Endoscopic mucosal resection in the setting of Barrett's esophagus

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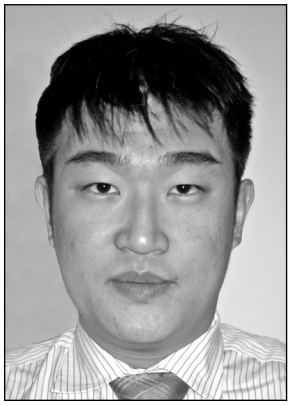
Endoscopic mucosal resection (EMR) is a technique that was originally developed in 1978 for early gastric cancer (1). Given the relative simplicity, safety and effectiveness of the technique, it has become an endoscopic alternative to surgery in resecting flat and polypoid neoplasms of the mucosa by longitudinal section through the submucosa for curative intent. Moreover, EMR is increasingly being used in submucosal neoplastic lesions and intramucosal cancers. Still considered a novel procedure by endoscopists outside Japan, the present article will outline the current indications for EMR as it pertains to Barrett's esophagus and distal esophageal lesions. Other areas where EMR may be used, but not discussed in the present paper, include the stomach for gastric cancers, the colorectum for adenomas and, recently, the duodenum.



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It is well recognized that there is an increased risk for developing esophageal adenocarcinoma in patients with Barrett's esophagus. The Canadian Association of Gastroenterology recommends regular endoscopic surveillance with biopsy. Endoscopic surveillance with biopsy is performed to detect dysplastic lesions, particularly high-grade dysplasia (HGD) and intramucosal carcinoma (IMC), which are associated with a high risk of progression into invasive carcinoma. Presently, up to 33% of patients diagnosed with HGD on biopsy and treated with surgery ultimately have invasive cancer in their esophagectomy specimens (2). Unfortunately, endoscopic biopsy samples alone are prone to interobserver variability (2) and, therefore, repeat sampling, ideally with jumbo biopsies and expert pathological confirmation, is recommended in all cases.

Traditionally, esophagectomy has been the preferred treatment option for HGD and IMC (3-5), and in cases of early invasive cancer, irrespective of the risk of lymph node involvement or hematogenous dissemination. Although high cure rates are achieved with esophagectomy, there are significant treatment-related morbidity and mortality, ranging between 2% and 7% in experienced centres and as much as 20% in others (6-8). Furthermore, high-risk cardiovascular patients may not be able to tolerate the anesthesia or esophagectomy itself, leaving very few options available for these patients.

Interestingly, the incidence of superficial esophageal cancer (invading no deeper than the submucosa) appears to be increasing (3,9,10). Epidemiologically, it is also notable that there has been a shift toward more adenocarcinomas and fewer squamous cell cancers in the esophagus (11,12).

Fortunately, for both HGD and IMC, lymph node metastasis has been negligible and low, respectively (13-16). Given the multitude of issues aforementioned, the demand for endoscopic approaches leading to definitive therapy created both ablative techniques and EMR. Compared with the ablative endoscopic methods of tumour eradication such as laser, photodynamic therapy and plasma coagulation, EMR has the distinct advantage of producing a histological specimen. With the EMR specimen, the completeness of resection and the level of tumour invasion may be more accurately assessed than with endoscopic ultrasound alone (17-19).

FAMILIARIZATION WITH EMR

Given the advantages of a definitive histological diagnosis, preserving the integrity of the esophagus, potential for cure, and markedly reduced procedural morbidity and mortality, EMR has been enthusiastically explored. There is now clear evidence that EMR is a reasonable alternative to esophagectomy in the appropriate settings (see 'Indications' and 'Efficacy and Complications') (18,20-23), at least in expert hands.

The discussion of EMR and its studies with respect to esophageal neoplasms necessitates the familiarization of pathological definitions. Esophageal neoplasia can be classified according to the internationally accepted Vienna classification, which is based on the histopathology of endoscopic biopsies (24).

The 'Seattle biopsy protocol' is recommended for mapping Barrett's esophagus during the endoscopic evaluation (25), but for the purposes of the present article we will not elaborate on the biopsy techniques.

Another classification system based on an expansion of the existing American Joint Committee on Cancer (AJCC), the tumour-node-metastasis (TNM) staging system is useful for distinguishing between the various types of T1 esophageal cancers, thereby determining the prognosis and guiding management (see 'Indications') (14,15). According to this expanded classification system, mucosal tumours are divided according to the depth of their invasion (Table 1).

