1 Introduction: Endoscopic Submucosal Dissection to Per Oral Endoscopic Myotomy (POEM)

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Introduction

The development of Per Oral Endoscopic Myotomy (POEM) for esophageal achalasia is, in large part, the result of large-population screening for GI malignancy. While screening for colorectal cancer in average-risk patients over the age of 50 is well-accepted in America, there is no equivalent screening protocol to address esophageal or gastric cancer. In Japan, on the other hand, the rates of both gastric adenocarcinoma and squamous carcinoma of the esophagus are much higher than those observed in Western countries. As a result, screening upper endoscopy is not only more widespread, but also more sophisticated, involving adjuncts such as chromoendoscopy, narrow band imaging, magnification endoscopy, and more recently endocytoscopy. A large number of lesions are detected (the National Cancer Center in Tokyo alone treats more than 10,000 gastric lesions per year) and some form of resection is recommended for the vast majority. This is partly the result of differences in the pathologic interpretation between Japanese and Western pathologists (a lesion with “high grade dysplasia” or “carcinoma in situ” in the West may be considered “cancer” in Japan). Based on the observation that early lesions have a very low rate of lymph node metastasis, local resection is often preferable to surgery and a number of endoscopic techniques have evolved for this purpose.

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This chapter will trace the development of the POEM procedure from its roots in the endoscopic resection of esophageal and gastric lesions. We will follow the progression of the technical components, from simple colorectal polypectomy to *en bloc* resection of "strips" of tissue, and finally to dissection of the submucosal space and submucosal tunneling. We will also examine the evolution of the equipment necessary for the procedure, including the creation of distal caps and the development of specialized knives.

Endoscopic Mucosal Resection (EMR)

Strip Biopsy

In 1955, two years before the development of the fiberoptic endoscope, Rosenberg reported the "saline lift" technique, in which he injected saline into the submucosal space to increase the distance between the mucosa and the muscle layer, thereby reducing the risk of perforation during polypectomy in the rectum and distal colon [1, 2]. In Germany, Deyhle et al. developed a similar technique for the resection of sessile colon polyps in 1973, and they reported the first true *en bloc* EMR of a small gastric lesion using a wire snare in 1974 [3–5]. In Japan, Tada et al. also applied the saline lift to the resection of early gastric lesions. They utilized submucosal saline injection followed by resection of the mucosal bleb with a wire snare. Their technique was initially published in Japanese in 1984, and ultimately they published a large series in English in 1993 [6].

An alternate technique, dubbed the "lift and cut biopsy," was originally described by Martin et al. in 1976 [7]. Rather than pushing the mucosa away from the muscle layer with saline, they utilized a double-snare technique, using one snare to grasp and elevate the mucosa, and the other snare to resect the specimen. Takekoshi et al. applied this to early gastric cancer in Japan beginning in 1978 [8]. They used a grasper to elevate the mucosa and an electrocautery wire snare to resect the lesion. In their series of 308 lesions over 15 years, they noted that the size, depth, location, and differentiation of the lesion affected their ability to completely excise lesions. The rates of incomplete resection were as high as 57% for undifferentiated carcinomas, lesions larger than 1–2 cm, and lesions on the anterior or posterior wall. The technique was most useful for small, well-differentiated lesions on the lesser curve.

The original "strip biopsy" merged the "saline lift" with the "lift and cut biopsy," beginning with a submucosal saline injection, then elevating the mucosa with a grasper, and finally resecting the specimen with a wire snare.

Monma et al. and Makuuchi et al. applied the "strip biopsy" (injection, lifting, and snaring) to lesions of the esophagus and published reports in Japanese in 1990 [9, 10].

Band Ligation

Publications in Japanese by Masuda et al. in 1993 and in English by Chaves et al. in 1994 reported use of a variceal ligating device, similar to the technique of Van

Stiegmann, in which flat lesions were converted into "polyps" by grasping tissue and strangulating it at the base with a ligating band [11, 12]. The "polyp" could then be resected in the usual fashion with a wire electrocautery snare. The technique eventually became known as the "EMR-L." While beginning in the colon, EMR-L was applied to lesions of the esophagus by Fleischer et al. who published their series in 1996 [13].

