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LARGE INTESTINE (B CASH, SECTION EDITOR)

Update on Difficult Polypectomy Techniques

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Abstract Endoscopists often encounter colon polyps that are technically difficult to resect. These lesions traditionally were managed surgically, with significant potential morbidity and mortality. Recent advances in endoscopic techniques and instruments have allowed endoscopists to safely and effectively remove colorectal lesions with high technical and clinical success and potentially avoid invasive surgery. Endoscopic mucosal resection (EMR) has gained acceptance as the first-line therapy for large colorectal lesions. Endoscopic submucosal dissection (ESD) has been reported to be associated with higher rate of en bloc resection and less risk of short-time recurrence, but with an increased risk of adverse events. Therefore, the role of colorectal ESD should be restricted to lesions with high-risk morphologic features of submucosal invasion. In this article, we review the recent literature on the endoscopic management of difficult colorectal neoplasms.

Keywords Adenoma · Colonic polyps · Colonoscopy · Endoscopic resection · Polypectomy

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Abbreviations

APC	Argon plasma coagulation
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
IBD	Inflammatory bowel disease
LSTs	Laterally spreading tumors
OR	Odds ratio

Introduction

Colorectal cancer is the third leading cause of cancer death in the USA [1]. Screening colonoscopy is the cornerstone of effective colorectal cancer prevention. Colonoscopic polypectomy reduces colorectal cancer mortality through early detection and removal of precancerous lesions that have potential to progress to cancer [2, 3]. The majority of colon polyps found during routine screening colonoscopy are small, less than 1 cm in diameter, and are easily removed. However, endoscopists often encounter polyps that are technically difficult to remove, due to their size, location, or morphology. Approximately 10–15 % of colon polyps are categorized as difficult polyps [4]. Although there is no standard definition, polyps larger than 2 cm in diameter and polyps occupying at least two haustral folds or located in certain anatomic regions (such as those involving the ileocecal valve or close to the dentate line) are considered difficult polyps [4].

Large sessile colorectal polyps were traditionally managed with surgical resection, with significant morbidity of 14–46 % [5, 6] and mortality of about 7 % [7, 8]. With technical advances and experience in endoscopic polypectomy, the majority of difficult polyps can now be treated by endoscopic resection. Advanced endoscopic techniques for difficult polypectomy include endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and hybrid EMR-

ESD technique. Endoscopic resection has been shown to be an effective and safe intervention for large colorectal polyps. In a 2015 meta-analysis of 50 studies including 6442 patients and 6779 large colorectal polyps (≥20 mm in size), successful polypectomy using advanced endoscopic resection techniques (EMR and/or ESD) was achieved in 90 % of patients [9]. Overall, 8 and 1 % of patients underwent surgery due to non-curative endoscopic resection or due to adverse events, respectively. Endoscopic recurrence was detected in 13.8 % of cases. Data from a large Australian multicenter cohort suggest that endoscopic resection of colonic advanced mucosal neoplasia appeared to be safer than surgical resection with a lower predicted mortality rate (0 % endoscopic mortality rate vs 3.3 % surgical mortality rate) [8]. Therefore, endoscopic management should be considered the first line of treatment for advanced colorectal mucosal neoplasia. This review provides an overview of recent literature on endoscopic management of difficult colorectal lesions.

Endoscopic Mucosal Resection

EMR has been increasingly used for endoscopic curative therapy of large colorectal polyps with very high technical success. In a multicenter Australian colonic EMR study, complete endoscopic resection of sessile colorectal polyps sized ≥20 mm using EMR technique was achieved in one session in 89 % of cases [10••]. Although local recurrence is a concern after EMR of large non-polypoid colorectal lesions, in this series, recurrent adenomas after EMR were typically diminutive and could be managed endoscopically in 93 % of cases. These findings are consistent with a recent meta-analysis which showed that >90 % of local recurrences could be successfully treated with only one endoscopic retreatment [11]. Overall, 98 % of cases treated with EMR were able to avoid surgery [12]. Therefore, EMR is accepted as the first-line therapy for large colorectal lesions whenever expertise is available (Fig. 1).