INDICATIONS

Currently, the usual North American recommended treatment for HGD and IMC in Barrett's is esophagectomy because cancer is found in up to 40% of esophagectomy patients (26). An alternative to esophagectomy is close surveillance in HGD. In

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TABLE 1
Mucosal tumours classified according to their depth of invasion along with the corresponding American Joint Committee on Cancer (AJCC) staging

Tumours	Depth of invasion (AJCC staging)
Mucosal	
M1	Limited to the epithelial layer (Tis)
M2	Invades the lamina propria (T1a)
M3	Invades into, but not through, the muscularis mucosae (T1a)
Submucosal	
SM1	Penetrates the shallowest one-third of the submucosa (T1b)
SM2	Penetrates into the intermediate one-third of the submucosa (T1b)
SM3	Penetrates the deepest one-third of the submucosa (T1b)

Data from reference 15

TABLE 2
The Japan Gastroenterological Endoscopy Society classification system based on visual and endosonographic features

Tumour type	Visual and endosonographic features
Type I	Polypoid or protuberant
Ip	Pedunculated
I (ps)/(sp)	Subpedunculated
Is	Sessile
Type II	Flat
IIa	Superficial elevated
IIb	Flat
IIc	Flat depressed
Type III	All ulcerated
Type IV	Lateral spreading

contrast, endoscopic therapy in the case of HGD and mucosal Barrett's cancer is recommended independent from operability of the patient in European countries as stated by the German Society for Digestive Diseases (27). There is evidence that EMR can be applied both safely and effective in HGD, as well as early cancer in which the likelihood of metastasis is justifiably low; namely, in superficial cancers (28-31). The Japan Gastroenterological Endoscopy Society (JGES) is the most experienced with EMR, and has developed a classification system to help define the indications and outcomes of EMR based on visual and endosonographic features (32).

The JGES endoscopic criteria for esophageal cancers most suitable for EMR are:

- A diameter of less than or equal to 2 cm;
- Involvement of less than one-third of the circumference of the esophageal wall; and
- Limitation to the mucosa of the esophagus.

Additionally, the JGES has developed a classification system based on visual and endosonographic features to facilitate guidance on indications and to study the outcomes related to EMR for early endoluminal cancers (Table 2).

Using the JGES classification system, it has been stated that the 'ideal' candidate for EMR has a solitary, small (less than 2 cm in diameter), flat lesion (IIa, IIb and IIc) that is limited to the mucosa (33).

Contrary to univariate analysis, which includes patients with more advanced lesions, poor or undifferentiated tumour differentiation has not been identified as an independent risk factor for lymph node metastasis or tumour recurrence in multivariate analysis (34).

Based on various studies (13-16), it appears that M1 and M2 tumours are not usually associated with lymph node metastases and thus would be suitable for EMR. Hence, if one has either a biopsy or EMR-proven M1 or M2 sample, these would be respectively amenable to EMR and managed as a potentially cured patient with follow-up surveillance. The risk for nodal metastases with M3 tumours ranges between 6% and 12%, and for these patients, EMR offers a chance for cure but with a consequent risk of relapse and death from inadequate tumour removal. Two studies (35,36) evaluating this classification system in the esophagus confirmed that M1 and M2 lesions did not show any lymph node metastasis, while SM2 and SM3 lesions showed approximately 40% nodal metastasis. These studies also showed a 10% to 15% rate of nodal metastasis in M3 and SM1 lesions (35,36) similar to the studies mentioned before.

A helpful modality for planning EMR is high frequency (20 MHz to 30 MHz) endoscopic ultrasonography (EUS) because it remains the most sensitive method to determine the depth of tumour penetration and may give lymph node metastasis information. Recently completed studies comparing pre-EMR EUS staging and previous endoscopic biopsy staging to staging, with the final histological diagnoses obtained either through EMR or esophagectomy, support the strategy of EUS followed by EMR to guide management via accurate staging (17,18,37). Due to the technical difficulty involved, it is recommended that EUS be performed by an experienced endosonographer (38).

To summarize, EMR is useful as the final step in diagnostic workup of patients with HGD or carcinoma in Barrett's esophagus. It is also a reasonable treatment option in M1, M2, and some M3 and SM1 lesions depending on patient preferences and comorbidities. A lesion's endoscopic and endosonic appearance is recommended to help identify lesions amenable to EMR.