Evolution of the Distal Cap

Inoue and Endo modified the "lift and cut biopsy," adding a transparent overtube to improve their ability to control and resect esophageal mucosa by grasping and snaring. In 1990, they reported a series of 11 cases, including resection of a small focus of adenocarcinoma in a short segment of Barrett's esophagus, and they found that it was possible to resect both large and near-circumferential segments of mucosa in piecemeal fashion, leaving the underlying muscle layer intact [14].

Makuuchi developed a special overtube, which he combined with submucosal saline injection, suction (rather than grasping), and snaring to resect larger fragments of esophageal mucosa than had previously been possible [15]. Kawano et al. modified the so-called "Makuuchi tube" to include a lateral window, which served as a mucosal trap [16]. The main limitation of the tube technique, however, was that it could only be applied to lesions of the esophagus.

To address the shortcomings of the transparent overtube, Inoue et al. developed a transparent plastic cap that attached to the distal tip of the endoscope in 1992 and published their initial series in 1993, calling their technique the "EMR-C" [17]. A refinement published by Inoue et al. in 1994 added a small ridge to allow for easy seating of the snare at the distal end of the cap [18]. The basic idea of grasping, strangulating, and resecting tissue was the same as with EMR-L, but the EMR-C procedure combined strangulation and resection into a single step. The technique was applied to a series of colonic lesions published by Tada et al. in 1996 and to resection of the duodenal ampulla by Izumi et al. in 1998 [19, 20]. In effect, the EMR cap served as a portable tube that traveled with the endoscope and allowed for the injection, suction, and snare technique to be applied to lesions anywhere in the gastrointestinal tract that could be reached with the endoscope.

Large-Volume Injection

The main complication associated with both the EMR-L and EMR-C techniques is involvement of the muscle layer within the resected specimen, causing full-thickness perforation. Anticipating this, early ex vivo pilot studies conducted in Japan involved resected surgical specimens, including human esophagus, stomach, and colon. EMR-C was performed at various locations and with various volumes of injected saline (ranging from 0 to 20 mL), while simultaneously examining the bowel wall under ultrasound guidance. The purpose at the time was to determine safety parameters regarding the size of the distal cap, volume of submucosal saline injection, strength of the suction, and ideal location within the bleb for placement of the wire snare; however, of particular interest is the finding that large-volume saline injection in the esophagus caused semi-circumferential submucosal dissection, creating a space of approximately 1 cm (the diameter of a standard gastroscope) between the mucosa and the muscle layer without any apparent disruption of the mucosa itself.

Endoscopic Submucosal Dissection (ESD)

From EMR to ESD

Beginning in 1982, Hirao et al. added a “pre-cutting” step to the original “strip biopsy.” They began with submucosal injection with a solution of hypertonic saline and epinephrine, and followed this by cutting the mucosa circumferentially around the lesion using a needle knife. In doing this, the intended specimen retracts, effectively increasing the size of the lesion that can safely be resected with the cutting snare. They utilized the technique in 106 patients with lesions of the stomach ($n = 101$) and esophagus ($n = 5$) and published their series in 1988 [21]. The step of pre-cutting anticipated what would later become a critical step in ESD.

Hosokawa and Yoshida added a triangular plate protected by a ceramic tip to the end of a needle knife in 1995, developing the first insulated tip (IT) knife, which they published in Japanese in 1998. The following year, Gotoda et al. modified the “pre-cutting” technique of Hirao et al. using the IT knife rather than the needle knife to resect two rectosigmoid lesions [22]. They felt that the IT knife was easy to use and that the insulated tip minimized the risk of perforation. The upper limit of lesions that could be resected with pre-cutting and snaring, however, remained approximately 3 cm.