Key components of EMR include (1) assessment of the lesions for resectability, (2) optimal positioning of the lesion, (3) submucosal injection, (4) resection technique, (5) assessing completeness of resection, and (6) retrieval of the specimen.

Assessment of Colorectal Lesions

The first step in performing endoscopic resection of colorectal polyps is to evaluate whether the lesions are suitable for endoscopic removal. Important factors include polyp location, size, morphology, and surface pattern. Extension of a polyp into the appendiceal orifice may not allow complete resection, and referral for surgical resection is appropriate in this situation. Although location at the dentate line or involvement of the ileocecal valve has been considered more challenging, recent reports indicate high rates of complete removal in expert hands [13–15]. Size is not a contraindication to endoscopic resection, and complete circumferential lesions or those extending over several folds may be amenable to complete endoscopic resection [10••].

Morphology and surface pattern provide important signs of prevalent cancer and possible submucosal invasion. Lesion morphology should be evaluated carefully for risk of submucosal invasion and degree of fibrosis, which will dictate suitable treatment options. The Paris classification has been used to describe the morphology of smaller lesions [16]. Flat depressed lesions with a component of Paris 0-IIb or IIc have an increased likelihood to contain prevalent cancer. Larger lesions can be further described as laterally spreading tumors (LSTs) and classified as granular and non-granular in appearance. Granular-type LSTs have even or uneven nodules on the surface, whereas non-granular-type LSTs have a smooth surface [17]. Risk factors of submucosal invasion include presence of a large nodule (larger than ⩾1 cm) in granular-type LST and a non-granular surface [17].

Surface pattern has been traditionally examined with chromoendoscopy and applying Kudo classification. A Kudo pit pattern type V suggests prevalent cancer with submucosal invasion. High-resolution imaging with digital chromoendoscopy allows similar recognition of high-risk features. Using narrow band imaging, a surface pattern can be classified using the Sano classification (modified Kudo) [18] or narrow-band imaging international colorectal endoscopic (NICE) classification [19]. A Sano or NICE type III suggests prevalent cancer. In the presence of clear signs of deep submucosal invasion, endoscopic resection is less likely to achieve complete resection with clear margins and surgical removal may be preferred. If endoscopic resection is performed, the area of the lesion with highest risk of invasion should be removed en bloc and adequately prepared for pathological examination to allow assessment of the deep margin. En bloc resection can be performed by various techniques: EMR (for lesions <25 mm in size), ESD, or surgery [10••].

Lesions with gross features of malignancy (friability, induration, firm/hard consistency, and ulceration) are not usually amenable to endoscopic resection [20, 21]. Conversely, early colorectal carcinoma with small risk of lymph node metastasis has been increasingly treated with endoscopic approach. Early colorectal carcinoma is defined as cancer in which invasion is limited to the mucosa or submucosa. Traditionally, intramucosal colorectal carcinoma was thought to carry no risk of lymph node metastasis. However, there has been a case report of lymph node metastasis in intramucosal carcinoma [22]. For submucosal invasive carcinoma, lymph node metastasis occurs in 6–17 % of cases [23]. It is important to risk stratify the colorectal submucosal invasive carcinoma into low or high risk for lymph node metastasis before treatment.

