 2). The degree of cautery effect was calculated as a percentage of the entire thickness of the resected specimen (Fig. 3). A single pathologist (G.Y.L.), who was blinded to the endoscopic resection technique used, completed the histological assessment of the resected specimen. Values for all results are expressed as means $\pm$ SEM. Statistical analysis was performed using analysis of variance (ANOVA) for multiple comparisons. A-priori power calculations showed that a sample size of 36 (12 in each group) would be needed for a power of 80% and a significance level of 0.05.

Fig. 1A,B. Endoscopic mucosal resection using a cap-fitted endoscope (EMRC) Procedure. **A** Suction of target mucosal lesion (*dark thicker line*) into prelooped cap attached to endoscope. **B** Application of electrocautery to resect target mucosal lesion

The animals were carefully monitored during each procedure for behavioral signs of distress. After the experiments, the animals were killed humanely using pentobarbital overdoses. Any identifiable resection site was examined postmortem, grossly and microscopically, for evidence of perforation or hemorrhage.

Results

Three pigs were randomized to undergo gastric EMR of either the gastric antrum or gastric body by EMRC (with both small and large cap) or standard EMR. The randomization process was successful and each pig had equivalent numbers of large-cap, standard-cap, and standard-snare EMR techniques performed by a single operator. There were no complications such as perforation or bleeding associated with the EMRs performed. All animals were killed after the experiment without any signs of distress. All 36 resection specimens were retrieved. The characteristics of the resection techniques are shown in Table 1.

Large-cap EMRC provided a statistically larger resection specimen (as assessed by weight and maximum diameter) than either the small-cap EMR or the standard EMR. Similarly, small-cap EMRC resulted in a statistically significant larger resection specimen than standard EMR. There was no statistically significant difference in procedure time between any of the three types of EMR resection. There were no immediate complications associated with gastric EMR using either the large-, or small-cap EMRC or standard EMR (Table 1).

Fig. 2A,B. Assessment of histological depth of gastric EMR resection specimens. **A** No evidence of submucosa. **B** deep submucosa resected. H&E, $\times 40$

Fig. 3A,B. Assessment of diathermic injury of gastric EMR resection specimens. **A** Minimal diathermic injury (15%). **B** Maximum diathermic injury (100%). H&E, $\times 40$

Table 1. Characteristics of resection techniques

Treatment	<i>n</i>	Weight (g)	Maximum diameter (mm)	Time (min)	Complications
Standard EMR	12	0.10 ± 0.02	7.50 ± 0.85	20.0 ± 2.4	0
EMRC (14 mm)	12	$0.26 \pm 0.05^*$	$11.30 \pm 0.57^*$	17.4 ± 1.0	0
EMRC (17 mm)	12	$0.38 \pm 0.03^{**}$	$13.60 \pm 0.33^{**}$	15.0 ± 0.8	0

* $P < 0.04$ compared with standard EMR; ** $P < 0.05$ compared with EMRC (14 mm)

Values are means $\pm$ SEM

Table 2. Histological characteristics of the resected specimens

Treatment	<i>n</i>	Deepest histological layer			Diathermic effect (%)
		Mucosa only	Superficial SM	Deep SM	
Standard EMR	12	50%	50%	0%	50.8 ± 8.4
EMRC (14 mm)***	12	8%	33%	58%	19.2 ± 3.4
EMRC (17 mm)	12	6%	25%	69%	15.0 ± 1.5

*** $P < 0.006$ when compared with standard EMR

Values are means $\pm$ SEM

No deep submucosa was identified in any standard EMR resection specimen. Overall, 50% of standard EMR resection specimens contained only mucosa, and the remaining 50% contained only superficial submucosa. This is in contrast to the small-cap EMR resection specimens, of which 33% had evidence of superficial submucosa, with 58% also having evidence of deep submucosal involvement. This difference was statistically significant when compared with the standard EMR technique (58% vs 0%; $P < 0.006$). Likewise, the large-cap EMR resection specimens contained superficial

submucosa and deep submucosa in 25% and 69% of cases, respectively. There was no statistically significant difference of histological involvement between the small-cap EMRC and the large-cap EMRC resection specimens (Table 2).

When the degree of diathermic injury was assessed, there was statistically significant greater diathermic injury in the standard EMR resection specimen when compared with either the small EMR cap or the large EMR cap ($P < 0.006$). Diathermic injury was independent of the size of the resection specimen.

