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Endoscopic management of mucosal lesions in the gastrointestinal tract

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Abstract/Summary

With the increasing role of endoscopy in patient evaluation, more mucosal lesions, including gastric, duodenal and colonic polyps, are encountered during routine examinations. It is imperative for gastroenterologists to become familiar with the endoscopic management of these various gastrointestinal lesions. In this article, various resection techniques will be discussed, including hot/cold forceps polypectomy, hot/cold snare polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection. The article will also discuss the evidence regarding the efficacy and safety of these techniques and the future direction of endoscopic management of mucosal lesions in the gastrointestinal tract.

Keywords

1) Fundic gland adenoma
2) Gastric adenoma
3) Duodenal adenoma
4) Endoscopic mucosal resection (EMR)
5) Endoscopic submucosal dissection (ESD)
6) Diminutive colon polyps
7) Colon adenoma
8) Snare polypectomy
Due to the increased role of upper and lower endoscopy in the evaluation of patients, more mucosal lesions are discovered, which presents a new challenge for gastroenterologists regarding the management of these lesions. Some mucosal lesions are benign in nature, and some harbor malignant potential. It is important to recognize the premalignant lesions and remove them using safe and efficacious techniques. Large sessile lesions are difficult to remove, and surgery was primarily performed. However, surgery is associated with significant morbidity, mortality, and increased cost. Currently, there are many techniques available for resection of these lesions including snare polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). There are many factors that influence the endoscopist's decision in choosing the appropriate technique to resect mucosal lesions, including size, location, and morphology. The key is to resect each lesion in its entirety to avoid the risk of recurrence.

In this review, endoscopic management of various mucosal lesions in the gastrointestinal tract will be discussed. Emphasis will be placed on mucosal lesions in the stomach, duodenum, and colon. For endoscopists, it is important to understand the strengths and limitations of various endoscopic techniques for the resection of the different types of mucosal lesions. The evidence behind each approach will be discussed to aid in the decision-making process.

GASTRIC MUCOSAL LESIONS
Gastric polyps are categorized as mucosal/epithelium or submucosa. Mucosal-based lesions include the following: fundic gland polyps, hyperplastic polyps, adenomatous polyps, and hamartomatous polyps.

**Fundic Gland Polyps**

Fundic gland polyps (FGPs) are the most common type of gastric polyp reported in upper endoscopy (Figure 2). They may be seen in 0.8%-23% of all upper endoscopy evaluations. FGPs can be categorized into sporadic FGP, polyps associated with acid suppression such as chronic proton pump inhibitor (PPI) use, and those associated with familial adenomatous polyposis (FAP) [1]. In one study, nearly 74% of the gastric polyps that were evaluated had the final diagnosis of FGP on biopsy [2]. Dilated oxyntic glands with flattened parietal and mucous cells are distinct histological features of FGPs. FGPs are rarely associated with *Helicobacter pylori* infection. According to multiple studies, patients who take PPIs for more than or equal to five years had quadruple the risk of developing FGPs [3,4].

**Endoscopic management**

During upper endoscopy, biopsy should be performed on gastric polyps to confirm the diagnosis and rule out any evidence of dysplasia. Certain characteristics of FGPs require a more aggressive approach, such as those with polyp size greater than or equal to 1 cm, ulceration, or unusual location like at the gastric antrum [5]. FGPs rarely exceed 1 cm in size. FGPs that are greater than or equal to 1 cm in size require complete removal because there is a higher possibility of dysplasia. If possible, PPI should be discontinued in these patients [6]. When removing the
larger FGPs, the use of cold or hot snares is recommended as opposed to forceps. Surveillance upper endoscopy is currently not recommended for sporadic FGPs without dysplasia. High-grade dysplasia in Western countries corresponds to intramucosal cancer in Eastern countries. High-grade dysplasia lesions should be resected endoscopically, and follow-up should be conducted after one year.

Importantly, for young patients with more than 20 FGPs, it is important to consider FAP (Figure 1).

In contrast to PPI-associated FGP, which has low malignant potential, FGP associated with FAP have a definite dysplasia risk between 30%-50% [6]. Colonoscopy is recommended in this case. For patients with FGP-associated FAP, upper endoscopy should be performed about every two years after the age of 18 to evaluate for possible gastric dysplasia [7].

**Hyperplastic polyps**

Hyperplastic polyps (HPs) are the second most common gastric polyp and is the result of inflammatory proliferations of gastric foveolar cells. They are typically less than 2 cm in size and are predominantly located around the gastric antrum. There are two subtypes of hyperplastic polyps in the stomach. The first subtype of polyp is strongly associated with chronic inflammation in the setting of *Helicobacter pylori* infection, atrophic gastritis, or autoimmune gastritis. Endoscopically, they are found
mainly in the antrum of the stomach [5]. The other subtype occurs in the cardia and near the gastroesophageal (GE) junction of patients with chronic reflux disease [8]. HPs rarely progress to malignancy, but polyps that are pedunculated and larger than 1-2 cm are at increased risk of malignancy. It is estimated that 5%-19% of HPs harbor some element of dysplasia or focal cancer [9]. Synchronous malignancy may also arise from the remaining gastric mucosa, particularly if associated with chronic gastritis [7]. Prevalence of dysplasia arising in hyperplastic polyps can range from 1.9% to 19%, and cases of adenocarcinoma range from 0.6% to 2.1% [1].

**Endoscopic management**

Because of the malignant potential arising from the remaining gastric mucosa, resection of HPs must be accompanied by forceps biopsies of the surrounding gastric mucosa or gastric mapping. HPs can arise in the background of chronic atrophic gastritis, which is a precursor lesion for gastric adenocarcinoma. Thorough evaluation of the extent of the atrophic gastritis must be performed. A seven-biopsy protocol is recommended, and this consists of three specimens from the antrum (one should be from the incisura), two from the lesser curvature, and two from the greater curvature of the stomach body [5].

