Polypectomy for Large Polyps with Endoscopic Mucosal Resection

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KEYWORDS

• EMR • Endoscopic mucosal resection • Wide-field EMR
• Comparative effectiveness data • Cap assisted EMR • Cold snare EMR
• Underwater EMR

KEY POINTS

- Most noncancerous colon polyps, regardless of size, can be safely and effectively managed with organ-preserving techniques such as endoscopic mucosal resection (EMR)
- The 4 contributors of success in an EMR procedure include time, team, tool, and techniques
- Proper preprocedural planning (including review of images beforehand, and proper bowel preparation) is essential for safe and efficient EMR

INTRODUCTION

The foundation of modern endoscopic mucosal resection (EMR) was laid in 1955 by a surgeon named Norman Rosenberg. In his quest to increase safety during the fulguration of rectosigmoid polyps, he realized that after a submucosal saline injection, even a 10-s colonic burn with an electrosurgical dissection knife did not injure the muscularis propria.[1] The reason this technique is safe and efficacious is that the submucosal saline cushion acts as a heat sink for electrical energy to prevent deep mural injury. This is critical given the fact that healthy colonic tissue has an average total thickness of only 2–4 mm.[2,3]

Nearly 20 years later, Peter Deyhle's group released 2 landmark papers describing successful endoscopic polypectomy in humans, first with the resection of proximal colon pedunculated polyps in 1971,[4] then with the saline-assisted resection of distal colon sessile polyps in 1973.[5] The importance of these 2 studies cannot be overstated

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Abbreviations	
ADR	adenoma detection rate
AADR	advanced adenoma detection rate
BBPS	Boston Bowel Preparation Score
BBS	bowel bubble score
CI	confidence interval
cm	centimeter(s)
CPT	Current Procedural Terminology (R)
CRC	colorectal cancer
EGD	esophagogastroduodenoscopy
EMR	endoscopic mucosal resection
ESD	endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
FDA	Food and Drug Administration
FICE	Fujinon Intelligent Color Enhancement
IQR	interquartile range
JNET	Japanese NBI Expert Team classification
K	inter-observer agreement (Kappa statistic)
LR	laparoscopic resection
LSL	laterally spreading lesion
mm	millimeter(s)
NBI	Narrow Band Imaging
NICE	Narrow Band Imaging International Colorectal Endoscopic classification
OR	odds ratio
s	second(s)
SEER	Surveillance, Epidemiology, and End Results program

as it demonstrated the ability of colonoscopy to remove polyps painlessly, with most polypectomy sites healing in 7 days, thereby sparing the patient "both a laparotomy and a lengthy stay in the hospital."

The next advancement in the field was the realization by Inoue and colleagues that the fitment of a transparent distal attachment cap allowed sufficient suction, and therefore, larger-sized en-bloc resection, during EMR of sessile and flat lesions across the esophagus, stomach, and colon.[6,7] Despite the fundamental technique of EMR being known for several decades (under various names such as the "strip biopsy,"[8] "endoscopic resection with hypertonic saline and epinephrine,"[9] and "endoscopic mucosectomy"[10]), concerns persisted that polyps above a certain size were too dangerous to remove endoscopically. Indeed, 1 gastroenterology practice guideline in 2000 stated "[polyps >2 cm] cannot be completely or safely excised during colonoscopy, and the patient should be referred for primary surgical resection."[11] Nonetheless, interest in, and perfection of the technique continued unabated at medical centers worldwide, in line with a general medical trend to advance minimally invasive, outpatient treatments.

This article aims to provide the reader a compendium of what is known about this modality, technical considerations including how to manage the more common clinical scenarios, and new advances in the field.

COMPARATIVE EFFECTIVENESS DATA

Endoscopic polypectomy reduces not only the subsequent risk of colorectal cancer (CRC)[12] but also of CRC mortality.[13] However, surgical referrals for large colon polyps, even of nonmalignant polyps, continue to occur in the background of the referring

physician's unawareness of endoscopic options. In a population-based study of more than 4000 patients from France, Le Roy and colleagues found that 4.1% of patients (175/4251) who underwent colonoscopy for fecal occult blood in stool were referred directly to surgery for nonmalignant polyps; disturbingly, none of these individuals were evaluated by a tertiary endoscopic center beforehand. Subgroup analysis surprisingly confirmed that the referring gastroenterologist was a risk factor for inappropriate surgical referral.[14]

Fortunately, there is increasing awareness that EMR, even complex wide-field EMR, is successful in expert hands. For instance, in a 5-year tertiary referral center study by Raju and colleagues, 76% of patients (155/203) underwent successful EMR as an alternative to surgery; the success rate conceivably could have been even higher, were it not for technical failure in 14 cases due to prior intervention or tattoo, thereby requiring salvage surgical resection.[15] Moss and colleagues were also able to achieve a remarkably EMR high technical success rate (1000/1134%, 88%) in a nationwide Australian cohort in lesions as large as 12 cm; even in instances of adenoma recurrence, almost all were successfully managed by repeat endoscopy (135/145%, 93%).[16]

As a result, EMR is now clinically accepted as a first-line treatment of most eligible colonic lesions, meaning those lesions without evidence of deep submucosal/transmural invasion of cancer.[8,17] Beginning in 2014, dedicated Current Procedural Terminology (CPT) codes were established for upper (43211 esophagoscopy, 43254 EGD) and lower (45349 flexible sigmoidoscopy, 44403 colonoscopy through stoma, 45390 colonoscopy) gastrointestinal EMR procedures.[18]