Discussion

The use of EMRC provided a larger resection specimen when compared with a standard EMR snare technique when assessed using two parameters: weight and maximum dimension. Furthermore, use of a larger cap (17-mm outer diameter) resulted in a statistically significant greater resection specimen compared with use of the smaller cap (outer diameter 14mm). Since en-bloc resection of a mucosal lesion is preferred over piecemeal resection, especially when further pathologic assessment of depth of invasion and margin involvement is planned, the ability and increased likelihood of EMRC resecting larger pieces of mucosa during a single endoscopic mucosal resection is an important benefit over a standard EMR technique. Although the larger cap is currently only suitable for use in the colon in humans, due to its size and the discomfort and risk associated with esophageal passage, the development of a new flexible larger cap (XB01-740-503; Olympus Endotherapy, Olympus America, Melville, NY, USA) may allow for use in the upper gastrointestinal tract with improved EMR results.

Although perceived as more cumbersome and requiring greater expertise, EMRC did not take longer than standard EMR using a regular snare in this single-operator series. In fact, standard EMR is often prolonged by the inability of the snare to readily entrap the mucosa (which happened often during our study) and difficulty in easily retrieving the resected specimen. This downside to the use of regular snares during standard EMR may be improved through the use of either spiked snares or stiffer snares. Furthermore, the use of a blunt “grasping” forceps to grab and tent the mucosa may improve the ability of standard EMR. This technique, however, requires the use of a dual-channel endoscope, as well as a second operator. These additional techniques were not formally evaluated during this study.

Gastric EMRC and standard snare EMR are safe techniques. During a total of 36 gastric mucosal resections, there was no evidence of immediate bleeding or perforation. Subsequent pathologic postmortem examination of the resected stomachs confirmed the absence of any perforation. Further survival animal studies would be necessary to study delayed complications such as bleeding.

The use of EMRC resulted in deeper histological resection. When comparing a standard EMR with a small-cap EMRC, no deep submucosa was resected using the standard EMR. However, up to 60% of small-cap EMR resection specimens included deep submucosa. This difference was statistically significant. Interestingly, however, although use of the large-cap EMR resulted in a significantly greater resection speci-

men (by both weight and maximum dimension), it did not result in a statistically significant deeper histological involvement when compared with the small-cap EMR. The use of suction probably explains why EMRC results in greater resected depth when compared with standard EMR. Again, it is possible the use of a “grabbing” forceps in combination with a standard EMR may result in greater resection depth, but this has not been formally tested. Although most gastric lesions requiring endoscopic resection are confined to the mucosa, occasionally, small lesions with minute submucosal penetration may benefit from EMR [19]. Hence, a technique that consistently and reliably results in a resection of deeper parts of the submucosa would result in a greater chance of a successful EMR. Furthermore, as endoscopic ultrasound and high-frequency ultrasound preresection staging is not 100% accurate, the use of a technique that results in a deeper histological layer analysis would be essential to ensure complete resection.

As full and complete histological evaluation of the resected specimen for depth of involvement, as well as margin involvement, is necessary to dictate further clinical management and offer longterm prognosis, it is important to avoid excessive tissue injury to the resected specimen. The use of EMRC resulted in less diathermic injury to the resection specimen compared with standard EMR. Reducing the diathermic injury to the peripheral margin of the specimen, where the histological analysis is at its most important, is a significant advantage of EMRC. A pure cutting current was used in this study to potentially minimize the amount of current injury to the tissue, without any significant immediate bleeding complications. Although tissue injury is inversely proportional to the size of the resection area, we did not find a correlation between size of resection specimens and degree of tissue injury [20]. While the use of different snares may account for the differing degrees of injury, it is likely that the mechanical forces from the use of suction in EMRC may decrease the amount of cautery and time required to resect the mucosa and account for this difference. As this is an animal experimental model, further studies on the effect of cautery on tissue pathology interpretation in humans are needed before recommendations for optimal cautery conditions in humans can be made.

Finally, although there was no significant difference between our three groups in the length of the procedure, we have noticed the superior ability of EMRC to successfully and safely retrieve the resected specimen without the need for a retrieval basket, forceps, or snare. Although, in this study, all resected specimens were retrieved undamaged, we have anecdotal clinical experience of damage to and fragmentation of resected specimens after standard EMR, which ultimately prevents satisfactory pathologic analysis.