Another technique used to detect dysplasia, metaplasia, or abnormal mucosal changes is chromoendoscopy. It involves the topical application of stains or dyes to the gastrointestinal mucosa. In particular, phenol red staining is used to detect *Helicobacter pylori* in peptic ulcer disease and early gastric cancer. Methylene blue is
used to help identify intestinal metaplasia and dysplasia in the stomach. The sensitivity and specificity for the detection of intestinal metaplasia range from 76% to 94% and 87% to 97%, respectively [10].

All asymptomatic HPs ≥ 1 cm and those that are symptomatic (bleeding, gastric outlet obstruction) should be resected completely. Testing for *H. pylori* should be performed, and if positive, appropriate treatment should be initiated. For patients with successful removal precursor lesions but who remain infected with *H. pylori*, the risk of metachronous gastric cancer can increase by as much as 4% per year. By eradicating *H. pylori*, this reduces the risk of developing gastric cancer by approximately three fold [11]. Surveillance EGD should be performed one year after the initial resection of HP and then if no recurrence is noted, the surveillance interval can be lengthened to 3-5 years [7]. However, in Eastern countries, the risk of *H. pylori* infection is high, and these patients usually undergo annual surveillance for gastric cancer.

**Gastric adenomatous polyps**

Gastric adenomas can be found anywhere in the stomach, but are is mainly located in the antrum.

They accounts for about 6%-10% of gastric polyps in Western countries [7]. Most of the lesions are flat or sessile. Similar to that of colonic adenomas, the histology of gastric adenomas may be divided into tubular, villous, or tubulovillous types. They
typically arise in patients with history of atrophic gastritis or intestinal metaplasia associated with *H. pylori* infection. Gastric adenomas > 2 cm in size harbor the greatest risk of malignant transformation and should be considered for endoscopic resection.

**Endoscopic management**

Given the risk of malignancy and the association with synchronous and metachronous gastric adenocarcinoma, gastric adenoma > 2 cm or adenoma with higher risk of carcinoma should be completely endoscopically resected [5,7]. Sampling of other parts of the stomach may be necessary to evaluate for possible malignancy. Surveillance endoscopy should be performed at 6-month intervals if the polyp is not completely resected or the histology of resected polyp shows evidence of high-grade dysplasia [7]. Otherwise, one-year follow-up is sufficient to evaluate for any evidence of recurrence, and this applies to lesions that have been completely resected.

**Endoscopic resection of gastric mucosal lesions**

In general, polyps larger than 1 cm should be resected. Suspicious solitary gastric polyps based on conventional white-light imaging (C-WLI) in conjunction with magnifying narrow-band imaging (M-NBI) encountered during endoscopy should be at least sampled with biopsy [9]. The combination of C-WLI and M-NBI increases the accuracy, sensitivity, and specificity in identifying gastric malignancy [12]. Based on the biopsy results, the decision can be made whether additional treatment is
needed. For patients with hyperplastic and adenomatous polyps, it is important to biopsy the surrounding gastric mucosa to evaluate for presence of malignancy, *H. pylori*, atrophic gastritis, or neuroendocrine hyperplasia.

Overall, gastric polyps that require endoscopic resection include symptomatic polyps (bleeding, gastric outlet obstruction), adenomas > 2 cm, dysplastic polyps, fundic gland polyps > 1 cm, hyperplastic polyps with bleeding risk or risk of malignancy, and polyps associated with juvenile polyposis syndrome. Based on the recent American Society of Gastrointestinal Endoscopy recommendations, in the setting of multiple polyps, the endoscopist is advised to resect or biopsy the largest polyps and take representative biopsies from other polyps [9].

Techniques involved in resection of gastric mucosal lesions include snare polypectomy, forcep polypectomy, EMR, and ESD. Details of each technique will be discussed in the colorectal mucosal lesion section.

Many different techniques for EMR are available, including injection-assisted EMR, cap-assisted EMR, and ligation-assisted EMR. EMR provides potential cure for patients with superficial cancer of the stomach [13,14]. A recent retrospective study of 158 of gastric adenomas with low-grade dysplasia (LGD) demonstrated en-bloc resection and complete resection rates of EMR were 91.1% and 90.5%, respectively. The study also demonstrated low complication rates, with bleeding and perforation rates of 1.3% each. Based on the study, EMR is an effective treatment for gastric
adenomas with LGD < 2 cm [15]. However, at other institutions, EMR is considered inappropriate for R0 resection (negative and lateral margin), even for small lesions of < 2cm.

ESD has been shown to be a useful method for the complete resection of gastric adenomas, and it improves the en-bloc resection rate of gastric adenomas regardless of size and location [16,17]. Compared with EMR, ESD allows for a more complete resection and more accurate pathologic diagnosis of superficial gastric lesion. Compared with EMR, ESD has success rates between 95% to 98% for en-bloc resection and survival rate at five years of 83% to 97% [18,19]. In other large Asian series, patients with early gastric cancer undergoing ESD have en-bloc resection rates ranging from 86% to 97% and rates of R0 resection ranging from 88% to 93% [20]. Based on prior study, ESD has a lower recurrence rate compared to EMR group after endoscopic resection of gastric lesion, approximately 1%, but is much more time-consuming and has a modestly higher complication rate[20]. Based on recent meta-analyses, ESD was associated with higher rates of en-bloc resection (92% vs 52%) and lower rates of local recurrence (0.8% vs 5.05 to 6.4%) than EMR [21,22].

DUODENAL MUCOSAL LESIONS

Duodenal polyps are reported in 0.3%-4.6% of patients during upper endoscopy examination [23]. It is increasingly identified in asymptomatic individuals during routine upper endoscopy. Duodenal polyps can be categorized to mucosal and submucosal lesions. Mucosal lesions include gastric heterotopia, Brunner’s gland
tumors, and duodenal adenomas. Most of the duodenal adenomas are located in the descending duodenum. Submucosal lesions include carcinoid tumors and gastrointestinal stromal tumors (GIST).