ESTABLISHED TECHNIQUES

The first technique to be discussed is EMR with a transparent cap. This involves marking the lesion with electrocautery to help distinguish the lesion after the injection. After marking, the target is lifted by injection of a fluid, usually a diluted adrenaline (1:100,000) of approximately 5 mL into the submucosal layer. A transparent cap with a gutter or ridge is attached to the distal end of the endoscope so that positioning of the crescent-shaped EMR snare is allowed. After the snare is preloaded into the gutter, suction is applied into the cap to form a pseudopolyp. The pseudopolyp in turn is cut with the diathermy loop and then captured. The specimen is then fixed for the pathologist.

A second technique is known as EMR with a ligation device. In this method, a variceal ligation device is used for EMR (Figures 1 and 2). After a lesion is sucked into the tube, a rubber band is released to form a pseudopolyp. Once the ligation device is detached, the pseudopolyp is removed at the base with a diathermy snare under or above the rubber band. The standard multibander ligation devices necessitate the removal of the endoscope to disassemble the ligation device and reintroduce the endoscope to remove the pseudopolyp with a standard polypectomy snare.

Figure 1) *Endoscopic mucosal resection with ligation device setup*

Figure 2) *Endoscopic mucosal resection with ligation head setup*

A prospective randomized study (39) found no significant difference with respect to size of the resected specimens or complications among the first two described techniques.

Other resection devices, through which both banding and snare can be simultaneously performed, have been developed and appear promising in terms of saving both time and requisite skill level, but given the purposes of the present article they will not be discussed.

EFFICACY AND COMPLICATIONS

The available data with long-term results demonstrates the effectiveness and safety of EMR in patients with HGD and IMC in Barrett's esophagus. For example, a study of 64 patients in Germany (20) who had either IMC or HGD showed impressive results. In this study, patients were separated into two groups – 35 'low risk' lesion group (types I, IIa, IIb, IIc less than 20 mm in diameter, limited to the mucosa, and histologically well to moderately differentiated tumours) and 29 'high risk' (all other) lesion group. This study reported a complete remission rate of 97% in 'low risk' patients and 59% in the 'high risk' group. The only complication reported was minor bleeding amenable to endoscopic hemostasis.

Numerous reports (32,40-46) have supported the finding of a low recurrence rate following EMR of isolated lesions. A few Japanese studies are worth highlighting because they report promising long-term follow-up data. In one large Japanese report (41), which included 142 patients with esophageal cancer, who were followed for nine years, the five-year survival rate was 95% and none of the deaths were cancer-related. Another group in Japan reported no statistically significant difference in the five-year survival rate of M1 and M2 esophageal cancer patients treated by EMR or esophagectomy (86% versus 83%) (35).

Complications that have been described thus far can be divided into immediate, late and recurrence. It has been found that complications increase with piecemeal resection (47).

Immediate complications were noted in one study (35) in 12.9% of procedures related to bleeding specifics (10%) and mediastinal emphysema (2.9%). Perforation is rare with an incidence of less than 1% and is associated with piecemeal resection (47).

Late complications (after five days) in the same study was seen in 7.2% of procedures, and could be divided into esophageal stricture due to scarring (5.8%) and ulcer bleeding (1.4%) (35). Strictures tended to occur in patients with over three-fourths of the circumference of the esophagus exposed to a mucosal defect or if the length of the resection was longer than 3 cm (48). Nevertheless, these strictures were able to be resolved with endoscopic dilation (48).

Recurrence of dysplasia was found to be more likely in patients having multiple or circumferential lesions (49). It is not yet known how the completeness of resection will correlate to recurrence rates, but one study (37) has shown an overall persistence/recurrence rate of 47% despite following established guidelines, perhaps attributable to their high number of positive margins. Disturbingly, there is recent evidence showing a high rate (32%) of metachronous changes on follow-up (50). These metachronous lesions develop in residual Barrett's mucosa during follow-up, in spite of the fact that complete local remission was achieved in 98% of procedures (50). Because metachronous lesions may be a field defect, it is recommended that EMR should involve all areas of Barrett's esophagus.

FUTURE DIRECTION OF EMR

Expanded uses for EMR including salvage therapy, combining EMR with ablative techniques and the advent of more effective equipment is underway. More research into how best to apply the technique and follow these patients is also underway. Parallel advances are being made in using EMR in other areas of the alimentary tract, representing an exciting time for endoscopists.

CONCLUSION

The current article presented the evidence behind EMR in an effort to demonstrate the useful diagnostic and therapeutic aspects of it. EMR appears to be a viable option for treating patients with Barrett's esophagus with HGD, IMR and some superficial cancers. Compared with other endoscopic techniques, it provides a histological assessment of tumour grade and depth of invasion that can lead the way to the best management strategy. There are a few complications associated with this procedure, the worst of all being recurrence, which fortunately appears to be rare.

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