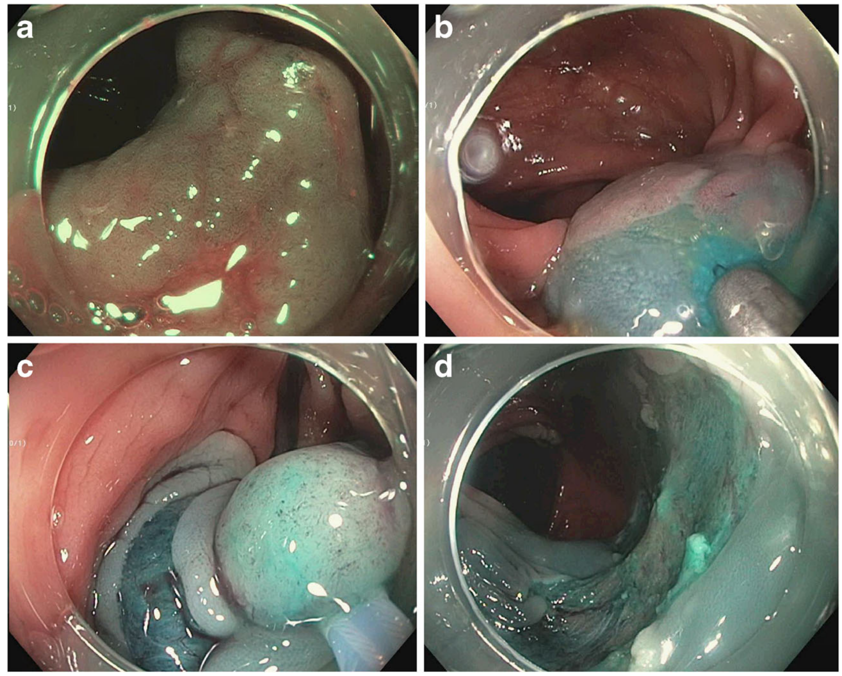

Fig. 1 Endoscopic mucosal resection (EMR) for a large, granular, sessile adenoma on top of a fold. **a** Assessment of the lesion surface pattern using narrow band imaging. **b** The submucosa below the lesion is injected using diluted methylene blue in saline. **c** Piecemeal EMR was performed with a snare. **d** Lesion site after piecemeal resection

Histopathologic features such as submucosal invasion depth >1000 μm, poorly differentiated adenocarcinoma or signet ring cell carcinoma, grade 2–3 tumor budding (high grade), and presence of lymphovascular invasion are associated with increased risk of lymph node metastasis in colorectal submucosal cancer (Table 1) [16, 24–29]. Data from several retrospective studies demonstrated that in patients with endoscopically resected T1 colorectal cancer with none of these risk factors, endoscopic follow-up could be recommended. The presence of any of these risk factors, however, was associated with lymph node metastasis and local recurrence; thus, the patients should undergo an oncologic surgical resection [27–31]. Furthermore, there are differences in risk of disease recurrence between submucosal colon cancer and rectal cancer. In a large retrospective study including 549 patients with submucosal colon cancer and 209 patients with submucosal rectal cancer, local recurrence was significantly higher in patients with high-risk submucosal rectal cancer treated with endoscopic resection alone compared to similarly treated patients with high-risk submucosal colon cancer [32]. In that particular study, the submucosal invasive colorectal cancer lesions were classified as lesions at low risk for lymph node metastasis (low-risk group) if the following criteria were fulfilled: (1) complete resection, (2) well-differentiated or moderately differentiated adenocarcinoma, (3) absence of vascular invasion, and (4) depth of submucosal invasion less than 1000 μm. Lesions without any of these features were considered to be high risk for lymph node metastasis (high-risk group). In low-risk patients undergoing only endoscopic resection, the rates of recurrence, 5-year disease-free survival, and 5-year overall survival for submucosal colon and rectal cancer were 0 vs 6.3 % ($p < .05$), 96 vs 90 %, and 96 vs 89 %, respectively. For high-risk patients undergoing only endoscopic resection, these values were 1.4 vs 16.2 % ($p < .01$), 96 vs 77 % ($p < .01$), and 98 vs 96 %, respectively. For high-risk patients undergoing surgical resection that included lymph node dissection, these values were 1.9 vs 4.5 %, 97 vs 95 %, and 99 vs 97 %, respectively. Based on these data, patients with submucosal invasive colon cancer with low-risk features could be treated with endoscopic en bloc resection whereas surgical resection should be considered in those with high-risk features or submucosal rectal cancer.

Submucosal Injection

Submucosal lifting of the lesion is a critical part of EMR and ESD. This provides a submucosal cushion to minimize the risk of adverse events such as perforation and transmural tissue injury and facilitates a more complete removal of large colon lesions [33]. During submucosal injection, a polyp that does not separate from the muscularis propria (the non-lifting sign) could indicate cancer extension to the deep submucosa or beyond. However, submucosal fibrosis from other reasons, such as prior attempted polypectomy, submucosal injection, tattooing, or chronic mucosal inflammation and biopsy, can also result in non-lifting of lesions.