**Duodenal adenoma**

Duodenal adenomas are categorized into sporadic duodenal adenomas and adenoma associated with FAP. In addition, duodenal adenomas can present as ampullary or nonampullary. Ampullary adenomas are rare, with an estimated 3,000 cases reported annually in the United States [24]. The risk of carcinoma is greater with ampullary adenomas with incidence of transformation to invasive carcinoma ranging from 25% to 85% [24]. However, all adenomas present with some risk of malignant transformation, thus duodenal adenomas should be resected.

Duodenal adenomas are commonly associated in patients with FAP. The location of the adenoma is commonly around the ampulla or distal duodenum.

There is increased risk of malignant transformation of duodenal adenomas in patients with FAP, and the risk of duodenal cancer can range from 3%-5% in this group of patients [25].

Duodenal adenocarcinoma is the second most common cause of death in FAP patients, thus stringent surveillance and management is crucial. Cumulative risk of duodenal cancer may be as high as 10% by 60 years of age [26]. The interval of surveillance of duodenal adenomas is determined by the Spigelman stage. The
Spigelman stage ranges from stage 0 to stage 4, and the higher the stage indicates increase severity of the polyp burden. Patients with Spigelman stage 4 have the highest risk of developing duodenal cancer, between 7%-36%, as oppose to stage 0-3 which only harbors about 0.7% risk of developing duodenal cancer [27]. The Spigelman grading system is based on the number of polyps, polyp size, histology, and the grade of dysplasia (Table 1). Patients with higher Spigelman stage require more frequent interval of endoscopic surveillance (Table 2).

Traditional approaches for removal of duodenal polyps involve local surgical excision or radical surgery, but this entails high rates of recurrence and significant morbidity and mortality. In 1973, the first endoscopic excision of duodenal adenoma was described [28]. Since then, additional studies on the role of endoscopic techniques in removal of duodenal polyps continues to expand.

Endoscopic management of ampullary adenoma

Initial endoscopic assessment of ampullary adenomas plays an important role in the diagnostic and treatment process. Lesions that are firm, ulcerated, non-lifting with submucosal injection, and friable suggest likely submucosal invasion and high risk of malignancy. These lesions should undergo surgical resection.

Endoscopic ultrasound (EUS) provides useful information in evaluating patients with ampullary adenoma. EUS allows evaluation of extent of intraductal extension, extension beyond the muscularis propria, and periampullary lymph node involvement [29]. Endoscopic retrograde cholangiopancreatography (ERCP) is
performed to evaluate both biliary and pancreatic duct evaluation whether there is any evidence of extension into any of the duct. Some investigators recommend surgical intervention for any evidence of intraductal involvement [30]. Other studies have shown that endoscopic resection can still be attempted for lesions with less than 1 cm of extension into the common bile duct or pancreatic duct [31].

The use of submucosal injection during endoscopic ampullectomy remains controversial, and in most experts’ opinions, is thought to be counterproductive and make the papillectomy more difficult. Both pure cutting current and blended current have been used but neither is demonstrated to be superior over the other. The ampullary adenoma can be resected en-bloc or in piecemeal fashion. For lesions that are > 2 cm, piecemeal resection may be required. Ablative therapies such as argon plasma coagulation (APC) are commonly used to eliminate residual adenomatous tissue [29].

Complications associated with ampullectomy include bleeding, perforation, pancreatitis, and cholangitis. Different studies have endorsed placement of pancreatic duct stents to reduce the risk of post-ERCP pancreatitis [32,33]. One prospective, randomized controlled trial indicates that pancreatic stent placement does have a protective effect in reducing post-ampullectomy pancreatitis [32]. Late complications include development of biliary and pancreatic ductal stenosis. Patients that undergo endoscopic ampullectomy usually have a high recurrence rate. According to one study, the recurrence rate is 58.3% over a follow-up period of
85 months [34]. Due to the high rate of recurrence after endoscopic ampullectomy, biopsy at the prior ampullectomy site should be performed during subsequent endoscopy examinations despite normal appearance at the previous resection site. It is recommended that patients should undergo endoscopic surveillance at six-month intervals in the first two years after ampullectomy. If no recurrence is detected after two years, annual surveillance is recommended to detect late recurrence [34]. Importantly, ampullary adenomas in patients with Spigelman stage 4 may require surgical intervention such as Whipple surgery.

Endoscopic management of nonampullary duodenal adenoma

Nonampullary duodenal adenomas (NDA) are found predominantly in the second part of the duodenum (Figure 3). They can occur sporadically or be associated with FAP or Peutz-Jeghers syndrome. These lesions do carry the risk of malignant transformation to duodenal cancer, and removal of these lesions is recommended. Endoscopic resection of duodenal lesion is technically more challenging due to the location and the higher rates of complication, including bleeding and perforation compared to other parts of the gastrointestinal tract. Endoscopic resection in the duodenum is faced with many limitations. First, it is difficult to maneuver the endoscope in the small bowel due to the narrow lumen and location in the retroperitoneum. The presence of multiple folds and Brunner's glands presents a challenge to achieve a reasonable fluid cushion after submucosal injection. Furthermore, the duodenal wall is thin, which further increases the risk of bowel perforation.
The general principle of duodenal adenoma resection is similar to that of the resection of polyp or mucosal lesion involved in the right side of the colon. Snare EMR after submucosal injection is commonly used in the removal of mucosal lesions in the duodenum. Based on one retrospective study, EMR was effective in achieving complete resection of 23 out of 27 (85%) lesions [35]. The use of EMR also led to changing the final histology diagnosis to either high-grade dysplasia or carcinoma in 44% of cases [35]. Other studies also support the finding that EMR is a safe and effective method for removing large sporadic NDA [36]. Overall, the complete resection rate of NDA using EMR ranges from 79% to 100% [28]. Lesions larger than 20 mm are usually removed with piecemeal resection, but this method carries an increased risk of recurrence. The long-term outcome of EMR of sporadic duodenal adenomas seems variable, with a recurrence rate between 0% to 36% [28,37]. However, smaller lesions < 2cm present with favorable outcomes. One retrospective study of 17 duodenal adenomas with an average size of 15.1 mm underwent EMR with a median post-resection follow-up period of 29 months indicating no evidence of recurrence [38].