The group of Yamamoto et al. developed a technique that utilized submucosal injection and pre-cutting, but did not require use of a snare. They used an insulated, single-tooth forceps attached to electrocautery that could both grasp and cut tissue, along with a modified transparent cap that was flat at the distal end to maintain the orientation of the forceps. An added benefit of the cap was to maintain visualization during retraction and dissection of the tissue. In 1998, they resected a 4 cm flat lesion in the rectum by injecting, pre-cutting circumferentially, and dividing the submucosal fibers under direct vision; and in 2000, they presented the *en bloc* resection of a 6 cm gastric lesion at the ASGE meeting in San Diego, CA [23, 24]. Further modifications included use of a tapered cylindrical (rather than flat) hood and a needle knife to more precisely control the location and depth of the electrocautery. In 2002, the group published a series of 70 cases using this refined technique [25].

Evolution of Knives

In 2004, Rösch et al. reported their initial experience using the IT knife (rather than the needle knife) in 37 patients with admittedly poor results, but as this modified *en bloc* form of EMR (eventually renamed ESD) became more popular, the equipment and procedural techniques evolved quickly [26].

Oyama et al. published a series in 2005 with improved rates of *en bloc* resection using a "hook knife" (initially reported in Japanese in 2002), which consisted of a right-angle modification of the needle knife [27]. The knife could be rotated to the optimal direction and then used to hook and retract the tissue prior to cutting, resulting in improved precision and safety.

In 2004, Yahagi et al. reported (in Japanese) the use of a "flex knife." Created from a twisted snare and a flexible sheath, the knife was soft and flexible with a bumper on the end to easily control the depth of incision, reducing the risk of disruption of the muscle layer. In the same year, Inoue et al. reported (also in Japanese) an ESD using the triangle-tipped (TT) knife, which essentially removed the ceramic tip from the IT knife, exposing the multidirectional triangular tip.

As equipment continued to evolve, the "flush knife" was developed, combining a cutting needle tip with a water jet to reduce the number of instrument exchanges and aid in the development of the submucosal space. In 2007, Toyonaga et al. published (in Japanese) their initial experience using the flush knife for resection of gastric lesions.

Submucosal Tunneling

One of the technical challenges of ESD is control of the specimen as it is being dissected off the underlying muscle layer. The standard technique involves submucosal injection, followed by mucosal pre-cutting, and then division of the submucosal fibers; in the final step, the endoscopist must simultaneously retract the specimen to provide visualization, while at the same time developing the submucosal space to dissect and divide the fibers. As a possible solution to this difficulty, von Delius et al. reported "endoscopy of the submucosal space" in 2007 [28]. In a pig esophagus model, they essentially reversed the last two steps. They performed a submucosal injection and then entered the submucosal space through a mucosotomy, dividing the submucosal fibers and creating a tunnel under the lesion without any pre-cutting. Once the mucosa containing the lesion had been completely dissected off the underlying muscle layer, they completed the resection by "post-" cutting the mucosa. With this technique, they were able to demonstrate successful resection of lesions of various sizes, including complete *en bloc* circumferential donuts, which are particularly difficult (though still possible) using the standard ESD technique. Although submucosal tunneling was never widely adopted for ESD, it was a critical innovation for the development of the POEM procedure.

POEM

Experimental Endoscopic Myotomy

The first reported endoscopic esophageal myotomy actually predates the initial EMR techniques. In 1980, Ortega et al. reported the outcomes of six dogs followed by 17 patients who underwent an endoscopic myotomy procedure for achalasia in a hospital in Venezuela [29]. Based on their dog experiments, they determined an optimal depth of 3 mm for their hand-made wire needle knife, and then applied this to human patients, performing two blind 1 cm incisions through the mucosa just above the squamo-columnar junction. Surprisingly, they reported at least partial improvement in all patients, no cases of full-thickness perforation, and only a 17.6% (3/17) rate of procedural bleeding. Their procedure, of course, was not widely adopted, and the endoscopic options for the next three decades were limited to esophageal dilation or Botox injection.