From a health economics perspective, several articles highlight the advantages of EMR over surgical resection. Jayanna and colleagues found that, among an Australian cohort of more than 1300 patients who underwent EMR between 2010 and 2013, the mean anticipated cost savings per patient was $7602 when compared with a cost model for comparable, complication-free colon surgeries. Additionally, the hospital length of stay per patient was significantly reduced with EMR versus surgery (2.81 nights, 95% confidence interval (CI): 2.69–2.94, $P < .001$).[19] Keswani and colleagues similarly analyzed the costs and adverse events between the surgical and endoscopic resection of nonmalignant colon polyps. They compared a historical cohort of patients undergoing surgical resection for nonmalignant colon polyps over a 10-year period (2003–2013) versus those undergoing EMR during a 3-year period (2011–2013) at a single-center academic medical center in the United States. Not only was there a trend for lower adverse events in the EMR group versus the surgical resection group (10% vs 18%, $P = .09$) but also the length of stay in the EMR group was significantly lower (0 vs 5 days, IQR 4,7, $P < .0001$). The overall costs of EMR (including rescue surgery whereby needed) were significantly lower than the costs of primary surgical resection ($2152 vs $15,264, $P < .0001$).[20] Likewise, a thought-provoking Markov model by Law and colleagues found that the only situation in which laparoscopic colon resection (LR) is economically superior to EMR requires that 3 conditions are met: (1) technical success of index EMR, less than 75.8% of cases, (2) the adverse event of EMR, greater than 12%, and (3) the cost of laparoscopic resection, <$14,000. In routine clinical practice, none of these conditions are typically met; therefore, EMR is a superior modality compared with LR.[21] There are also complications associated with surgery. In a retrospective cohort study of nearly 500 colon surgeries over a 5-year period (2013–2018) in a high-volume Australian academic medical center, Louis and colleagues found that, of the 181 surgeries undertaken for benign pathologies, over 75% (136/181) experienced some type of complication as defined by the Clavien–Dindo classification. Additionally, although

over half of the complications in the study were minor (53.2% grade I and II), these were associated with a 15.8% and 36.8% increase in hospital costs, respectively ($P < .0001$).[22]

PREDICTORS OF SUCCESS – TIME AND TEAM

A successful EMR begins with proper planning at the outset. This includes reviewing high-resolution photos beforehand to help the endoscopist formulate a resection strategy. Furthermore, EMR requires a dedicated block time—it should not be booked in a high-throughput, open-access room. The endoscopist should not feel rushed during the key phases of an EMR procedure that may increase the risk of technical failure, or increase the risk of complications. Ability to review high-resolution photos beforehand can help the endoscopist formulate a resection strategy.

Another key determinant to the success and safety of any EMR procedure is proper bowel preparation. In a single-center, cross-sectional study, Guo and colleagues determined that both the Boston Bowel Preparation Scale (BBPS) and the bowel bubble score (BBS) impact both adenoma detection rate (ADR) and advanced adenoma detection rate (AADR). The authors found that a colon segment's ADR jumped to 10.8 versus 3.2% for a Boston Bowel Preparation Score (BBPS) of 3 versus 1; likewise, the AADR jumped from 1.6% to 4.5% ($P < .05$). There was a similar trend toward increased ADR/AADR with a lower BBS (ie, fewer bubbles in the lumen).[23] Similarly, a nearly 15-year observational study of more than 25,000 American patients found that a systematic approach to CRC prevention (named the "CLEAR" protocol for Clean the colon, Look Everywhere, and complete Abnormality Removal) resulted in a 67% reduction in CRC compared with the Surveillance, Epidemiology, and End Results program (SEER-18) population.[24]d

Next, the importance of a highly skilled team cannot be understated—not just the nursing staff, but also other members of the multidisciplinary team such as the radiologist and the anesthesiologist. For instance, a nurse highly skilled in EMR can function similar to a professional golf caddie, highlighting a more optimal resection technique or even alerting the endoscopist to impending danger. Additionally, a skilled anesthesiologist can help optimize sedation during complex cases, and a skilled radiologist can help look for subtle radiographic clues that either makes an EMR contraindicated, or help identify complications in a timely manner.[25]

PREDICTORS OF SUCCESS – TOOLS AND TECHNIQUE

Before Patient's Arrival on the Unit

A successful EMR begins before the procedure itself. For instance, it is critical to educate the referring physicians that before referral, they should not attempt partial endoscopic resection, nor should they tattoo within 5 cm (or even underneath) the lesion, lest it results in massive submucosal fibrosis. This not only increases the technical complexity of the procedure (up to procedural failure) but also may increase the risk of complications including perforation. In fact, lesions that are obviously large and bulky, or are in an immediately recognizable landmark (eg, rectal vault, or cecal pit), do not need tattoo marking before referral for EMR. Similarly, referring gastroenterologists should avoid overly aggressive biopsies to reduce the risk of submucosal fibrosis.[26]

EMR Tools

Cap-assisted endoscopic mucosal resection

A cap attached to the distal end of the scope is a useful adjunctive method used to help with EMR, particularly among flat lesions. After submucosal injection or filling

the lumen with water, suction or even gentle pressure can be applied so the tissue can fill into the cap for better tissue capture. Additionally, a cap can deflect folds allowing better visualization of the entire lesion.[27] Multiple caps exist (including purpose-designed cap EMR kits) which help facilitate the EMR procedure. Depending on the cap's snugness of fit onto the endoscope and the complexity of the EMR procedure, the use of waterproof anesthesia tape (Hy tape, Hy-Tape International, Patterson, NY) may help secure the cap onto the endoscope to reduce the likelihood of the cap from dislodging and unnecessarily distracting the endoscopist with a foreign body retrieval.[28]

Choice of snare

Multiple snares sizes and configurations exist; little data support the superiority of one snare choice over another. As reviewed in a recent European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline, the most important determinant is an endoscopist's familiarity with the performance characteristics of a particular choice of snare. While monofilament snares may potentially allow faster tissue resection and therefore, reduced likelihood of colonic wall thermal injury (vs polyfilament snares may better grip the mucosa in flat polyps), this has not yet been systematically proven.[29]

Endoscopic Mucosal Resection Technique

Management of antithrombotic agents

The management of antithrombotic agents is discussed in detail in a separate chapter (Chapter 8).

Inspection

A high-quality inspection of the lesion is a necessity before performing EMR to determine if the lesion is appropriate for EMR. Lesions most suitable for EMR are either pedunculated or nonpedunculated laterally spreading lesions (LSL), which are nonpolypoid lesions larger than 10 mm in size.[30]

Inspection begins with viewing the lesion under high-definition white light and measuring the size of the lesion and location of the lesion. The next step is to determine if the lesion is granular or smooth. Nongranular LSL have a higher tendency to have submucosal invasion at 12% compared with 6% with granular LSL.[31] In a recent study, granular-mixed LSL has almost a 10% risk of having underlying submucosal invasive cancer, especially with lesions more than 4 cm or in the rectum.[32]