Intraprocedural bleeding occurs during EMR in approximately 9% and post-procedural bleed can be around 0%-12%. Perforation risk after EMR is estimated to only 0.6% [23] [39]. In one study of 121 nonampullary duodenal tumors treated with EMR, ESD, or polypectomy, none of the patients died from primary duodenal malignancy after a followup period of more than one year. Furthermore, there were no local recurrences during 51-month median follow-up [37].
ESD is performed for resection of some NDA. A critical aspect of performing successful ESD in duodenal adenoma is the submucosal dissection process [40]. During the dissection, it is important to preserve the submucosa layer on the dissection surface in order to not expose the surface of the muscularis propria and decrease the risk of perforation. Importantly, it is suggested that prophylactic control of bleeding during duodenal ESD leads to better procedural outcome [40]. Specifically, blood vessels are coagulated with hemostatic forceps before additional cutting takes place. Carbon dioxide insufflation is also utilized during duodenal ESD to limit the risk of complications. In one retrospective study, duodenal ESD does present acceptable en-bloc resection and complete resection rate at 78.6% and 85.7%, respectively. However, the complication rate is extremely high [41]. Another study from Japan also corroborates the findings. In this study, 41 nonampullary large superficial duodenal lesions were resected using ESD. 92.7% of lesions were successfully resected, and the complete resection rate was 89.5%. Perforation during ESD occurred in 39%, and delayed bleeding occurred in 18.4%. Importantly, after a median observation period of two years, no local recurrence or distant metastasis was observed [42]. ESD of duodenal lesions should be undertaken only in very expert settings with great caution.

The most feared complications associated with duodenal ESD include bleeding and perforation. The rate of post-procedural bleeding after ESD ranges between 6.7% and 22.2% [43,44]. Due to the thin wall of the duodenum, the rate of perforation is much higher in duodenal ESD, ranging from 21% to 35.7% [41,45].
COLONIC MUCOSAL LESIONS

**Diminutive and small colonic polyps**

The majority of polyps encountered during colonoscopy are diminutive and small. Approximately 80%-90% of lesions are less than 10 mm in size during routine colonoscopy examination [46]. Questions remain regarding the optimal technique for removal of these polyps.

**Optimal resection technique for small and diminutive colorectal polyp**

Currently, there is a lack of consensus on the optimal technique in the removal of diminutive (≤5mm) and small (6-9 mm) colorectal polyps. The current techniques available in removing diminutive polyps include cold biopsy forceps, hot biopsy forceps, hot snare, and cold snare. Snare polypectomy is commonly used for pedunculated and sessile lesions that are 5 mm to 20 mm in size. Various snare instruments are available, including oval, hexagonal, barbed, duckbill, and mini snares, and dedicated cold snares [47]. Multiple studies have been performed to compare the efficacy of different techniques in removal of small polyps. Recent studies have found that cold polypectomy appear to be a safe and efficacious technique in removing smaller sized polyps.

Cold polypectomy techniques include cold biopsy forceps and cold snare polypectomy. Jumbo biopsy forceps have reported to achieve high complete histological eradication rate for removing diminutive polyps and short withdrawal time [48]. Another study performed on the efficacy of jumbo biopsy forceps for the
removal of 223 diminutive polyps. The overall rate was 85%, and the efficacy decreases as the size of the polyp increases [49].

One prospective randomized controlled study in Korea was conducted to compare the complete resection rates of cold snare polypectomy and cold forceps polypectomy for the removal of adenomatous polyps ≤ 7mm. Among the 145 polyps, the overall complete resection rate for adenomatous polyps was significantly better in the cold snare group compared to that of the cold forceps group (96.6% vs 82.6%; \( p = 0.11 \)). For larger polyps ranging between 5 mm to 7 mm, the cold snare technique was much more efficient in removing the polyp compared to the cold forceps technique (93.8% vs 70.3%; \( p = 0.13 \)) [50]. Another randomized controlled study performed in 2013 also corroborates this finding. In this study, 117 polyps (≤ 5 mm) were removed using either cold snare vs cold forceps. The rate of polyp eradication was significantly higher in snare group vs the forceps group (93.2% vs 75.9%, \( p = 0.009 \)) [51].

With different studies supporting the use of cold snare technique in removal of diminutive polyps in the colon, various studies have examined the role of snare type in cold snare polypectomy. One recently published randomized, prospective study compared different types of cold snare in complete resection of small colon polyps. 210 eligible polyps (10 mm or smaller) were randomized into dedicated cold snare (Exacto cold snare by US Endoscopy) vs traditional cold snare (Snare Master by Olympus). The complete resection rate was significantly greater using the dedicated
cold snare than with the traditional cold snare [52]. Another study examined the role of snare type in the cold snare polypectomy. One hundred and fifty-seven polyps ranging from 3 mm to 7 mm were removed using either thin wire mini-snare (0.30 mm) or thick wire mini-snare (0.47 mm). Completeness of excision was significantly higher with thin wire snare compared to that of the thick wire snare (90.2% vs 73.3%, \( p < 0.05 \)) [53]. The study concluded that snare type plays an important role in the complete excision of small polyps using the cold snare technique. Additional studies need to be conducted to corroborate the findings.

Perhaps, it is important to acknowledge that both the technique and specific tool are both important in increasing the complete resection rate of small polyps.