In 2004, Kalloo et al. reported their experience with endoscopic transgastric peritoneoscopy (and liver biopsy) in a pig model, suggesting this as a possible alternative to laparoscopy [30]. This generated renewed interest in performing surgical procedures endoscopically and led to the development of a field known as natural orifice transluminal endoscopic surgery (NOTES). The bulk of research generated during the NOTES era involved the (now rarely performed) transgastric or transvaginal approaches to appendectomy or cholecystectomy. In September of 2007, however, Pasricha et al. published a refined version of the endoscopic myotomy for achalasia [31]. In four pigs, they performed a submucosal injection followed by mucosal incision and entered the submucosal space, developing a tunnel with a pneumatic balloon (rather than by directly dissecting the submucosal fibers as reported by von Delius earlier in the same year). Following this, they directly cut the circular muscle with a needle knife under direct vision, proceeding from distal to proximal and providing a significant improvement in safety when compared to Ortega's initial description.

Early Experience with Human POEM

The first human POEM was performed by Haruhiro Inoue in Yokohama, Japan, in September of 2008 [32]. The technique incorporated several important refinements to make Pasricha's porcine model suitable for clinical application.

Patients were anesthetized with a cuffed endotracheal tube to help protect against pulmonary aspiration, and positive pressure ventilation was applied to overcome any potential mediastinal or pleural pressures that might be generated by endoscopic insufflation. In addition, carbon dioxide rather than air insufflation was used based on theoretical concerns for the possible development of mediastinal emphysema or air embolization. In the initial series of 17 patients, postprocedure CT scans did reveal some small collections of mediastinal or pleural gas; however, these did not appear to be clinically significant. Of interest, one patient unexpectedly developed capnoperitoneum, which resulted in elevated peak pulmonary pressures; this resolved with simple needle decompression of the peritoneal space, but reinforced the importance of using CO_2 and limiting the volume of insufflation to the lowest level possible.

Initially, an oblique distal attachment, similar to one of the early EMR-C caps, was used to aid in visualization and to protect the mucosa from inadvertent thermal injury. In later iterations of the procedure, a straight, tapered ESD cap allowed more precise control during entry into the submucosal space. Following submucosal injection and longitudinal mucosal incision (horizontal incision resulted in an easier entry, but a much more difficult closure), the submucosal tunnel was created. In the porcine model, this was done with blind inflation of a pneumatic balloon; however, there is potential for misplacement of the balloon and inadvertent damage to the esophageal mucosa or blood vessels. In clinical practice, the submucosal fibers were divided under direct vision, similar to ESD or the submucosal endoscopy described by von Delius, providing more precise control and better hemostasis [28].

Division of the circular muscle layer also differed from the experimental model. While Pasricha et al. performed a retrograde myotomy with the needle knife, the first POEM cases were done in an anterograde direction with the TT knife, which was initially developed for ESD. In doing this, it was possible to dissect the circular muscle, layer by layer, to identify the intermuscular space, and then to use the TT knife to hook the circular muscle bundles away from the longitudinal fibers, maintaining direct vision and protecting the longitudinal layer for the entire length of the dissection.

In addition to the technical performance of the procedure, there were several open questions at the beginning of the clinical experience: which o'clock location to choose for the myotomy; whether to perform a selective (circular) or full-thickness (circular and longitudinal) myotomy; how to identify the esophagogastric junction (EGJ) from within the submucosal tunnel and ensure adequate gastric myotomy length; and the optimal length of the esophageal myotomy. Each of these remains an open question to some extent.

The initial o'clock location was chosen to mimic the surgical cardiomyotomy; that is, the anterior position. One of the main concerns was the inability to perform a concurrent anti-reflux procedure (such as a partial fundoplication in the case of a surgical myotomy). Care was therefore taken to avoid damage to the angle of His, which may form a natural anti-reflux barrier. At the 2 o'clock position, which endoscopically leads to the lesser curve of the stomach, the angle of His (located in the 8 o'clock position) is theoretically preserved. In two cases, a posterior (5 o'clock) myotomy was attempted, but this was found to be technically challenging due to the interference of the spine in maintaining accurate positioning of the endoscope tip. The 2 o'clock position was therefore chosen as the default location.

In regard to the thickness of the myotomy, all procedures were started with the intention of performing a selective (circular) myotomy in order to avoid damage to mediastinal structures. In doing this, the longitudinal muscle fibers were found to be thin enough to spread apart widely simply from the pressure of the endoscope, and postprocedure lower esophageal sphincter pressures decreased to the normal range without division of the longtitudinal fibers.