EMR should be limited to LSL that has superficial submucosal invasion or less than 1000 μm depth of invasion, which highlights the importance of accurate preprocedural inspection with endoscopic classifications such as the Kudo pit pattern or the Narrow Band Imaging International Colorectal Endoscopic (NICE)/Japan NBI Expert Team (JNET) classification (**Fig. 1**). Beyond this level of invasion, there is a high risk for incomplete resection with EMR, and other treatment modalities should be considered such as endoscopic submucosal dissection (ESD) or surgery. All 3 major endoscope manufacturers are equipped with optical imaging technology to emulate chromoendoscopy through various modalities, and are activated with a push of a button (narrow-band imaging (NBI)—Olympus Corporation, Center Valley, PA; Fujinon Intelligent Chromoendoscopy (FICE) – FUJIFILM Corporation, Wayne, NJ; iSCAN – Pentax of America, Montvale, NJ), although a systematic review and meta-analysis of 17 randomized control trials failed to establish superiority of virtual chromoendoscopy over conventional dye chromoendoscopy for dysplasia detection in inflammatory bowel disease (IBD).[33] LSL that are brown to dark brown with disrupted or irregular vessels and irregular surface patterns are likely classified as NICE type 3 and has a

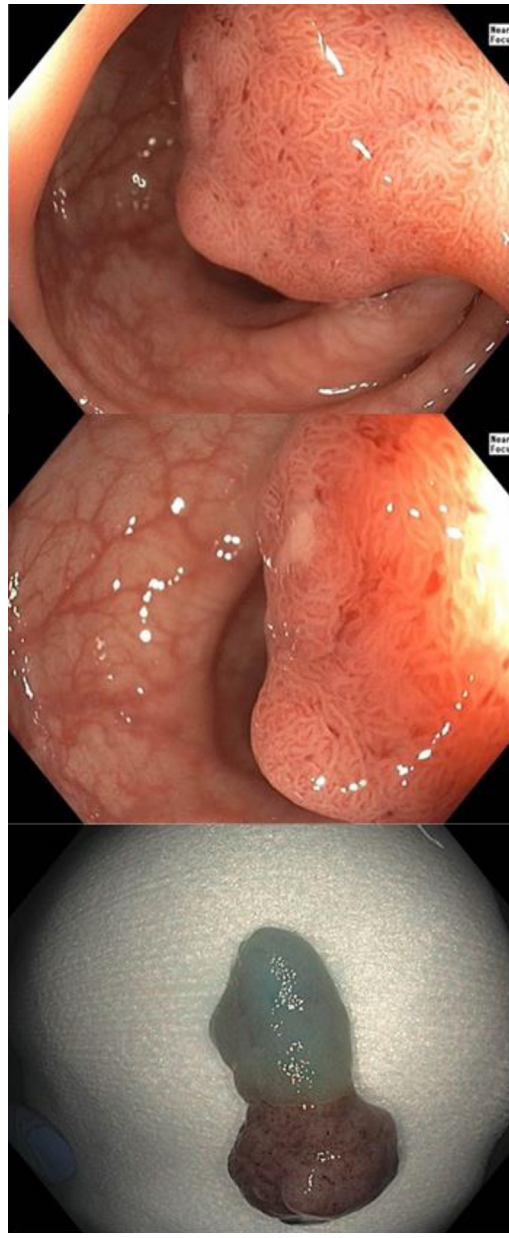

Fig. 1. Example of a JNET 2b pedunculated polyp. Based on the endoscopic appearance, the decision was made to perform EMR with contrast-enhanced submucosal injection. Pathology confirmed intramucosal cancer with wide negative margins (8 mm, Haggitt Level 0).

high probability of deep submucosal invasion.[34] The Paris Classification should also be used to help stratify which lesions are more likely to have advanced disease.[35] This highest risk configuration are LSL with a central depression; Paris 0-IIc lesions have an overall risk of 27%–36% for submucosal invasion with nearly all lesions

greater than 20 mm having submucosal invasion.[36,37] After a thorough inspection of the lesion is performed and there is a low probability of deep submucosal invasion, preparation can be made for the EMR of the lesion.

Even if a lesion does not seem to have high-risk endoscopic features, a simplified scoring system may be invaluable in determining not only the EMR approach but also whether the lesion should even be resected by the endoscopist or instead be referred to a dedicated tertiary referral center. The "SMSA" score (with attendant components of Site, Morphology, Size, and Accessibility), first developed by Gupta and colleagues, is an easy-to-use, 4-Level scoring system which helps stratify an endoscopist's ability to undertake polypectomy of various polyp configurations, and more importantly may predict the likelihood of EMR technical failure. There was very high interobserver reliability for polyp scores (interclass correlation coefficient 0.93) and levels (K = 0.888). This was subsequently validated in a United Kingdom (UK)-based cohort of 114 patients; 20% of patients with a Level 4 polyp (8/41) experienced incomplete endoscopic resection, compared with no patients with a Level 2 polyp (0/9) ($P < .001$).[38,39]

Preparation for endoscopic mucosal resection

At the time of the procedure, before attempting EMR, it is imperative to be in an optimal endoscopic position for resection. This entails ensuring the scope is in a straight position without any looping. For lesions in the right colon, it may be necessary to retroflex to see the full extent of the lesion in the posterior aspect of an interhaustral valley. Similarly, the lesion should ideally be located at the 6 o'clock position whereby the biopsy channel is located to improve mechanical leverage of injection/snaring, which in turn increases the likelihood of technical success. Finally, the patient should be positioned so that any fluid will not settle in the resection site, as fluid (and potentially bleeding) can obscure the field of view and thereby increase the risk of complications or adenoma recurrence. Once an optimal position has been achieved, the next step involves lifting the polyp from the underlying submucosa to facilitate resection and minimize perforations and bleeding.

Injection-assisted endoscopic mucosal resection

Injection-assisted EMR involves injecting into the submucosa to lift the lesion from the muscularis propria to facilitate adequate resection and limit the risk of perforation. Numerous agents are available for submucosal injection. The ideal submucosal agent is one that provides a durable lift to reduce the need for frequent, repeated injections. Colloid plasma volume-expanding solutions such as sodium hyaluronate and hydroxyethyl starch have been shown to have a significant benefit over normal saline for sustained lift, increased rate of en bloc resection, and decreased risk for residual lesions.[40] However, at least one such FDA-approved lifting agent has been demonstrated, in a case series of 58 endoscopic resection specimens, to result in findings including severe submucosal fibrosis with multinucleated giant cells, and deposition of amorphous, pale blue-gray, finely granular material.[41] This has important clinical implications not only for the pathologist but also for the interventional endoscopists who may be referred cases of incomplete EMR resection from the community.