Few studies have compared the efficacy of hot snare and cold snare in removal of smaller sized polyp. Cold snare polypectomy has been shown to exhibit similar efficacy compared to hot snare polypectomy and results in fewer complications.

With hot snare polypectomy, there is concern regarding thermal injury and post-polypectomy cautery syndrome [49]. One prospective series examined 148 polyps ranging from 5 mm to 9 mm in size, and 77 polyps were removed with cold snare while 71 polyps were removed by hot snare polypectomy. The procedure time was significantly shorter in the cold snare group compared to hot snare group (25 sec vs 70 sec, \( p < 0.001 \)). Both methods had a similar number of post-procedure complications. Furthermore, both methods had an equal number of polyps that were not completely removed [54]. These results are supported by another prospective randomized study. Four hundred and fourteen patients with small and diminutive polyps ranging from 3 mm to 8 mm were included the randomized study. Cold snare
technique had shorter mean procedure time compared to that of hot snare polypectomy. In addition, there was no early (within 24 hours) or late post-polypectomy bleeding (24 hour to 30 days) in either technique [55]. From this study, cold snare polypectomy is safe, effective, and faster than hot snare. Other studies have also supported the fact that cold polypectomy is superior to hot polypectomy in procedure time and post-polypectomy abdominal symptoms. Also noted in this study is that both techniques have similar bleeding risk and complete polyp resection [56]. Patients using anticoagulation with polyps up to 10 mm were randomized into cold snare or conventional polypectomy, which includes electrocautery. The study showed that the cold snare technique is associated with less bleeding risk than hot snare technique and should be the preferred method in removing small polyps in patients taking anticoagulation [57]. Overall, cold snare polypectomy seems to be the better procedure for small and diminutive polyp removal compared to hot snare polypectomy.

Despite the various methods available for diminutive polyp resection, there is still risk of incomplete resection. In one randomized study, 62 polyps were randomized into three separate arms (hot snare, cold snare, and cold biopsy forceps). One out of 10 diminutive polyps were still incompletely resected using one of the standard techniques [58].

**Suction pseudopolyp technique**
As described in a 2009 paper, the suction pseudopolyp technique provides a different take in removing small nonpolypoid lesions in the colon. The technique involves the following steps. First, luminal air is slightly suctioned during endoscopic examination. Second, the snare is passed down the biopsy channel before reaching the end of the colonoscope. Afterwards, the polyp is aspirated into the suction channel, and continuous suction is applied while the colonoscope is gently pulled backwards for distance of 2 cm to 5 cm. Afterwards, release the suction and allow the colonic wall to form a pseudopolyp. Cold snare is rapidly performed before the polyp could return to its original shape [59].

In one prospective randomized controlled trial, 148 polyps between 3 mm and 7 mm were removed by either using cold snare polypectomy or the suction pseudopolyp technique. Completeness of excision and polyp retrieval rate were found to be not significantly different. Overall, both techniques were found to be safe and effective, but a larger multicenter trial is needed to confirm the study results [60].

**Large colonic mucosal lesions**

Careful endoscopic assessment is important for large (≥10 mm) and gigantic polyps (≥30 mm). Focused examination of the lesion helps to determine the choice of therapeutic options. In particular, this may dictate whether endoscopic or surgical treatment is better suited for the removal of the mucosal lesion.
**Endoscopic assessment**

Colonic adenomas are classified as either polypoid or nonpolypoid type. Based on the Paris classification, polypoid lesions include pedunculated (0-Ip) and sessile-shaped (0-Is) lesions. Nonpolypoid lesions may be subdivided into superficial elevated (0-IIa), flat (0-IIb), and depressed (0-IIc). Typically superficial elevated lesions 20 mm or larger are termed lateral spreading tumors (LSTs). LSTs can be divided into granular LSTs, nongranular LSTs, or mixed-type based on surface appearance [46]. Understanding the morphology allows the endoscopist to select the proper technique in removing the colon polyp.

Changes of homogenous pit patterns seen on the colon surface can be helpful in determining the degree of neoplasia and even depth of invasion. Pit pattern are classically seen with the use of dye spray and are classified by the Kudo system. Type III (small tubular or round pit pattern that is smaller than normal pit) and Type IIII (tubular or round pit that is larger than the normal pit) are usually associated with tubular adenoma. Type IV (dendritic or gyrus-like pit) is associated with tubulovillous histology. Type V (irregular arrangement) or Type V (loss or decrease of pits) is associated with intramucosal or invasive malignancy[61]. More recently, surface patterns have been described using optical enhancement methods without dye spray and include the Sano and Narrow Band Imaging International Classification for Endoscopy (NICE) classification systems [62]. There are three subtypes of the NICE classification, and these are organized based on color, vessel, and surface pattern. Type 1 and 2 can be treated endoscopically. However, Type 3
indicates likely deep submucosal invasive cancer and need for surgical operation for removal [63].

**Endoscopic mucosal resection of large colorectal lesions**

EMR is a technique first described in 1973 and is used for resection of lesions confined to the mucosa or submucosa of the colon. Lesions limited to the mucosa and superficial layers of submucosa are more suitable for EMR [64]. Adenoma of the colon represents one of the most important premalignant lesions of the gastrointestinal tract. Specifically, large (> 2 cm) colon polyps have been reported to be found in 0.8% to 5.2% of patients undergoing colonoscopy [65]. Larger size adenoma is associated with increased risk of developing into high-grade dysplasia or cancer. Compared to regular snare polypectomy, EMR has a higher successful complete resection rate for large colon polyps (> 2cm). Lesions that are between 1.5 cm and 2 cm can be removed by the en-bloc method. En bloc is desirable becuase this provides thorough histological evaluation and leads to a lower adenoma recurrence rate [65]. On the other hand, lesions that are greater than 2 cm may require piecemeal mucosal resection. Success rates of EMR have been reported between 90% and 100%. Endoscopic mucosal resection can be performed safely in elderly patients (≥80 years) with low rates of complications [66].