Several anatomic landmarks of the EGJ were noted during the first few cases: narrowing followed by widening of the submucosal space; pallisade vessels in the submucosal layer, which are located in the distal esophagus; and increased submucosal vasculature upon reaching the gastric space. Markers that were identified later include blue discoloration of the mucosa on retroflexed view of the gastric cardia and identification of a spindle vein in the submucosal space.

The total length of the endoscopic myotomy began with the length of its surgical counterpart. In the first seven cases, the mean total myotomy length was 4.9 cm. In the next ten cases, the myotomy was extended to a total length of 10.4 cm, resulting in better symptom relief and demonstrating one of the main advantages of POEM over the surgical myotomy: the ability to endoscopically perform an extended esophageal myotomy.

Summary and Future Trends

The first endoscopic myotomy for achalasia, performed in Venezuela in 1980, involved two cuts through the esophageal mucosa and into the circular muscle, with the blind hope of cutting only circular muscle fibers and avoiding a full-thickness esophageal perforation. Due to obvious safety concerns, the idea was abandoned. In subsequent years, several parallel advancements in equipment and endoscopic techniques provided the tools necessary for the first POEM procedure nearly 30 years later.

Beginning in the 1950s, submucosal saline injection was utilized to increase the distance between the mucosa and the underlying muscle layer to improve the safety of colorectal polyp resection. In the 1970s and 1980s in Germany and Japan, this was applied to early lesions of the stomach and esophagus. Endoscopists created an artificial saline “polyp” that could be resected in the usual fashion with a wire snare. An alternate technique around the same time utilized a grasper to lift the mucosa, which was then resected with the wire snare. A combination of the “saline lift” and the “lift and cut” biopsy produced the “strip biopsy” (saline injection, lift, and cut), which became a standard EMR technique.

To increase the size of lesions that could be resected with EMR, one group in Japan developed a “pre-cutting” technique, in which the mucosa was incised circumferentially around the lesion, resulting in contraction of the intended specimen. Clear plastic overtubes were utilized to better control the specimens during the “lift and cut” technique; eventually, clear plastic caps were developed to overcome the limitations of the bulky overtubes, and the technique of cap EMR (“EMR-C”) emerged. Pilot experiments on ex vivo surgical specimens to determine safety parameters for EMR-C (including the size of the cap, volume of injection, and amount of suction) revealed that large-volume submucosal saline injection could develop the submucosal plane without damaging the overlying mucosa.

As time progressed, the submucosal injection, pre-cutting of the mucosa, and a modified dissection cap were combined (again in Japan) to allow for dissection of the submucosal space under direct vision, significantly increasing the size of specimens that could be resected *en bloc*, and later being renamed to ESD. This advancement led to the rapid evolution of caps and knives, including the creation of the TT knife. Equipment originally intended for ESD was later applied to the first POEM procedures.

Despite the advancements with caps and knives, the ability to retract the specimen with the endoscope while dissecting the submucosal space under direct visualization remained difficult. Fortunately, a group in Germany reported "submucosal endoscopy" to reduce the need for retraction. They pioneered the technique of tunneling under a lesion, completing the dissection before incising the mucosa. Meanwhile, a group in Texas reported an endoscopic myotomy in a porcine model. They used a balloon to blindly develop the submucosal space and then cut the circular muscle from distal to proximal. Finally, refinements by Inoue et al. applied the principles of ESD (including large-volume injection, CO_2 insufflation, and submucosal tunneling under direct vision) in order to safely perform the procedure in human patients. The first POEM procedures sought to mimic the surgical myotomy; the esophageal portion of the myotomy was later extended to take full advantage of the endoscopic approach.

Several controversies remain regarding the POEM procedure, such as the ideal location, length, and thickness of the myotomy. It is also difficult to ensure adequate dissection has been carried out on the gastric side, and several adjuncts have been developed, including use of a second endoscope, radio-opaque clips, or intraprocedure esophageal distensibility measurements [33–35]. Future research may determine the optimal patient populations that benefit from POEM and help to answer the open questions regarding the technique.

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