Staining dye such as methylene blue is also often added to the submucosal agent to facilitate the identification of the lateral margins of the LSL and also improve the recognition of inadvertent injury to the muscularis propria and perforation.[42] Additionally, dilute epinephrine (1:100,000–1:200,000) may also be added to the mixture to further enhance the submucosal cushion and decrease the risk of bleeding.[43]

The submucosal injection technique is important in obtaining an adequate lift. Dynamic injection should be performed rather than static injection. Dynamic submucosal injection involves injecting a small amount of solution to confirm entry into the submucosal space, followed by continued injection. As the solution is being injected, multiple maneuvers can be performed to enhance the lift including: the tip of the endoscope is deflected into the lumen, pulling back slightly of the needle catheter, and desufflating the lumen (**Fig. 2**).[44] It is important to note that there is a balance between not injecting enough and injecting too much—the goal of submucosal injection is to create a "sharp-peaked mountain" rather than a flat "rolling hill." Not only can the latter obscure the endoscopist's field of view but also it can produce excessive submucosal tension and reduce a snare's tissue grip, making EMR difficult.

After submucosal injection, it is important to assess for the adequate lift before proceeding to resection. If the lift is inadequate, either nonmalignant (submucosal fibrosis from an adjacent tattoo, prior attempts at resection or biopsies) or malignant (deep submucosal cancer invasion) causes may be responsible. Regardless of the cause, such lesions should be approached with caution, and if necessary, referred to an even higher level of care.[26]

Underwater-assisted endoscopic mucosal resection

An alternative to injection-assisted EMR to lift the lesion is underwater-assisted EMR. Instead of injecting into the submucosa to lift the agent, the entire lumen is filled with

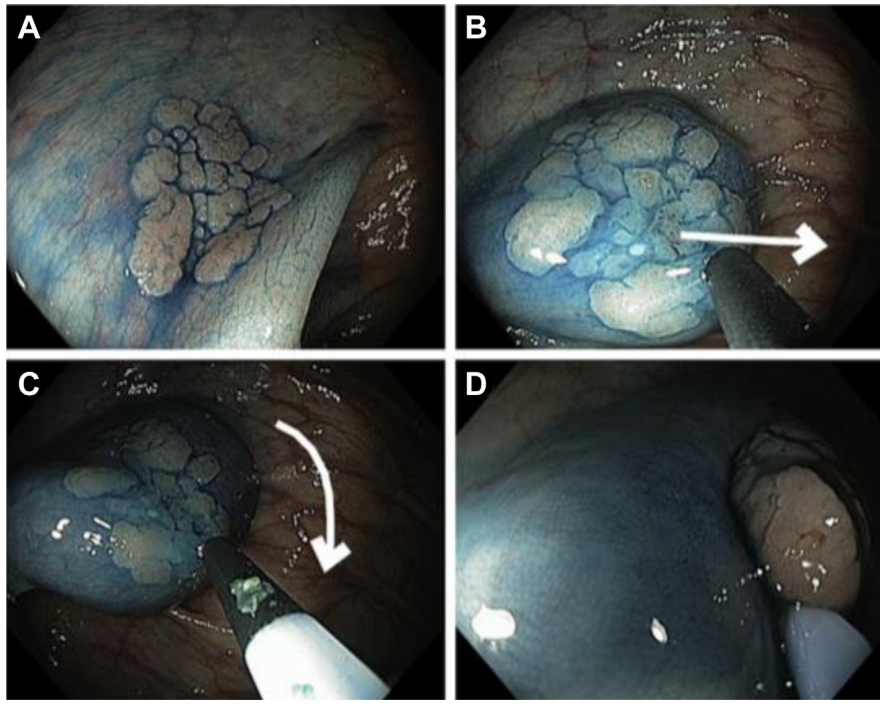

Fig. 2. Example of dynamic injection. First, the lesion's border is delineated with dilute indigo carmine (*A*). Next, during submucosal injection the endoscope is actively steered right (*B*), then clockwise (*C*). This promotes the desired direction of lift. Finally, the lesion is removed en-bloc via EMR (*D*). *(From* Soetikno R, Kaltenbach T. Dynamic submucosal injection technique. Gastrointest Endosc Clin N Am. 2010 Jul;20(3):497-502.)

water instead of gas, allowing for the mucosa and submucosa to involute and rise above the muscularis propria.[45] A meta-analysis of 7 studies with 1237 polyps revealed almost 2-fold increased rate of en-bloc resections using underwater EMR, especially for lesions $\geq$ 20 mm, which correlated with a 70% decreased risk for recurrence.[46]

Resection technique

Once adequate lesion lift has been achieved either through submucosal injection or underwater EMR technique, resecting the lesion can begin. In general, resection should begin at the area that is most difficult to access. The goal is to have en-bloc resection with a 2–3 mm margin of normal mucosa, which is possible for lesions 20 to 25 mm. A snare is used to capture the lesion; in situations of difficult-to-grasp lesions, enhanced measures may be necessary, including the use of specific snares such as crescent snares or braided snares, the use of a cap-fitted endoscope, wherein one suctions the lesion into the cap until "blue out" occurs, followed by immediate snare closure, or potentially even the use of hybrid ESD techniques. Once it is determined the grasped tissue is desired (ie, no obvious entrapment of muscularis propria), the snare is then lifted up into the lumen, and the lesion is resected.

Larger lesions resected with EMR require piecemeal resection. Piecemeal resection should be performed in an organized manner, using the edge of the previous mucosal defect as the next area for resection. This avoids leaving islands of adenoma. Efficient piecemeal resection includes repeating the following 3 steps: submucosal injection, 1 to 3 snare excisions, followed by cleaning and inspection of the mucosal defect. If the snare needs to be cleaned or exchanged, retrieving the resected pieces can typically be performed at the same time (**Fig. 3**).[25]