Several submucosal injectates are commercially available. Each agent has inherent advantages and limitations. Normal saline is a commonly used solution for submucosal injection; however, it dissipates rapidly, necessitating repeated submucosal injections. Alternative agents that are not as rapidly absorbed have been studied, such as

Table 1 Risk factors for lymph node metastasis base on histopathologic factors

Histopathologic finding	Incidence of lymph node metastasis (%)
Depth of submucosal invasion	
SM1	<1–12
SM2	6–21
SM3	15–38
<1000 μm	1.2–3.4
≥1000 μm	13–15
Lymphovascular invasion	
Yes	12–35
No	2.9–11.9
Histological grade	
Well/moderately differentiated	6–12
Poorly differentiated	30–70
Tumor budding	
Yes	25–38.9
No	6–10

Source: [16, 24–29]. The depth of submucosal invasion is divided into three groups: superficial, intermediate, and lower third in thickness of the submucosa

SM submucosa

glycerol and hyaluronic acid (0.4, 0.13, 0.15 %) [34–36], succinylated gelatin [37], hydroxyethyl starch [38], and sclerosing agent (polidocanol) [39]. They are not widely used in routine practices.

A randomized trial of submucosal injection with succinylated gelatin vs normal saline in 80 patients undergoing EMR for sessile colonic lesions ≥20 mm found that submucosal injection using succinylated gelatin significantly improved efficiency of EMR by reducing the number of resections for piecemeal EMR by half [37]. The succinylated gelatin group also had fewer injections per lesion, lower injection volume, and shorter procedure duration.

Hyaluronic acid has been studied for submucosal injection, as it provides a long-lasting mucosal lifting for EMR. In a small case series of EMR of 32 colonic lesions and 1 duodenal lesion using an over-the-counter 0.15 % hyaluronic acid for submucosal injection, en bloc resection was achieved in 26 of the 28 lesions smaller than 25 mm [36]. Two lesions with residual tissue had fibrosis from prior incomplete endoscopic resections and required ablation with argon plasma coagulation. For five larger lesions (3–6 cm), piecemeal EMR was performed. There was one adverse event (post-polypectomy bleed). The efficacy of 0.13 % hyaluronic acid has also been studied in a randomized study of 196 patients with colon polyps (<20 mm) [35]. EMR using 0.13 % hyaluronic acid resulted in a higher rate of compete resection compared to the normal saline group (79 vs 66 %; $p<0.05$). In addition, high mucosal elevation was maintained more frequently in the hyaluronic acid group (84 vs 54 %; $p<0.01$).

Hydroxyethyl starch is a synthetic colloid solution used for plasma volume expansion. It has been evaluated in an animal model for submucosal lifting in EMR with good results. In a randomized trial of 49 patients with colorectal LSTs larger than 30 mm in diameter, submucosal injection with hydroxyethyl starch produced a more sustained mucosal elevation and lower procedure time than normal saline plus epinephrine (median time 18.5 vs 20.15 min; $p<0.001$ and 20.1 vs. 22.8 min; $p=0.013$, respectively). However, rates of post-procedure bleeding and perforation were similar between the two groups [38].

A recent systematic review and meta-analysis (in abstract form) comparing normal saline (254 patients) vs viscous solutions (250 patients) as the agent for submucosal injection prior to EMR for colorectal polyps (mean polyp sizes 20.8 and 21.4 mm, respectively) demonstrated higher rates of en bloc resection (odds ratio [OR] 1.91; 95 % confidence interval (CI) 1.11–3.29) with a lower rate of residual lesions (OR 0.54; 95 % CI: 0.32–0.91) using viscous solutions, without significant change in complications [40]. Viscous solutions may, therefore, be a better option for submucosal injection during EMR.

Injection into the submucosal space is paramount, as injection into the muscularis propria or into the mucosa may provide a false non-lifting sign [41]. Dynamic injection with gentle withdrawal of the needle and change in angle to mold an ample submucosal bleb may facilitate submucosal injection [42].

