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World J Gastroenterol 2008 April 7; 14(13): 1984-1989
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

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Endoscopic mucosal resection in the upper gastrointestinal tract

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Received: December 15, 2007 Revised: January 31, 2008

Abstract

Endoscopic mucosal resection (EMR) is a technique used to locally excise lesions confined to the mucosa. Its main role is the treatment of advanced dysplasia and early gastrointestinal cancers. EMR was originally described as a therapy for early gastric cancer. Recently its use has expanded as a therapeutic option for ampullary masses, colorectal cancer, and large colorectal polyps. In the Western world, the predominant indication for EMR in the upper gastrointestinal tract is the staging and treatment of advance dysplasia and early neoplasia in Barrett's esophagus. This review will describe the basis, indications, techniques, and complications of EMR, and its role in the management of Barrett's esophagus.

Key words: Endoscopic mucosal resection; Mucosal resection; Barrett's esophagus; Barrett's dysplasia; Therapeutic endoscopy

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Ahmadi A, Draganov P. Endoscopic mucosal resection in the upper gastrointestinal tract. *World J Gastroenterol* 2008; 14(13): 1984-1989 Available from URL: http://www.wjgnet.com/1007-9327/14/1984.asp DOI: http://dx.doi.org/10.3748/wjg.14.1984

INTRODUCTION

Endoscopic mucosal resection (EMR) is a technique used to locally excise lesions confined to the mucosa. Its main role in therapeutic endoscopy is the treatment of advanced dysplasia and early gastrointestinal (GI) cancers[1-4]. Tada *et al* published the first case report of EMR in 1984 as a treatment option for early-stage gastric carcinoma[5]. Since then, EMR has been used diagnostically and therapeutically in both the upper and lower GI tracts, and has significantly lower morbidity and mortality compared to surgical management[6].

EMR is most commonly used to locally treat early gastric and esophageal dysplasia/cancer. However, there are several reports describing EMR as a therapeutic option for ampullary masses, colorectal cancer, and large colorectal polyps[7-10]. In the Western world, the predominant indication for EMR in the upper GI tract is the staging and treatment of early neoplasia in Barrett's esophagus. This review will describe the basis, indications, techniques, and complications of EMR, and its role in the management of Barrett's esophagus.

BASIS OF EMR

The GI wall is comprised of 5 layers: mucosa, deep mucosa, submucosa, muscularis propria, and serosa or adventitia. The two major components are the mucosal and the muscular layer. The submucosa consists of loose connective tissue that attaches the above layers together. The mucosal and muscular layers can be separated from each other by injection of fluid into the submucosal layer. This allows for safe resection of mucosal lesions without causing damage of the deeper muscle layer[11].

EMR has become standard practice because of its following distinct advantages: (1) advanced dysplasia and most early neoplastic lesions are free of lymph-node metastases, and can be treated with curative intent simply by local resection[12]; (2) EMR provides tissue specimen for histology and staging[13]; (3) EMR is minimally invasive and carries lower morbidity and mortality compared to traditional surgical approaches[14]; and (4) surgery can be performed after EMR if advanced neoplasia or incomplete resection is detected on histologic evaluation of the EMR specimen.

EMR also has some disadvantages: (1) EMR is labor intense, time consuming, and requires advanced endoscopic skills; (2) larger lesions can only be resected in piecemeal fashion which precludes evaluation for completeness of the resection at the lateral margins; (3)

there is uncertainty regarding the long term outcome of patients treated with EMR due to the lack of randomized trials directly comparing EMR with surgery; and (4) EMR is poorly reimbursed in the US.

TECHNIQUES OF EMR

Once a mucosal lesion is identified, it is helpful to perform chromoendoscopy ± endoscopic ultrasound to further define the size and borders of the lesion, and determine its depth of invasion[15-17]. Both chromoendoscopy and narrow band imaging can help improve detection of dysplastic lesions, and further delineate the borders of the lesion. Additionally, computer tomography (CT) imaging can help determine the size of the lesion and rule out distant metastatic disease prior to proceeding with EUS. Although it can be challenging to determine intramucosal from submucosal neoplasias, the risk of pre-existing lymph node metastases must be discussed with the patient prior to pursuing EMR. Ultimately, histopathologic evaluation of the EMR specimen is the most important predictor of lymph node metastasis. Surgical management of early esophageal/gastric malignancies should be based on the histological analysis of the EMR specimen (i.e. depth of invasion) as well as each patient's surgical morbidity and mortality risks.

