Endoscopic mucosal resection : established indications, potential indications and perspectives

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Introduction

Endoscopic mucosal resection (EMR) has progressed tremendously since the first report of saline injection to assist removal of a flat colonic polyp in 1973 (Deyhle-1973). However, it was Tada who first applied an EMR technique (termed "stripped-off biopsy") to early (gastric) cancer (Tada-1984). Since these early reports, new techniques have been developed and are being applied to early cancers and high grade dysplasia in the esophagus, stomach, duodenum and colon. As experience has grown, indications have evolved and endoscopists are becoming more aggressive by performing larger resections. As these techniques evolve, it becomes critical that endoscopists understand the appropriate indications for this procedure and that they stay abreast of new developments. This is the purpose of this paper.

Established indications

A simplified concept summarizing the indications for EMR are the presence of cancer or high grade dysplasia confined to the mucosa or superficial submucosa without lymph node metastasis. The key to determining the candidacy of a patient for EMR is being able to predict the presence or absence of lymph node metastases and the depth of penetration of the lesion into the gut wall. We owe much of this work to our Japanese colleagues who have systematically and very carefully cataloged the relationship between various characteristics of a lesion and the likelihood of lymph node metastases. Lesion characteristics that predict applicability ot EMR are somewhat dependent upon the location of the lesion. These characteristics are listed in table I. For the esophagus, depth, differentiation, size and circumferential involvement are the most important factors. In the stomach, differentiation of the lesion, size and appearance are the critical issues with the appearance being divided into 5 individual or combinations of descriptive categories... Those 5 patterns include protruded, superficial elevated, flat, shallow depressed and excavated. In the colon, the appearance, size and mucosal appearance are the critical issues. The appearance is described as depressed, flat or protruded and the pit pattern is described according to 6 different appearances (2 subcategories under type III). The analyses of these factors help determine the eligibility of patients for EMR.

In esophageal lesions, the depth of penetration is one critical factor in predicting the presence or absence of lymph node metastases. For squamous carcinoma, if the lesion is confined to the superficial mucosa (m1 or m2) the incidence of lymph node metastases is 0. When the lesion penetrates into the muscularis mucosa (m3), lymph node metastases are seen in 9% of cases. When the superficial submucosa is penetrated (sm1), the rate goes up to 15% and with deep submucosal penetration (sm2 or sm3), the incidence of lymph node metastases goes up to 40%. (Makuuchi-2001) High frequency ultrasound probes (12, 20 and 30 MHz) is the most common technology used to determine the depth of penetration. There was some hope that optical coherence tomography (OCT) might also play a role in staging superficial cancers but it appears that this technology is unlikely to be widely applied. Other characteristics that affect the applicability of EMR for squamous cell carcinoma of the esophagus include the size of the lesion and the circumferential extent. Currently, absolute indications for EMR include extension into m1 or m2, lesion size < 3 cm and involving $\leq 75\%$ of the esophageal circumference. Relative indications (those patients who are poor surgical risks) include m3 to sm1 lesions ≥ 3 cm and they may be more than 75% circumferential. (Makuuchi-2001) It should be noted that all EMR techniques if applied circumferentially in the esophagus, almost invariably will produce significant stricturing.

For early gastric cancer, a key issue is the incidence of lymph node metastases and only those lesions with either no or an extremely low incidence of lymph node metastases would be considered amenable to EMR techniques. Depth, differentiation, size and appearance can all help predict the incidence of lymph node metastases. In general, only well differentiated tumors are felt to be amenable to EMR. The appearance is important and in general, protruding or flat lesions have the least chance of deep invasion or lymph node metastases. However, if a Ilc lesion (shallow depressed) is confined to the mucosa and is less than 20 mm, EMR can be performed. Size is also important and only lesions less than 20 mm in diameter should undergo EMR. In summary, IIa-c

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Table I. — **Characteristics determining eligibility of EMR**

Esophagus
- depth
- differentiation
- size
- circumferential involvement

Stomach
- appearance
  - I - protruded
  - IIa - superficial elevated
  - IIb - flat
  - IIc - shallow depressed
  - III - excavated
- differentiation
- size

Colon
- appearance
  - protruded
  - flat
  - depressed
- mucosal pattern
  - I - round pits
  - II - stellar
  - III_L - large tubular
  - IIIs - small tubular
  - IV - branch like
  - V - irregular
- size

lesions that are less than 20 mm in diameter and confined to the mucosa have a 0% incidence of lymph node metastases. A IIa lesion with extension into the submucosa which is less than 20 mm in diameter also has a zero incidence of lymph node metastases. Mucosally confined, well differentiated Ilc lesion has an incidence of lymph node metastases of less than 1% and these would also be considered amenable for EMR. However, a lesion that extends into the submucosa and is 30 mm or greater in diameter will have a 30% incidence of lymph node metastases and therefore is not amenable to local resection by the EMR technique.