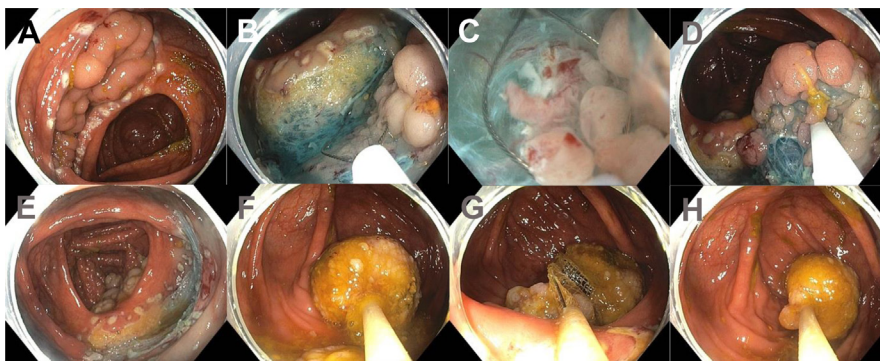

Fig. 3. Multiple core concepts of EMR are demonstrated in this series of photographs. (*A*) Using a cap-fitted colonoscope, the borders are marked using snare tip coagulation current prior to commencing. (*B*) The ileocecal valve is typically lipomatous; the fat seen is distinguished from a true perforation by the presence of blue-staining submucosa underneath the fat. (*B*) and (*C*) Flat components require various combinations of braided stiff snare, underwater EMR to promote mucosal floating, & lumen desufflation to promote a pseudopolyp formation (sometimes, to the point of "blue out"). (*D*) Wherever possible, dynamic injection should promote "sharp-peaked mountains." (*E*) In this example, polyp fragments are deposited in the cecal pit to promote efficient postprocedure fragment retrieval. (*F–H*) The retrieval basket (Roth Net, STERIS Corporation, Mentor, OH) with proper technique can be repeatedly closed, opened, & closed again, without losing prior fragments, to promote efficient fragment retrieval in a single pass.

Once the lesion has been completely removed, close inspection of the entire EMR field including the edges should be performed to evaluate for any adverse events including evaluating for any residual lesions, perforation, or bleeding.

Adverse Events

Residual lesion

For lesions larger than 25 mm, it is not typically possible for en-bloc resection with 2–3 mm of normal mucosal margin; instead, piecemeal resection is needed. Residual lesions can occur in up to 20% to 25% with piecemeal resections, especially in lesions greater than 40 mm in size, flat polyps, polyps in the right colon, and polyps in a difficult location such as the appendiceal orifice or ileocecal valve.[47] As discussed above, optimal technique for piecemeal resection is to resect in an organized manner at the edge of the previous resection. An adjunctive technique to decrease the risk of residual lesions includes ablating the edges of the EMR defect using argon plasma coagulation or snare tip coagulation. Using snare tip coagulation may be preferred because there is no additional cost of using the same snare for EMR as well as the snare tip for thermal ablation. This technique involves exposing 1 to 2 mm of the snare tip and gently moving along the margin of the EMR defect using soft coagulation to burn the edges. Margin thermal ablation can be very effective, with a multicenter randomized controlled trial revealing a 4-fold reduction in recurrence rates from 21% to 6%.[48]

In general, piecemeal resections should be followed with a surveillance colonoscopy in 6 months to assess for any residual lesions. Close inspection of the postmucosectomy scar with high-definition white light and NBI should be performed. A typical adenomatous pattern suggests residual lesions. Of note, if clips were placed previously, clip artifact can be present and should not be mistaken for residual lesions.[49] Clip artifact in general presents as a nodular elevation with normal pit pattern. Additionally, inflammatory nodules can be present, but these also should not be mistaken for residual lesions as they do not have the typical adenomatous pit pattern.

Perforation

Perforation is the most serious adverse event of EMR. A meta-analysis of 50 studies of EMR for lesions $\geq$ 20 mm revealed a perforation rate of 1.5%.[50] To decrease the risk of perforation, the first step is to ensure adequate lift of the submucosa. Another method to limit perforations is to ensure only the submucosa is captured in the snare. When one captures the desired tissue with the snare, before cutting, lift the tissue away from the wall to evaluate if it slightly mobile. If the muscularis propria is captured in the snare, the tissue will not move much, and the wall of the lumen may move instead. An additional sign that muscularis propria may be involved in the inability to transect the tissue within a reasonable amount of time (typically within 3–5 seconds of coagulation current pedal being depressed). In this instance, the snare should be relaxed and deflected upward to loosen the tissue.

The EMR defect should be inspected carefully for signs of deep mural injury or perforation. It is also important to evaluate the underside of the specimen and the EMR bed for the "target sign"/"reverse target sign," respectively. The target sign is composed of an inner white-gray circle, which is the muscularis propria, surrounded by the color of the dye in the submucosal agent used to lift, while the reverse target sign is an area of nonstaining on the EMR bed (**Fig. 4**).[51] Perforations can be often closed endoscopically with a reported success rate of 90%, highlighting the critical importance of prompt identification and if suitable, endoscopic management of the perforation.[52,53] Recently in a new classification system developed by Burgess and colleagues, multivariate analysis identified three risk factors associated with deep

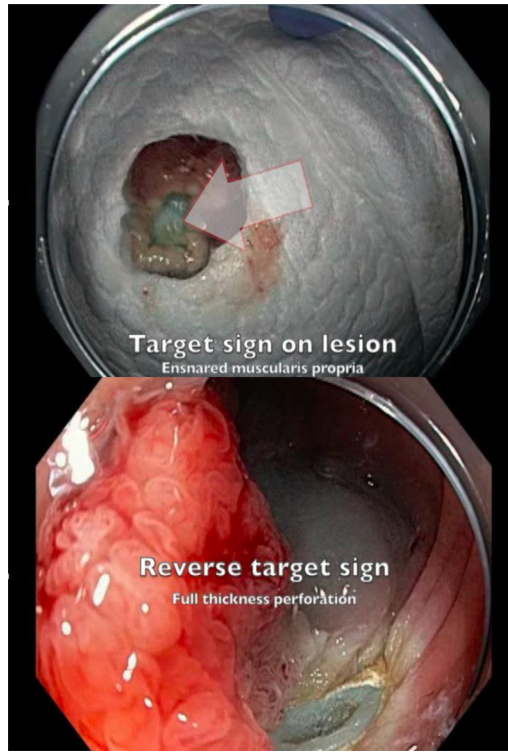

Fig. 4. Example of target sign (top) and reverse target sign (bottom) during EMR, indicating that perforation has occurred.

mural injury: transverse colon location (odds ratio (OR): 3.55, $P = .028$), en-bloc resection attempt (OR: 3.84, $P = .005$), and high-grade dysplasia or submucosal invasive cancer (OR: 2.97, $P = .014$).[54]