Gastric EMRC is more technically effective than and as safe and easy as gastric standard EMR. Use of the cap, especially the larger cap, is associated with the larger and deeper mucosal resection compared with the standard snare EMR technique. Less diathermic injury of the resection specimen associated with EMRC makes the pathologic assessment of depth and margin involvement more reliable. When possible, EMRC should be the EMR method of choice.

Acknowledgments Supported by an ADHF/ASGE Endoscopy Research Award.

References

1. Makuuchi H, Kise Y, Shimada H, Chino O, Tanaka H. Endoscopic mucosal resection for early gastric cancer. *Semin Surg Oncol* 1999;17:108–16.
2. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001;48:225–9.
3. Inoue H. Treatment of esophageal and gastric tumors. *Endoscopy* 2001;33:119–25.
4. Soetikno R, Inoue H, Chang K. Endoscopic mucosal resection. *Gastrointest Endosc Clin N Am* 2000;10:595–617.
5. Deyhle P, Largiader F, Jenny S. A method for endoscopic electroresection of sessile colonic polyps. *Endoscopy* 1973;5:38–40.
6. Takemoto T, Yania H, Karita M, Okita K. Significance of strip biopsy with particular reference to endoscopic mucosectomy. *Dig Endosc* 1989;1:4–9.
7. Tada M, Murakami A, Karita M, Yanai H, Okita K. Endoscopic resection of early gastric cancer. *Endoscopy* 1993;25:445–50.
8. Hirao M, Masuda K, Asanuma T, Naka H, Noda K, Matsuura K, et al. Endoscopic resection of early gastric cancer and other tumors with local injection of hypertonic saline-epinephrine. *Gastrointest Endosc* 1988;34:264–9.
9. Inoue H, Takeshita K, Hori H, Muraoka Y, Yoneshima H, Endo M. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. *Gastrointest Endosc* 1993;39:58–62.
10. Takeshita K, Tani M, Inoue H, Saeki I, Honda T, Kando F, et al. A new method of endoscopic mucosal resection of neoplastic lesions in the stomach: its technical features and results. *Hepatogastroenterology* 1997;44:1602–11.
11. Inoue H, Kawano T, Tani M, Takeshita K, Iwai T. Endoscopic mucosal resection using a cap: techniques for use and preventing perforation. *Can J Gastroenterol* 1999;13:477–80.
12. Inoue H. Endoscopic mucosal resection for esophageal and gastric mucosal cancers. *Can J Gastroenterol* 1998;12:355–9.
13. Chonan A, Mochizuki F, Ando M. Endoscopic mucosal resection (EMR) of early gastric cancer: usefulness of aspiration EMR using a cap-fitted scope. *Dig Endosc* 1998;10:31–6.
14. Yamaguchi Y, Takahashi S. Endoscopic mucosal resection (EMR) of early gastric cancer: usefulness of aspiration EMR using a cap-fitted scope. *Gastrointest Endosc* 1998;48:548–9.
15. Kojima T, Parra-Blanco A, Takahashi H, Fujita R. Outcome of endoscopic mucosal resection for early gastric cancer: review of the Japanese literature. *Gastrointest Endosc* 1998;48:550–4; discussion 554–5.
16. Low AH, Lee JG, Leung JW. Endoscopic mucosal resection with a cap-fitted endoscope versus freehand gastric mucosectomy in an animal model. *Gastrointest Endosc* 1999;50:608–12.
17. Torii A, Sakai M, Kajiyama T, Kishimoto H, Kin G, Inoue K, et al. Endoscopic aspiration mucosectomy as curative endoscopic surgery; analysis of 24 cases of early gastric cancer. *Gastrointest Endosc* 1995;42:475–9.
18. Tanabe S, Koizumi W, Kokutou M, Imaizumi H, Ishii K, Kida M, et al. Usefulness of endoscopic aspiration mucosectomy as compared with strip biopsy for the treatment of gastric mucosal cancer. *Gastrointest Endosc* 1999;50:819–22.
19. Gotoda R, Sasako M, Ono H, Katai H, Sano T, Shimoda T. Evaluation of the necessity for gastrectomy with lymph node dissection for patients with submucosal invasive gastric cancer. *Br J Surg* 2001;88:444–9.
20. Tucker R. Principles of electrocautery. In: Sivak M, editor. *Gastrointestinal endoscopy*. Philadelphia: W.B. Saunders; 1999.