One of the important features of EMR involves submucosal fluid injection. Typically, a sclerotherapy needle is used to inject the fluid into the submucosa. This provides a buffer to protect the deeper layers of the colonic wall to prevent perforation and
bleeding. The injectate also raises the polyp’s amplitude, and this makes it easier to remove the lesion [47]. Common agents used for lifting the base of the lesion include normal saline, hydroxypropyl methylcellulose, glycerol, 50% dextrose, hyaluronic acid, and hypertonic saline [67]. Normal saline is commonly used for submucosal injections, but its effect is ephemeral. Hypertonic solution seems to provide better and longer-lasting elevation [28]. Methylene blue and indigo carmine are used to confirm if the resection is in the correct plane. Generally, 3 mL to 10 mL of solution is needed to achieve adequate separation from the submucosa, and this reduces the risk of thermal and mechanical injury of the deeper layers. After submucosal injection, a snare is placed on top of the protruding lesion, and the lesion is resected using electrocautery with high-frequency current (Figures 4 and 5).

Several dedicated EMR snares are now available. One large randomized controlled trial of a stiffer EMR snare combined with an injection needle showed superior resection efficiency compared to standard snares with separate injection needles [68].

Approximately 1% to 11% of cases of large colorectal polyps after EMR can result in intraoperative/immediate bleeding or delayed bleeding (hours to weeks after the procedure) [69-71]. Most delayed bleeding occurs within two weeks after EMR. Predictors associated with risk for post-polypectomy bleeding including polyp size greater than 1 cm to 2 cm, flat or laterally spreading lesions, pedunculated polyp with thick stalk, proximal colon lesions, resection technique, and coagulation status
[67]. Immediate bleeding can be controlled by several methods. Treatment is indicated if active bleeding interferes with completion of the procedure or there is persistent bleeding by the end of the procedure. One method is to use the snare and place pressure at the residual stump, and this can usually control immediate bleeding in some cases. Dilute epinephrine (1:10,000 solution) can also be injected in the base of the stump to stop the bleeding, but the effect is temporary. Application of mechanical hemostatic devices is preferable to stop the hemorrhage for a longer duration of time. Methods include application of endoscopic clips on the bleeding site and application of thermal probes. Specifically, thermal probes are applied for about 3-5 seconds at the setting 15 J for a heater probe and 12 to 15 W for a bipolar coagulation probe [67]. Actively bleeding vessels seen during EMR can also be treated with grasping coagulation forceps (Coagrasper, Olympus Medical) using a soft coagulation mode.

In the setting of delayed bleeding, patients can be managed conservatively if hematochizia ceases at the time of admission because rebleeding from the EMR site is uncommon. If there is no sign of active bleeding or gross blood noted during bowel preparation, colonoscopy can be deferred unless patient requires re-initiation of anticoagulation agent. Otherwise, for patients with ongoing hematochezia or other signs of GI bleeding, urgent colonoscopy should be performed. Existing ulcers with clean bases or flat pigmented spots do not require additional treatment. However, if the ulcer demonstrates visible vessels, adherent clots, and active bleeding then further endoscopic treatment with clip placement,
electrocauterization, or epinephrine injection may be needed. Currently, there is lack of substantial data to support the use of prophylactic clip to prevent further bleeding episodes. It is at the discretion of the endoscopist whether to place a clip at the EMR site, but prophylactic clip placement can be considered in specific cases including proximal lesions or in patients requiring chronic anticoagulation agents [67].

EMR of smaller colonic lesions (less than or equal to 10mm) can be performed safely in the outpatient setting. According to one study, the risk of serious immediate bleeding was 0.10% to 0.56% [72]. However, it is generally not safe to perform this procedure of larger polyps in outpatient setting because of the high risk of delayed bleeding and immediate serious bleeding. With larger lesions, there is higher chance of hospitalization due to increased risk of complications such as bleeding and perforations.

Perforation can occur in about 1% to 2% of patients after therapeutic procedures such as EMR. The “target sign” after EMR indicates injury to the muscularis propria layer and the need for endoscopic closure (Figure 6).

Appropriate initial workup for perforation includes abdominal plain film and CT scan with oral contrast. Perforations up to 1 cm to 2 cm in size with low fecal burden or contamination can be managed conservatively with clip closure. Endoscopic clip placement and endoscopic suturing are both reasonable options for perforation closure. Mucosal clips are generally successful at closing linear perforations less
than or equal to 2 cm in size [67]. Surgery is indicated if there is failed endoscopic/conservative management, typically with signs of peritonitis. The decision to proceed with surgery should be made within 24 hours after the initial endoscopy because the patient is more likely to receive a colostomy if the surgery is performed after the 24-hour window [73].

Previous reports have indicated that the recurrence rate of colorectal lesions after EMR is variable, between 0% and 50%. A recent systemic review and meta-analysis indicates that the general recurrence rate of colorectal lesions is around 13.1% after EMR [74]. Piecemeal resection was associated with higher recurrence rate compared to en-bloc technique, with odds ratio of 4.4. Recent studies suggest that the application of prophylactic APC at the resection edge results in lower risk of recurrence of colonic lesions [75,76].

**Wide-field endoscopic mucosal resection**

Wide-field endoscopic mucosal resection (WF-EMR) is a novel technique for removing advanced colonic mucosal lesions of almost any lateral size. It is safe in laterally spreading and sessile adenoma. Based on a recent multi-center study from Australia, recurrence is similar to small lesions (2 cm to 4 cm) as long as the patient undergoes strict surveillance colonoscopy [77].