Bleeding

Bleeding is the most common post-EMR defect ranging from 2% to 11% in lesions greater than 20 mm.[55] Intraprocedural bleeding or bleeding recognized at the time of the procedure can usually be treated successfully without subsequent issues. However, delayed procedural bleeding can lead to increased morbidity for the patient given the need for possible admission, blood transfusions, and repeat colonoscopy. Risk factors for delayed bleeding include proximal colon location, polyp size, and intraprocedural bleeding.[55] Prophylaxis with clips or coagulation to prevent bleeding for all EMR sites has not been shown to be beneficial or cost-effective.[56] Moreover, clipping a wide-field EMR defect may not be possible. A 2019 multicenter randomized controlled trial did reveal certain patients may benefit from prophylactic clipping to prevent bleeding including lesions greater than 20 mm in the proximal colon.[57] Subsequently, a 2021 study investigating the cost-effectiveness of universal versus selective clipping in both Spanish and American economic contexts found that selective clipping was cost-effective only in a specific situation: those with a high risk of bleeding (based on a Spanish Endoscopy Society EMR group delayed bleed risk score (GSEED-RE2 score) > 6[58]), if the cost of the clip was below €394 or $154, respectively.[59]

Cold snare endoscopic mucosal resection

Traditionally, EMR has been performed using hot snare or with an electrosurgical current for possible increased efficacy of resection. However, hot snare EMR has been shown to have increased risk for delayed bleeding and perforation given the damage to deeper vessels and also deep mural injury, respectively.[60] Once a curiosity in

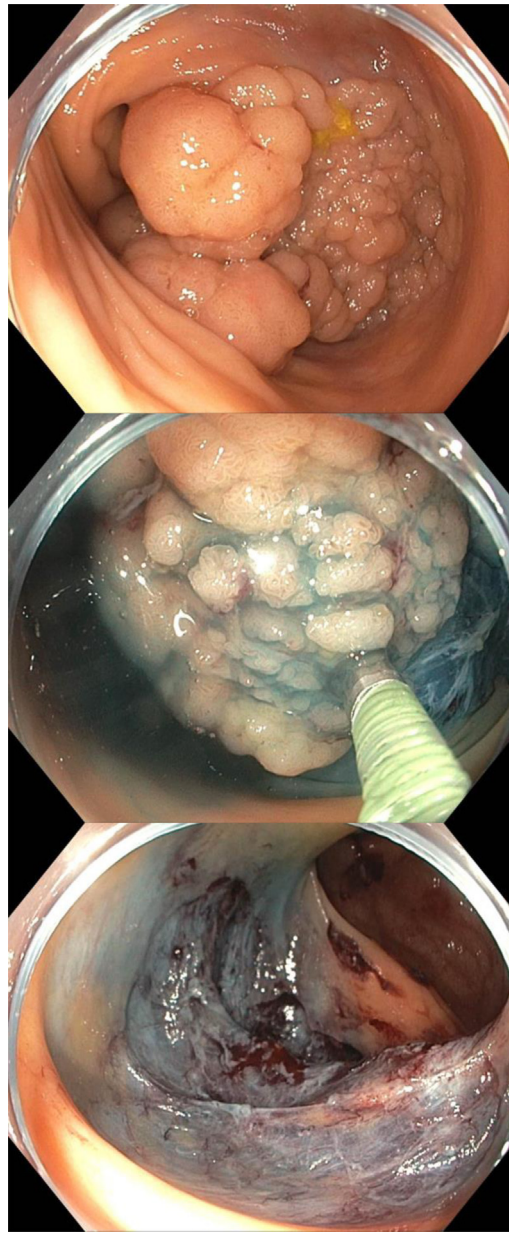

Fig. 5. Sequence of images showing cold snare EMR technique. Notice the lack of significant bleeding.

gastrointestinal literature,[61] in recent years cold snare polypectomy and EMR has become increasingly performed as an alternative to traditional hot snare EMR (Fig. 5. The benefit of cold snare EMR is the lack of any electrocautery-induced injury and therefore, a decreased risk in delayed bleeding and perforation. The possible concerns of cold snare EMR include possible difficulty in complete resection and subsequent decreased efficacy of complete removal of the lesion and risk of residual adenoma. One of the first applications of this technique was described in a 2015 series of 30 patients (15 duodenal polyps, 15 colon polyps). The median size of polyp was 20 mm in both locations, with the largest polyp being 60 mm and circumferential in the duodenum. All resections were successful, with only one patient in the duodenal cold snare EMR group requiring hospitalization for bleeding likely secondary to long-term anticoagulation requirements, and one patient in the colon cold snare EMR group requiring emergency room visit due to right lower quadrant pain 1 day after resecting a 20 mm polyp near the appendiceal orifice; after a negative workup, the patient was managed expectantly. There were no episodes of postpolypectomy syndrome or perforations.[62] Three years later, Tutticci and Hewett described cold snare EMR for 163 procedures across 99 patients. All procedures were successful. Only 2/163 lesions, or 1.2%, had positive margins which were again successfully treated with cold snare EMR. The side effect profile was similarly favorable—only 4 patients (4/99, or 4%) experienced any adverse events, with the only admission in the series most likely unrelated to the procedure itself.[63] Most recently, van Hattem and colleagues compared historical cohort of cold snare EMR (121 patients) to hot snare EMR (353 patients) in LSL $\geq$ 20 mm across 474 patients. The technical success rate for cold snare EMR was 100% and the residual adenoma rate was comparable between the 2 methods at 4% in 6 months. Furthermore, the study confirmed the superior safety profile of cold snare EMR, with no episodes of delayed bleeding nor deep mural injury, compared with hot snare EMR with 5.1% (18/353) having delayed bleeding and 3.4% (12/353) having deep mural injury.[64] However, this enthusiasm is somewhat tempered by a recent review by Suresh and colleagues of 310 polyps resected via cold snare EMR, among which a 34.8% recurrence rate (108/310) was noted. On multivariate analysis, risk factors included age ($P = .002$), polyp size ($P < .001$), and advanced polyp histology including tubulovillous adenoma or high grade dysplasia ($P = .023$).[65]

SUMMARY

With the most recent clinical guidelines recommending a start to CRC screening at age 45,[66] it is likely that the incidence of colonoscopic lesions requiring endoscopic resection will increase, thereby pushing the demand for EMR upward. In less than 70 years since Dr Rosenberg's first use of a saline wheal to protect against deep mural injury, using modern EMR techniques, the vast majority of lesions encountered today during colonoscopy are amenable to organ-preserving tissue resection techniques such as EMR, with excellent long-term clinical outcomes.