Several EMR techniques have been described in the literature. Multiple EMR techniques are available: (1) strip-off biopsy; (2) "inject, lift, and cut" method; (3) the "cup and suction" or EMR-cap technique; and lastly (4) EMR with band ligation[18]. Prior to pursuing any of the above methods, it is recommended that the periphery of the lesion be marked with either a needle knife, electrocautery, or argon plasma coagulator (APC). This allows for distinct identification of the borders of the lesion that is being excised. The absence of all markings assists in determining if the resection is complete.

Depending on the EMR technique used, lift injection may be required. No standardization of the type of injection solution exists. Various injectates that have been used include normal saline, normal saline plus epinephrine solution, 50% dextrose in normal saline, 10% glycerine/5% fructose in normal saline, hyaluronic acid, and a mixture of methylene blue and normal saline[18,19]. Injection of these various solutions can help lift the mucosa from the submucosa, and theoretically decrease the risk of perforation and reduce the risk of hemorrhage[20]. An additional advantage of injecting prior to EMR is identification of lesions that do not successfully lift, which generally suggests involvement of the submucosal layer, and thus are not candidates for resection[15].

Multiple electrosurgical currents are used during EMR, including blend, cut, and coagulation settings, depending primarily on operator preference. The electrosurgical setting most commonly used in the esophagus at Leeds is the ERBE "endo-cut mode" with a power setting of 45 watts[21]. In a recent editorial by Seewald *et al*, a pure coagulation current with the Erbotom at a setting 3- and 60-W output was used for electrosurgical resection[22].

(1) The strip biopsy is the least complex EMR technique, but is often limited to polypoid or nodular lesions only[23]. It is similar to standard polypectomy. Injection into the submucosa is not done. A diathermy snare is tightened around a lesion, which is subsequently removed with the application of an electrical cutting current. The strip biopsy technique can be applied to flat lesions by using either a barbed snare or ultra stiff snare[24].

(2) The "inject, lift, and cut" method is similar to the strip-off method. A two channel upper endoscope is needed. Prior to snaring the lesion, a submucosal injection is used to effectively lift the mucosa from the submucosa, thereby potentially reducing the risk of perforating the muscular layer. The lesion is then lifted by forceps and situated into a snare (*via* the second channel of a dual-channel endoscope), such that the lesion is resected at the base by applying electrocautery[20].

(3) The "cup and suction" or EMR-cap technique is the most frequently used method of EMR in the esophagus[25]. This technique was first described by Inohue *et al* in 1993[26]. This method requires a transparent plastic cap be attached to the distal tip of a single-channel endoscope. This is followed by injection of approximately 20 mL of lifting solution into the submucosa. A designated "duck bill" small-diameter snare is then placed within the rim of the transparent cap. Following this, the lesion is sucked into the cap as the snare is closed at the base of the lesion. Once suction has been released and it has been determined that the entire lesion is contained within the snare, the lesion is removed using electrocautery[27].

The advantages of the EMR-cap technique are that a standard single-channel endoscope can be used, and only one endoscopy assistant is required. In addition, it appears that there is a lower risk of bleeding compared to the strip-off method[21,25]. The disadvantage is that it may be difficult to ensure that the entire lesion has been aspirated into the cap, and occasionally, visualization of the lesion can be obscured by the cap itself. Furthermore, the snare tends to loose its shape after a single use and thus a new snare is usually required for each piece of tissue removed. This can quickly add to the cost of the procedure, particularly if a large surface area needs to be removed (e.g. long segment Barrett's esophagus).

(4) EMR with ligation is similar to the EMR-cap technique, in that suction of the lesion is required. However, unlike the EMR-cap technique, the lesion is suctioned into a ligation cylinder without prior submucosal injection. A rubber band is then deployed at the base to create a pseudopolyp. The pseudopolyp is subsequently removed at its base by tightening a snare just below the level of the rubber band[28]. The standard band ligator can be used, but a designated ligator that fits the single channel therapeutic upper scope is available (Duette, Cook Medical, Winston-Salem, NC). The main disadvantage of this technique with the standard ligator is that the endoscope must be withdrawn to remove the ligation cylinder before reinsertion for resection[29]. The Duette system, on the other hand, allows the passage of a snare *via* the therapeutic channel of the scope and multiple resections can be carried out sequentially without the need of removing the scope.