In the colon, appearance, mucosal pattern and size are the primary determinants of the presence or absence of lymph node metastases. The appearance is categorized into protruded, flat and depressed type. In general, the depressed lesions are of greatest concern reflected by the fact that a depressed cancer that is $\leq$ 5 mm in diameter has an 8% incidence of lymph node metastases and therefore would not be amenable to EMR (Kudo-2001). Flat and protruding lesions up to 10 mm in size have a low incidence of lymph node metastases (max of 1%) 'and would be considered amenable for EMR. All lesions greater than 1 cm in diameter (with the exception of a flat lesion) have a relatively high incidence of lymph node metastases (8-85%) and are not amendable to EMR. The depth of invasion is also important and if the cancer is confined the superficial layer of the submucosa (superficial one third) and the extension into the submucosa represents less than half of the total diameter of the lesion, then the lymph node metastases rate is 0%. If there is a broad extension of the lesion into the superficial submucosa or it extends into sm2 or sm3, the lymph node metastasis rate goes up as high as 20% and again, would not be amenable to EMR (Kudo-2001). Finally, pit pattern is most important in determining whether or not the lesion is a cancer but is not suitable in and of itself to determine resectability by EMR. All pit patterns that are seen can potentially undergo EMR.

Potential indications

To date, EMR has been predominantly a procedure performed in Asia, particularly in Japan. In "western" countries, screening and surveillance endoscopy are not commonly performed and as a result, early cancers are seldom detected. The exception of course is in the colon but there is discrepancy between findings in Japan and western countries in terms of flat adenomas and cancers. However, Barrett's esophagus is an entity relatively common in western countries in which screening and surveillance programs are routinely applied. As a result, this subgroup provides an opportunity to detect early lesions (high grade dysplasia. or mucosal cancer) potentially providing an opportunity for treatment by EMR. The optimal approach to these patients has not been defined. Some physicians favor resection by EMR while others prefer an ablative approach either photochemically with photodynamic therapy (PDT) or by thermal means. Despite differences in opinion, the trend in management is going toward resection with EMR. It is unclear however whether local resection of areas of HGD with Barrett's is sufficient therapy or whether the entire Barrett's epithelium needs to be removed. It does appear that the people at most risk for cancer are those who develop multifocal areas of HGD which would seem to provide a rationale for removal of all specialized intestinal metaplasia. It is know from both animal and human experience that circumferential EMR will result in a high incidence of significant esophageal stenosis and most feel that a staged resection will be required ; 50-75% of the esophagus is removed at one session and the remainder removed after healing. If widespread mucosectomy does become a standard treatment in patients with Barrett's and HOD, new techniques will need to be developed. Current techniques remove only a small area and piece meal resection of a large area of esophageal mucosa is likely more risky than removing a single large section and mapping the specimen for accurate pathologic evaluation is almost impossible. A recent study of cap or band ligation techniques for EMR in Barrett's esophagus suggested that in most cases of HOD, high grade dysplasia was left behind after EMR (Lewis-2004).

Perspectives

Current EMR techniques include saline injection with snare (Tada-1984), lift and cut (Takekoshi-1989), tube with suction (Makuuchi-1990), a cap (Inoue-1992), band ligation (Matsuda-1993) and IT knife with

dissection (Ono-1999). With the exception of the IT knife dissection, all other techniques remove only a small portion of the mucosa at one time. The Ono technique with the IT knife is quite difficult to perform and has a relatively high complication rate. Thus, techniques for wide spread mucosectomy in the esophagus (and perhaps stomach) and safer and easier techniques are needed. The submucosal injection is also a critical part of the procedure and needs further development.