CLINICS CARE POINTS

- Proper bowel preparation (including split-dose preparation and simethicone tabs) is essential to a safe and effective procedure
- Referring physicians should be encouraged NOT to perform certain interventions which may cause submucosal fibrosis for subsequent EMR attempts. For instance, tattooing of the lesion should be performed 5 cm distal to the lesion, not underneath the lesion. A partial polypectomy attempt should similarly be avoided at all costs. Similarly, they should take care

with newer-generation, FDA-approved viscous lifting agents, as it is now reported to put the lesion at risk for significant submucosal fibrosis.

- The entire team plays a role in safe and efficient EMR. For instance, the nurses should be in the top 5% of the unit. High-performing nurses engage in closed-loop communication, are extremely familiar with various EMR devices, can troubleshoot problems, and have situational awareness to offer intelligent insight into the proper resection strategy for each lesion.
- Proper use of a distal attachment cap will facilitate EMR procedures by maintaining proper focal length between the colonoscope and the lesion. Caps also help splay open folds to improve visualization (eg, at colon turns and at interhaustral valleys).
- Wherever possible, keep the lesion above the waterline. Not only does this facilitate visualization but also it enhances safety in the event of bleeding or perforation
- Dynamic injection should be used to promote the proper shape to the submucosal injection—aim for a sharp-peaked valley, rather than a rolling hill
- After each resection, carefully inspect the underside of the specimen and EMR bed for signs of deep mural injury ("target sign"/"reverse target sign")
- In the event of perforation, keep the perforation above the waterline, and clip the defect closed in a timely manner.

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DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Rosenberg N. Submucosal saline wheal as safety factor in fulguration of rectal and sigmoidal polypi. AMA Arch Surg 1955;70(1):120–2.
2. Haber HP, Benda N, Fitzke G, et al. Colonic wall thickness measured by ultrasound: striking differences in patients with cystic fibrosis versus healthy controls. Gut 1997;40:406–11.
3. Wiesner W, Mortelé KJ, Ji H, et al. Normal colonic wall thickness at CT and its relation to colonic distension. J Comput Assist Tomogr 2002;26(1):102–6.
4. Deyhle P, Seuberth K, Jenny S, et al. Endoscopic polypectomy in the proximal colon. Endoscopy 1971;2:103–5.
5. Deyhle P, Largiader F, Jenny S, et al. A Method for Endoscopic Electroresection of Sessile Colon Polyps. Endoscopy 1973;5:38–40.
6. Inoue H, Takeshita K, Hori H, et al. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. Gastrointest Endosc 1993;39(1):58–62.
7. Tada M, Inoue H, Yabata E, et al. Colonic mucosal resection using a transparent cap-fitted endoscope. Gastrointest Endosc 1996;44(1):63–5.
8. Karita M, Tada M, Okida K, et al. Endoscopic therapy for early colon cancer: the strip biopsy resection technique. Gastrointest Endosc 1991;37:128–32.

9. Fukuzawa M, Gotoda T. History of endoscopic submucosal dissection and role for colorectal endoscopic submucosal dissection: A Japanese perspective. Gastrointest Interv 2012;1:30–5.
10. Takemoto T, Tada M, Yanai H, et al. Significance of strip biopsy, with particular reference to endoscopic "mucosectomy". Dig Endosc 1989;1(1):4–9.
11. Bond J. Polyp guideline: diagnosis, treatment, and surveillance for patients with colorectal polyps. Am J Gastroenterol 2000;95(11):3053–63.
12. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:1977–81.
13. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. NEJM 2012;366:687–96.
14. Le Roy F, Manfredi S, Hamonic S, et al. Frequency of and risk factors for the surgical resection of nonmalignant colorectal polyps: a population-based study. Endoscopy 2016;48(3):263–70.
15. Raju GS, Lum PJ, Ross W, et al. Outcome of endoscopic mucosal resection as an alternative to surgery in patients with complex colon polyps. Gastrointest Endosc 2016;84(2):315–25.
16. Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 2011;140:1909–18.
17. Ahmad NA, Kochman ML, Long WB, et al. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. Gastrointest Endosc 2002;55:390–6.
18. Hwang JH, Vani Konda, Abu Dayyeh BK, et al. Endoscopic mucosal resection. Gastrointest Endosc 2015;82(2):215–26.
19. Jayanna M, Burgess NG, Singh R, et al. Cost analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. Clin Gastroenterol Hepatol 2016;14(2):271–8.
20. Keswani R, Law R, Ciolino JD, et al. Adverse events after surgery for nonmalignant colon polyps are common and associated with increased length of stay and costs. Gastrointest Endosc 2016;84(2):296–303.
21. Law R, Das A, Gregory D, et al. Endoscopic resection is cost-effective compared with laparoscopic resection in the management of complex colon polyps: an economic analysis. Gastrointest Endosc 2016;83(6):1248–57.
22. Louis M, Johnston SA, Churilov L, et al. The hospital costs of complications following colonic resection surgery: A retrospective cohort study. Ann Med Surg (Lond) 2020;54(37–42):37.
23. Guo R, Wang Y, Liu M, et al. The effect of quality of segmental bowel preparation on adenoma detection rate. BMC Gastroenterol 2019;19:119.
24. Xirasagar S, Wu Y, Tsai MH, et al. Colorectal cancer prevention by CLEAR principles-based colonoscopy protocol: an observational study. Gastrointest Endosc 2020;91:905–16.
25. Klein A, Bourke MJ. How to perform high-quality endoscopic mucosal resection during colonoscopy. Gastroenterology 2017;152(3):466–71.
26. Kim HG, Thosani N, Banerjee S, et al. Effect of prior biopsy sampling, tattoo placement, and snare sampling on endoscopic resection of large nonpedunculated colorectal lesions. Gastrointest Endosc 2015;81(1):204–13.
27. Soetikno RM, Gotoda T, Nakanishi Y, et al. Endoscopic mucosal resection. Gastrointest Endosc 2003;57(4):567–79.
28. Sanchez-Yague A, Kaltenbach T, Yamamoto H, et al. The endoscopic cap that can (with videos). Gastrointest Endosc 2012;76:169–78.e2.

29. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017;49:270–97.
30. Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic removal of colorectal lesions - recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2020;158(4):1095–129.
31. Bogie RMM, Veldman MHJ, Snijders L, et al. Endoscopic subtypes of colorectal laterally spreading tumors (LSTs) and the risk of submucosal invasion: a meta-analysis. Endoscopy 2018;50(3):263–82.
32. D'Amico F, Amato A, Iannone A, et al. Risk of covert submucosal cancer in patients with granular mixed laterally spreading tumors. Clin Gastroenterol Hepatol 2021;19(7):1395–401.
33. Resende RH, Ribeiro IB, de Moura DTH, et al. Surveillance in inflammatory bowel disease: is chromoendoscopy the only way to go? A systematic review and meta-analysis of randomized clinical trials. Endosc Int Open 2020;8:E578–90.
34. Hayashi N, Tanaka S, Hewett DG, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc 2013;78(4):625–32.
35. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58(6 Suppl):S3–43.
36. Soetikno RM, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008;299(9):1027–35.
37. Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. Gastroenterology 2001;120(7):1657–65.
38. Gupta S, Miskovic D, Bhandari P, et al. A novel method for determining the difficulty of colonoscopic polypectomy. Frontline Gastroenterol 2013;4:244–8.
39. Currie AC, Lucado AM, Gilani SNS, et al. Validation of the size morphology site access score in endoscopic mucosal resection of large polyps in a district general hospital. Ann R Coll Surg Engl 2019;101:558–62.
40. Yandrapu H, Desai M, Siddique S, et al. Normal saline solution versus other viscous solutions for submucosal injection during endoscopic mucosal resection: a systematic review and meta-analysis. Gastrointest Endosc 2017;85(4):693–9.
41. Olivas AD, Setia N, Weber CR, et al. Histologic changes caused by injection of a novel submucosal lifting agent for endoscopic resection in GI lesions. Gastrointest Endosc 2021;93:470–6.
42. Holt BA, Jayasekeran V, Sonson R, et al. Topical submucosal chromoendoscopy defines the level of resection in colonic EMR and may improve procedural safety (with video). Gastrointest Endosc 2013;77(6):949–53.
43. Hirao M, Hatakeyama H, Asanuma T, et al. [Endoscopic resection with local injection of hypertonic saline epinephrine for the treatment of early gastric cancer]. Gan To Kagaku Ryoho 1988;15(4):1466–72.
44. Soetikno R, Kaltenbach T. Dynamic submucosal injection technique. Gastrointest Endosc Clin N Am 2010;20(3):497–502.
45. Binmoeller KF, Weilert F, Shah J, et al. "Underwater" EMR without submucosal injection for large sessile colorectal polyps (with video). Gastrointest Endosc 2012;75(5):1086–91.

46. Choi AY, Moosvi Z, Shah S, et al. Underwater versus conventional EMR for colorectal polyps: systematic review and meta-analysis. Gastrointest Endosc 2021; 93(2):378–89.
47. Sidhu M, Tate DJ, Desomer L, et al. The size, morphology, site, and access score predicts critical outcomes of endoscopic mucosal resection in the colon. Endoscopy 2018;50(7):684–92.
48. Klein A, Tate D, Jayasekeran V, et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. Gastroenterology 2019;156(3):604–13.e3.
49. Pellise M, Desomer L, Burgess NG, et al. The influence of clips on scars after EMR: clip artifact. Gastrointest Endosc 2016;83(3):608–16.
50. Hassan C, Repici A, Sharma P, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut 2016; 65(5):806–20.
51. Swan MP, Bourke MJ, Moss A, et al. The target sign: an endoscopic marker for the resection of the muscularis propria and potential perforation during colonic endoscopic mucosal resection. Gastrointest Endosc 2011;73(1):79–85.
52. Verlaan T, Voermans RP, van Berge Henegouwen MI, et al. Endoscopic closure of acute perforations of the GI tract: a systematic review of the literature. Gastrointest Endosc 2015;82(4):618–628 e5.
53. Baron TH, Wong Kee Song LM, Zielinski MD, et al. A comprehensive approach to the management of acute endoscopic perforations (with videos). Gastrointest Endosc 2012;76(4):838–59.
54. Burgess NG, Bassan MS, McLeod D, et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. Gut 2017;66(10):1779–89.
55. Burgess NG, Metz AJ, Williams SJ, et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol 2014;12(4):651–61.e1-3.
56. Boumitri C, Mir FA, Ashraf I, et al. Prophylactic clipping and post-polypectomy bleeding: a meta-analysis and systematic review. Ann Gastroenterol 2016; 29(4):502–8.
57. Pohl H, Grimm IS, Moyer MT, et al. Closure prevents bleeding after endoscopic resection of large colon polyps in a randomized trial. Gastroenterology 2019; 157(4):977–984 e3.
58. Albeniz E, Gimeno-García AZ, Fraile M, et al. Clinical validation of risk scoring systems to predict risk of delayed bleeding after EMR of large colorectal lesions. Gastrointest Endosc 2020;91(4):868–78.e3.
59. Albeniz E, Enguita-Germán M, Gimeno-Garcia AZ, et al. The Answer to "when to clip" after colorectal endoscopic mucosal resection based on a cost-effectiveness analysis. Am J Gastroenterol 2021;116(2):311–8.
60. Yamashina T, Fukuhara M, Maruo T, et al. Cold snare polypectomy reduced delayed postpolypectomy bleeding compared with conventional hot polypectomy: a propensity score-matching analysis. Endosc Int Open 2017;5(7):E587–94.
61. Waye JD. Polyps large and small (Editorial). Gastrointest Endosc 1992;38(3): 391–2.
62. Choksi N, Elmunzer BJ, Stidham RW, et al. Cold snare piecemeal resection of colonic and duodenal polyps ≥1 cm. Endosc Int Open 2015;3:E508–13.
63. Tutticci NJ, Hewett DG. Cold EMR of large sessile serrated polyps at colonoscopy (with video). Gastrointest Endosc 2018;87:837–42.

64. van Hattem WA, Shahidi N, Vosko S, et al. Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods. Gut 2021; 70(9):1691–7.
65. Suresh S, Zhang J, Ahmed A, et al. Risk factors associated with adenoma recurrence following cold snare endoscopic mucosal resection of polyps >= 20mm: a retrospective chart review. Endosc Int Open 2021;9:E867–73.
66. Shaukat A, Kahi CJ, Burke CA, et al. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. Am J Gastroenterol 2021;116(3):458–79.