One of the most feared complications related to WF-EMR is post-polypectomy bleeding. Proximal colonic lesion is associated with significant delayed post-
polypectomy bleed after EMR [78]. In one prospective observational study, risk factors associated with intraprocedural bleeding included large lesion size, tubulovillous or villous histology, and a Paris endoscopic classification of 0-IIa and 0-IIc [71]. In the same study, post-endoscopic bleeding after WF-EMR occurred most frequently in the proximal colon. Different methods have been described to prevent post-polypectomy bleeding. In one randomized controlled study, patients were assigned to receive prophylactic endoscopic coagulation versus no therapy. Specifically, prophylactic endoscopic coagulation was performed using coagulation forceps to non-bleeding vessels in the resected margin. Overall, prophylactic coagulation did not significantly decrease post-polypectomy bleeding [79].

**Cap-assisted endoscopic mucosal resection**

Cap-assisted EMR (C-EMR) is reported to be an effective method for removal of non-pedunculated colon polyps. Attaching the cap to the colonoscope can help visualize and stabilize areas like the ileocecal valve, anorectal junction, or behind the folds. It has been reported in case series that C-EMR is a reasonable option in removing large LST of the cecum that infiltrate the distal ileum [80]. The cap allows easy intubation of the ileum and provides a better view for the endoscopist during the mucosal resection. Cap-assisted colonoscopy was reported in a recent meta-analysis to improve the polyp detection rate and cecal intubation rate [81]. One prospective, randomized controlled study of 329 patients demonstrates that cap-assisted colonoscopy helps to reduce procedure time. The polyp detection rate was higher for the cap-assisted colonoscopy during colonoscopic EMR compared to the control
Previously, C-EMR has been described in literature in resection on rectal carcinoid tumors [64]. Based on a recent retrospective review of 124 nonpedunculated colon polyps removed by C-EMR, the overall eradication rate was 91% and the complications rate was 10.2% [83]. In the same study, bowel perforation was noted in 3.9% (5/128) of procedures, with 3/5 of the procedures occurring in the proximal colon [83]. Currently, there is limited data on cap-assisted EMR in the colon, and additional studies are needed to validate the efficacy of this technique.

**Endoscopic submucosal dissection of large colonic mucosal lesion**

ESD is primarily used for lesions confined to the mucosa or superficial submucosa measuring greater than 20 mm in diameter. ESD has the advantage of achieving en-bloc resection regardless of lesion size, which results in lower recurrence [84]. It is performed when the lesion needs to be resected en bloc to evaluate the histological features. LST of granular, nodular type measuring ≥ 30 mm or LST of nongranular type measuring ≥20 mm are also lesions to be considered for ESD [85]. ESD is also indicated for lesions that are difficult to resect with conventional EMR, including lesions that show non-lifting signs after submucosal injection and recurrent lesions at the same location [84]. The technique is not suited for lesions with deep submucosal invasion.
For the procedure, the lesion is marked circumferentially by applying soft coagulation current. Submucosal injection is performed initially to provide a fluid cushion. The main solutions used for ESD are normal saline, glycerol, and hyaluronic acid. Normal saline is usually adequate for gastric ESD because the gastric wall is thicker. However, for the colon and esophagus, longer lasting solution is needed to lift the mucosal wall [86]. After the injection, a mucosal incision is made with short needle knife, and afterward, the lesion is further dissected from the other layers of the bowel wall by using electrocautery knives. There are two types of ESD knives used during the procedure: needle knives and insulated tip knives [86]. It is essential to continue the dissection through the submucosal layer and avoid injury to the muscularis propria. During the procedure, carbon dioxide insufflation is recommended because this is rapidly reabsorbed in the event of perforation. In a case-control series, the use of carbon dioxide for insufflation was associated with shorter operating times and lower use of sedation medication [87]. Recent meta-analysis also demonstrates that carbon dioxide insufflation results in reduced procedural and postprocedural pain during colonoscopy [88].

There are many risk factors that strongly correlate with increased difficulty in performing this procedure. One prospective study with 247 lesions demonstrates that location of the lesion particularly at the hepatic and splenic flexure, locally recurrent lesion, tumor size ≥ 50 mm, and tumor spreading across ≥ 2 folds were strong independent risk factors for longer procedure duration or perforation [89].
Recent studies have focused on the efficacy and safety of colorectal ESD. A recent meta-analysis and systemic review of 22 studies provided data on 2841 ESD lesions. Analysis from the study shows that ESD is extremely effective in achieving complete en-bloc resection in 88% of lesions that are ≥ 20mm. In addition, there is also small risk of post-en-bloc resection recurrence [90].

Complications associated with ESD include bleeding and perforation. A recent systemic review and meta-analysis found an overall bleeding rate of 2% for ESD, and all the cases were successfully managed endoscopically [90]. Intraprocedural and delayed bleeding are managed similarly to post-EMR. Various coagulation devices can be used to stop the bleeding, including monopolar Coagraspers, bipolar Hemo-Stat-Y, and hot biopsy forceps [86]. Based on another recent systemic review, perforation occurs in between 1.5% and 10% of cases after ESD. Lesions larger than 50 mm, lesions with nongranular LST morphology, and proximal colon lesions are the most important risk factors leading to perforation after ESD [69,91]. Most of the perforation observed after ESD can be managed conservatively with mucosal clip placement such as the over-the-scope clip and endoscopic suturing device [92,93]. An over-the-scope device not only serves to repair perforations but also can be used as an elective treatment tool for the removal of difficult polyps, including scarred polyps or polyps that failed previous removed [94]. In one study, endoscopic suturing of mucosal defects was performed in 12 patients, and closure of post-ESD defect was safe and fast without immediate or delayed adverse events [93].
Expert commentary

For early gastric neoplasia, EMR and particularly ESD are well established and effective alternatives to gastric surgical resection. Based on the severe morbidity of gastric surgery, endoscopic resection has now become the preferred method for most small, superficial gastric neoplasia.