Electrocautery Settings

There is considerable variability of electrosurgical current used for polypectomy. Comparative data to support a mode of electrosurgical current during EMR are limited. Cutting current rather than the blended or Endocut current has been associated with a higher risk of immediate post-polypectomy bleeding (OR 6.9; 95 % CI 4.4–10.9) [43], and thus, the use of pure-cut current should be avoided. Pure coagulation current and blended current are widely used; however, there is no evidence to support one over the other. Microprocessor controlled current adjusts the output to tissue resistance and, hence, potentially decreases the risk of deep tissue cautery injury. We routinely use microprocessor-controlled Endocut Q current for endoscopic resection of large colorectal polyps. Furthermore, the setting of electrosurgical current used for endoscopic resection may affect the quality of histological specimen. The Endocut current for polypectomy produces less cautery artifact and better quality of the polypectomy specimens, which in turn allows more accurate histological evaluation than those resected using the blended current [44]. Future studies are required to evaluate efficacy and safety of different modes of electrosurgical current used for endoscopic resection.

Snares

Snare utilization for EMR depends on size and morphology of lesions. For large colorectal lesions, many different kinds of snares may be needed during the resection. For instance, larger snares are used for initial removal of large polyp, and subsequently, smaller snares can be used for resection of residual polyps at the margins. Stiff snares allow better capture of sessile or flat polyps. There are limited clinical studies comparing safety and efficacy of different snares for EMR of large colorectal polyps. In a randomized study of 140 patients with large (>15 mm) sessile colorectal polyps, a combined unit of needle and snare (iSnare; US Endoscopy, Mentor, OH, USA) was superior to the snare alone with less procedure time and fewer number of piecemeal segments [45].

Carbon Dioxide Insufflation

The use of carbon dioxide for insufflation during colonoscopy has been associated with lower rate of intraprocedural and post-procedural abdominal pain compared with air insufflation [46, 47]. In the setting of EMR of large colorectal polyps, a prospective observational study demonstrated that the use of carbon dioxide led to a significantly lower rate of post-procedure admission compared with that of air insufflation [48]. This was mainly due to a decrease in post-procedure admission for abdominal pain. Therefore, when available, carbon dioxide insufflation should be used during endoscopic resection of large colorectal lesions.

Underwater Endoscopic Mucosal Resection

Underwater EMR without the need for submucosal injection has been reported to be an effective technique for management of large sessile colorectal adenomas. It was first described by Binmoeller et al. [49]. The authors observed during endoscopic ultrasound that, when filled with water, the muscularis propria of the colon wall remains circular and does not follow the involutions of the folds. Thus, using water for EMR raises adenoma-bearing mucosa from the muscularis propria without the need for submucosal injection. In the initial report of underwater EMR technique using piecemeal resection with a 15-mm duck-bill snare, complete resection was successful in all 60 patients with large sessile colorectal polyps (mean size 34 mm) and only 2 % had residual adenoma on follow-up colonoscopy [49]. Delayed bleeding occurred in 5 %, and all were managed conservatively. There were no perforations or cases of post-polypectomy syndrome. Recently, the same authors reported the use of underwater EMR of large colon polyps to achieve en bloc resection without submucosal injection [50]. The EMR was performed using a 33-mm stiff braided snare (Captivator II; Boston Scientific, Natick, MA) and pure cutting current (Autocut, effect 5, 80 W). Of 53 LSTs 2–4 cm in size, complete endoscopic en bloc resection was achieved in 55 % of lesions and complete histological resection verified in 79 % of the en bloc specimens. Two adverse events (4 %) occurred, delayed bleeding in one patient and abdominal pain in another. There were no perforations. Residual adenoma was found in 5 % of all resected adenomas during follow-up.

Underwater EMR has also been used as a salvage treatment of adenomas that recur after piecemeal resection. In a single-center retrospective study comparing underwater EMR to conventional EMR for recurrent adenoma after piecemeal EMR ($n = 80$), en bloc resection rate (47 vs 16 %) and endoscopic complete removal rate (89 vs 32 %) were significantly higher in the underwater EMR group [51]. Recurrence rate of adenomas on follow-up colonoscopy was also lower in the underwater EMR group (10 vs 39 %). Underwater EMR technique has been adopted by other centers [52, 53] and appeared to be easily learned by an endoscopist trained in traditional EMR [53].