Mucosal injection

A key issue with EMR that might improve its margin of safety and allow more endoscopists to perform the procedure is finding a more persistent and robust agent for submucosal injection. We have utilized a material called poly-N-acetylglucosamine (pGlucNac). This is a hydro gel consisting of the carboxymethyl derivative of pGlucNac formulated to a specific viscosity. This material is isolated and purified from a North Atlantic marine organism. Bench studies have show that it is biodegradable, biocompatible and has hemostatic effect by causing adherence of red blood cells (Kulling-1999). The material has a high viscosity and studies in a swine esophagus suggest that an 8 mm cushion can be produced which will persist for more than 20 minutes (Hino-2002). This cushion was compared to saline and provided a significantly greater cushion over all times measured from 0-20 minutes. Post mortem studies suggest that the material is completely gone by 4 weeks and produces minimal to no inflammation or fibrosis (Hino-2002). Chris Gostout at the Mayo Clinic uses another material called hydroxypropyl methylcellulose (HPMC) which is also biocompatible and viscous thus producing a more robust cushion that saline alone. (Feitoza-2003) An interesting paper was presented at Digestive Disease Week (DDW) this year describing the use of CO_2 gas to "dissect" the submucosa rapidly. It may be that in the future, a combination of techniques will be utilized such as CO_2 dissection of the submucosa and then implantation of a "filler" which will provide robust separation to allow safe resection of large parts of the mucosa. In an effort to develop a technique to allow larger resection of specimens in the esophagus, the Apollo Group (Table II) in conjunction with Olympus Corporation have developed a modified cap technique for wide spread EMR in the esophagus. The system consist of 2 caps ; one designed to produce a longitudinal cut and a second to perform a circumferential cut. The idea is to inject the submucosa to produce a robust and persistent separation of the mucosa from the muscularis propria, make two longitudinal cuts that will allow removal of 50-75% of the circumference of the esophagus and then follow this with a circumferential cut at the proximal margin of the resection area. This produces a "strip" of tissue which is then grasped at its proximal edge and literally stripped off of the muscularis propria down to the GE junction. The distal end of the strip is then removed with a polypectomy snare. The cap technique described has been tested in an animal model and is ready for evaluation in human trials. It is unclear at this point how complex this procedure will be to perform in humans. Certainly, there will be room simplification of EMR and we should continue to strive for wider and wider safety margins in EMR techniques. Towards that end, there were several presentations at DDW this year that introduce technology that may simplify EMR. The device consists of an overtube with a specially designed operating tip. One such device was presented by Swain, *et al.* They tested an overtube device with an operating tip (Swain-2004). The tip consists of a soft distal. tip, a rectangular-shaped window that can vary between 1-3 cm in length and diathermy hook that runs through grooves in the side of the window. The system works by passing an endoscope through the overtube near to the window. Soft suction is applied and then a needle is inserted into the submucosa and saline is infused. Suction is then applied bringing a rectangular shaped tuft of mucosa into the chamber of the operating tip. The diathermy probe is then slowly withdrawn in a motion similar to peeling a potato. A rectangular shaped specimen is produced exposing the deep muscle layer. The procedure can then be repeated for wider resection. This device has animal testing only and its safety and efficacy will have to be determined in humans. The obvious proposed advantage of this device is the simplicity of resection which just involves a thumb controlled slow withdrawal of the diathermy knife. A key issue will be whether the amount of tissue suctioned into the chamber can be controlled in a way that guarantees against perforation.

Robotics have been applied to laparoscopic surgery with variable success. As we embark on the new era of flexible endoscopic surgery, robotics may play a role in these emerging techniques. A company named endoVia (endoVia, Norwood, MA) has developed a computer controlled robotic system designed for flexible endoscopes. It consists of a computer workstation that has

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two joysticks that control two accessories running through sheaths attached to the lateral sides of a flexible endoscope. The endoscope provides visualization within the gut lumen and the joysticks allow full range of motion for the two accessories. The surgical accessories include tissue graspers, scissors, needle drivers and a hot needle knife. This system was tested in a Erlanger and live pig model in performing EMR (Rothstein-2004). Using this device, successful EMR was performed by injecting saline, and using graspers and scissors to resect away a section of gastric mucosa. The device was also used to plant and tie a suture which would be an important adjunctive procedure during EMR. It is unclear at this point whether this kind of sophisticated technology will in fact be cost effective. It would have to be proven to be much safer than current more simple and less costly techniques.

In summary, using current techniques, the indication for EMR are well established and depend on the absence of lymph node metastasis and that the depth of penetration is shallow enough to allow an adequate resection margin. New techniques are being developed to improve safety and to allow removal of larger lesions. This is clearly an exciting area of development in gastrointestinal endoscopy.

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