The role of EMR in the resection of duodenal adenoma is also well established. Currently, there is lack of standardization of endoscopic resection technique of duodenal adenomas. The natural history of sporadic duodenal adenoma is also uncertain, so it is important to balance risk and benefit, particularly in patients with significant comorbidity where observation alone may be adequate. ESD in the duodenum presents with high complication rates. Additional studies are needed to directly compare ESD and EMR in the treatment of duodenal adenomas. Specific roles and indications of ESD for the resection of duodenal adenoma will need to be defined in future studies.

For flat and laterally spreading polyps of the colon, EMR and ESD offer safe and effective alternatives to surgical resection. Additional studies looking at the complete resection rate, recurrence, and complications comparing EMR with other techniques are warranted

Five-year view
Given the dearth of short- and long-term follow-up evaluations of gastric polyps, future studies are needed to help pave the way for establishing an evidence-based guideline for the surveillance of gastric polyps.

Due to the minor risk of complications after snare polypectomy and EMR in the stomach, it is important to evaluate whether polyps may be biopsied or require actual polypectomy, particularly fundic gland polyps in the setting of PPI use. Additional studies are warranted to evaluate the complications following gastric polypectomy for benign polyps.

As noted in this review, snare type plays an important role in the resection of gastrointestinal mucosal lesions. Further investigation will be needed to compare different snare types during cold/hot snare polypectomy and EMR. Cold snare is emerging as the preferred method of resection of smaller (≤ 1 cm) colorectal polyps. Dedicated, stiffer snares with adequate submucosal lifting have become the preferred method for colorectal EMR.

Piecemeal resection is associated with a higher risk of recurrence of colorectal lesions, and patients undergoing piecemeal EMR require surveillance with repeated exam every 6-12 months until clearance is achieved.

Since the introduction of ESD in 1988, Western countries have less experience utilizing ESD to remove duodenal and colorectal adenomas. Currently, it is still not
incorporated or practiced in most institutions. Despite the fact that the procedure has been part of the endoscopic resection technique arsenal for at least 20 years, there is no exact standardized procedure for ESD. It is important to continue the effort to improve the technical ease and safety of the procedure to produce better outcome of mucosal lesion resection. Improved ESD standardization and equipment and increased implementation in Western countries will likely be focal points in the future.

EMR and ESD are both associated with moderate rates of post-procedural complications such as bleeding and perforation. The risk of perforation for ESD in the colon is estimated to be less than 5% or less than 2% if performed by an expert endoscopist. This risk is similar to that of EMR when the lesion size is more than 2cm. However, this is completely different from duodenal ESD because the risk of perforation remains high after ESD. Thus, more attention should be focused on duodenal lesions after ESD.

Current techniques to prevent or limit these complications still require further investigations. With the advent of the over-the-scope clip and suturing devices, future studies with larger patient pools are required to examine the efficacy of these instruments in limiting post-procedural complications.
Key issues

- Gastric polyps that require endoscopic resection include symptomatic polyps (bleeding, gastric outlet obstruction), adenomas of any size, dysplastic polyps, fundic gland polyps > 1 cm in size, hyperplastic polyps > 0.5 cm or larger, and polyps associated with juvenile polyposis syndrome.

- For patients with hyperplastic and adenomatous polyps, it is important to biopsy the surrounding gastric mucosa to evaluate for presence of malignancy, *H. pylori*, atrophic gastritis, or neuroendocrine hyperplasia.

- The interval of surveillance of duodenal adenomas associated with familial adenomatous polyposis is determined by the Spigelman stage.

- Pancreatic stent placement does have a protective effect in reducing post-ampullectomy pancreatitis.

- Based on recent studies, cold snare polypectomy is superior to other available methods including cold/hot forceps and hot snare polypectomy in removal of small and diminutive colonic polyp.

- Endoscopic mucosal resection is effective in removing large colonic mucosal lesions between 1.5 cm and 2.0 cm with an en-bloc technique and > 2 cm lesions using a piecemeal technique.

- Piecemeal resection is associated with higher recurrence rate compared to en-bloc technique.

- Cap-assisted EMR (C-EMR) is reported to be an effective method for removal of non-pedunculated colon polyps. Attaching the cap to the colonoscope can...
help in visualize and stabilize in areas such as ileocecal valve, anorectal junction, or behind the folds.

- ESD has the advantage of achieving en-bloc resection regardless of lesion size, and this results in lower recurrence. However, it has higher complication rates in the resection of duodenal and colon adenoma.
- Most of the perforation observed after ESD and EMR can be managed conservatively with mucosal clip placement, such as the over-the-scope clips and endoscopic suturing devices.
References

Reference annotations

* Of interest

** Of considerable interest


* Excellent review of endoscopic management of various gastric mucosal lesions.


**Most recent guidelines for management of gastric polyps by American Society of Gastrointestinal Endoscopy.**


**Most recent guidelines for management of ampullary ad nonampullary duodenal adenomas by American Society of Gastrointestinal Endoscopy.


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Financial and competing interests disclosure

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Figure Legends:

Figure 1: Extensive fundic gland polyposis of the stomach in a patient with Familial Adenomatous Polyposis (FAP).
Figure 2: 10 mm pedunculated fundic gland polyp with low-grade dysplasia found in the gastric body.
Figure 3: Non-ampullary sessile tubulovillous adenoma of the duodenum seen in second part of duodenum
Figure 4: A Paris classification IIa (superficial, elevated), granular lateral spreading 30 mm polyp in the proximal ascending colon.
Figure 5a: The same lesion as in Figure 4 seen approximately 6 months later with only a scar visible (white light).

Figure 5b: Same location using NBI to assess for residual tissue.
Figure 6: View of the underside of a resected polyp with a visible white circle within the blue submucosa, called a "target sign." The white central structure represents the muscularis propria indicating possible perforation.
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<td>Tubulovillous</td>
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<td>Moderate</td>
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Table 2. Management strategy for surveillance and treatment of different Spigelman stages

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<tr>
<td>Stage I</td>
<td>1-4 points</td>
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<td>Stage II</td>
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<td>7-8 points</td>
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<td>Stage IV</td>
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