The EMR-cap and EMR with ligation techniques have been prospectively compared to each other in a single-

center study performed by May A *et al*. In this study, 50 EMR-cap resections were compared to 50 EMR with ligation resections of early stage esophageal cancer. No significant difference in the maximal diameter of the resection specimen area was noted between the two groups. In addition, only one minor episode of bleeding was seen in each group, with no severe complications in either group. Therefore, it was concluded that both techniques are similar in efficacy and safety[30].

ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD)

ESD, one of the more recently described techniques, has been developed to perform single en-block resections of large mucosal lesions[31]. This technique involves the use of an electrocautery knife to dissect out mucosal lesions. Several knives have been developed for ESD, including triangle-tip knives, hook knives, insulation-tip knives, and flex knives[32-34]. In ESD with use of a triangle-tip knife, the borders of a mucosal lesion are marked by electrocautery and then injection of an epinephrine-saline solution into the submucosa is performed. This is followed by marginal cutting circumferentially, *via* electrocautery, around the previous markings. At this point, a high-viscosity solution (such as hyaluronic acid) is injected to provide a longer period of mucosal lifting to allow for actual submucosal dissection. Dissection is carried out by electro cauterization using the tip of the triangle-tip knife to free the mucosal lesion from the submucosa. Once completed, the freed mucosa is removed[27]. At present, the various knives used for ESD are not available in the US.

EMR COMPLICATIONS

As with any endoscopic procedure, complication rates are operator dependent and diminish with increased experience. The Japanese Society of Gastrointestinal Endoscopy calculated a complication rate of 0.5% based on all upper GI EMR's performed between 1993 to 1997[35]. A lower overall complication rate of 0.17% was reported by Kaneko *et al* in 1995. The mortality rate calculated by Kaneko *et al* was 0.0001%[36].

The risks of EMR include bleeding, pain, perforation, and stricture formation. Bleeding can occur at the time of the procedure, or be delayed for up to 12 h. Bleeding rarely occurs beyond 24 h after the procedure. Venous oozing is more common following esophageal EMR, whereas brisk bleeding is more common after gastric EMR of large and fundic lesions. Bleeding is most commonly treated endoscopically *via* electrocauterization, APC, or placement of metallic clips[37-40].

Dull pain following EMR generally results from denudation of the mucosa and subsequent exposure to gastric acid. This pain can often be controlled by proton-pump inhibitors. Sudden sharp pain, especially during or at the completion of the procedure, should raise suspicion of a perforation[41]. The risk of perforation following EMR of gastric lesions is 0.06%-5%[42]. Upper GI tract perforation can be managed conservatively with the combination of clipping, nasogastric tube suction, and broad-spectrum antibiotics[43].

Patients are at an increased risk of developing strictures if circumferential resections of the esophagus or gastric pylorus are performed[29,44,45]. These strictures are often responsive to dilation. To date, animal studies have not identified that prophylactic balloon dilation, esophageal stenting, or deep mural steroid injections prevent the formation of strictures[44].

INDICATIONS FOR EMR IN THE UPPER GI TRACT

Gastric malignancy

Per the Japanese literature, the indications for EMR in resection of superficial gastric cancers applies to well- or moderately differentiated adenocarcinoma and/or papillary carcinoma. Gastric cancers that penetrate the submucosa are at increased risk of lymph node metastases. Gastric cancer confined to the mucosa has a 0%-5% risk of lymph node metastases, compared to 10%-20% risk if the cancer involves the submucosa[46-49]. Thus, gastric lesions must meet the following criteria to be candidates for EMR: confined to the mucosa, < 2 cm for elevated lesions, < 1 cm for flat or depressed lesions, cannot be associated with an ulcer or ulcer scar, and cannot have venous or lymphatic involvement[50].

Esophageal squamous cell carcinoma

Currently, EMR is generally indicated for superficial well- or moderately differentiated squamous cell carcinoma without venous or lymphatic involvement that is limited to the lamina propria. This is based on a 0% risk of metastasis when the neoplasia is limited to the epithelium, compared to the 12% and 26% risk of metastasis when the neoplasia involves the muscularis mucosa and submucosa, respectively[51]. There is no consensus on the maximum size of the lesion that can be resected. EMR is not recommended for circumferential lesions secondary to the risk of subsequent stricture formation[15].

High-grade dysplasia and early adenocarcinoma in Barrett's esophagus (BE)

BE is associated with a 30-fold increased risk of esophageal adenocarcinoma, which remains one of most rapidly rising cancers in the Western world[52-54]. Although EMR has a clear role in squamous cell carcinoma, its role in BE is not clearly defined, although studies have determined that EMR is effective in removing visible lesions in BE[24,30,55]. In fact, current evidence suggests that EMR of high-grade dysplasia (HGD) and early cancer (EC) has similar success rates as surgical treatment[56-60]. According to Ell *et al*, the indications for EMR in the setting of Barrett's neoplasia include the following: lesions limited to the mucosa that are macroscopically flat, tumor size between 20-30 mm, and good to moderate differentiation on histology[56]. Additionally, research suggests that EMR has better diagnostic reproducibility compared to mucosal biopsies alone, implying a possible role in routine surveillance[61]. Certainly, the cost-effectiveness and availability of EMR

would need to be considered prior to pursuing EMR as a primary tool in the surveillance of BE.

In one of the largest studies evaluating the efficacy of EMR for treatment of HGD and EC, 97% complete remission was achieved in resection of "low-risk" lesions and 59% complete remission in resection of "high-risk" lesions. "Low-risk" lesions were defined as macroscopic lesions measuring up to 20 mm and limited to the mucosa. However, at an average 12 mo follow-up period, the combined recurrence and metachronous cancer rate was 14%[56]. In an Italian study, EMR was found to be an effective method of treating HGD and intramucosal cancer in 34 patients that did not have submucosal involvement, with all patients remaining in remission at a median follow-up of 34.9 mo. In addition, EMR changed the pretreatment diagnosis in 25.6% of the studied patients[62].

Recurrence of neoplastic disease after EMR is a potential limitation[56,59]. Therefore, circumferential resection, in which the targeted dysplastic lesion and the surrounding Barrett's mucosa are removed, has also been studied[63]. In two separate studies from 2003 and 2006, no recurrent or metachronous lesions were reported. This is in stark contrast to an 11% recurrence rate with circumferential resections at a mean follow-up of 18 mo in a study by Giovannini *et al*[24,29,55].

In addition to EMR, multiple ablative techniques have been evaluated in the management of HGD and EC in BE. These include photodynamic therapy (PDT), argon beam coagulation therapy, lasers, radiofrequency ablation, and yttrium-aluminum-garnet laser therapy[64-68]. In fact, a recently-published multicenter, randomized controlled trial has shown that photodynamic therapy with Photofrin is superior than omeprazole alone in eliminating HGD at 5 years follow-up (77% *vs* 39%, respectively)[69]. To improve eradication of neoplastic tissue and decrease recurrence rates, the combined use of EMR with ablative techniques have been described[59,70]. Theoretically, recurrence rates are expected to be much lower with combined modalities, because both visible and non-visible lesions would be eradicated.

Combined modality has been evaluated by the Wiesbaden group in two separate studies. In the first study, 28 patients underwent EMR, 13 underwent PDT, 3 underwent APC, and 6 patients received a combination of these therapies for the treatment of HGD or EC. Metachronous or recurrent lesions were seen in 23% of the patients at a mean follow-up period of 34 ± 10 mo. Amongst the patients treated with EMR alone, 6/28 patients (21.4%) developed metachronous or recurrent lesions, compared to 1/6 patients (16.6%) treated with combined modalities[59]. In a follow-up study of a total of 115 patients (EMR = 70, PDT = 32, APC = 3, EMR + PDT = 10) undergoing endoscopic treatment for HGD or EC, there was a 31% rate of metachronous or recurrent lesions over an average follow-up time of 34 ± 10 mo. Individually, the metachronous or recurrence rate was 30% (21/70) in the EMR group *vs* 37.5% in the EMR + PDT group[70]. It is important to note that the number of patients treated with the combined modality is markedly less than that treated with EMR alone.

CONCLUSION

Since its introduction as a potential treatment option of GI mucosal cancers in 1984, the indications for EMR are continuing to expand. Today, EMR has become an integral part of the therapeutic endoscopy armamentarium. Although there are no specific guidelines for EMR as a treatment option for HGD or early cancer in Barrett's esophagus, the literature indicates that EMR is similar to surgery in efficacy, but has less morbidity and mortality. As newer techniques of EMR, including circumferential mucosectomy, are developed, the potential of reducing recurrence and metachronous rates are inviting.

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