New Accessories

Endocuff (ARC Medical Design Ltd, Diagmed, Leeds, UK) is a new accessory made of plastic material with finger-like projections that can be attached on the tip of the colonoscope. In a case series of patients with large sessile colon polyps or surveillance of post-polypectomy scars in the sigmoid colon, this device improved endoscopic access in the sigmoid colon by holding the colon folds back [54].

Endoscopic Submucosal Dissection

ESD entails the use of electrosurgical knives to dissect the submucosa under the more superficial neoplastic lesion. This enables removal of larger and potentially deeper lesions with a curative intent than what can be accomplished with EMR [55]. In experienced hands, ESD appears to be an effective technique to achieve en block resection of large colorectal polyps with very low rate of adverse events. The role of ESD should be limited to lesions with high risk of containing submucosal invasion such as those with central depression or non-granular surface with a low risk of lymph node metastasis [56]. In a meta-analysis of 2841 ESD-treated colorectal lesions, histologically proven complete R0 resection rate was 88 % with a very low risk of recurrence of 0.07 %. Rate of bleeding and perforations were 2 and 4 %, respectively, and rate of surgical intervention following an ESD-related complication was 1 % [57].

ESD is also feasible for colorectal LST larger than 10 cm in size. In a retrospective case series including nine patients undergoing ESD for giant colorectal LST lesions, en bloc and curative resection rates were 88 and 100 %, however, with a high adverse event rate of 44 %. Profound bleeding occurred in one patient and perforations developed in two patients, but both were successfully treated by endoscopic clipping [58].

Hybrid Endoscopic Submucosal Dissection-Endoscopic Mucosal Resection

A modified technique of ESD, termed simplified or hybrid ESD, has been described by Toyonaga et al. when the lesions are resected by snaring after circumferential incision and submucosal dissection of the lesion margins [59, 60]. This modified technique between conventional EMR and full ESD was thought to make ESD quicker and safer. However, the available published data found no clear benefit of hybrid ESD over ESD. Compared to conventional ESD, hybrid ESD achieved lower rate of en bloc resection while rates of perforation and delayed bleeding were similar [59].

Learning Curve for Endoscopic Submucosal Dissection of Colorectal Lesions

ESD is technically demanding and has a higher rate of adverse events than EMR. Thus, sufficient training is crucial to ensure safe and high-quality resections. Several studies have evaluated the learning curve of ESD in the colon and rectum [61–63]. Compared to the stomach, colorectal ESD requires a higher level of skill and experience in interventional endoscopy because of the higher risk of adverse events. In a Japanese study, trainees could perform colorectal ESD safely and independently after preparatory training under the guidance of experienced specialists and experience with ≥30 cases. In this study, it should be noted that trainees were required to have a high level of skill in EMR techniques, experience with >20 gastric ESD cases, and assistance during >20 colorectal ESDs performed by experienced endoscopists prior to training in colorectal ESD [64]. A learning curve study of colorectal ESD at a European center evaluated one expert in therapeutic endoscopy who was a novice in ESD [61]. Training consisted of (1) five unsupervised ESDs on isolated stomach, (2) an observation period at an ESD expert Japanese center, (3) one supervised ESD on isolated stomach, and (4) retraining on one rectal ESD under supervision. The rectal ESD and colonic ESD learning curve showed that the en bloc resection rate was 80 % after 5 and 20 procedures, respectively. The operating time per square centimeter significantly decreased after 20 procedures for both rectal and colonic ESDs. Of 30 rectal and 30 colonic ESDs that were performed, perforation occurred in one patient during rectal ESD and in two patients during colonic ESD [61].

Factors predicting technical difficulty of colorectal ESD include flexure location, tumor size ≥50 mm or spreading across ≥2 folds, and tumors with scarring or those that are locally recurrent [65]. The degree of difficulty from these factors decreases as experience of the endoscopist increases. Therefore, lesions with these features are not suitable candidates for ESD in the early phase of training. For novices during the initial phase of learning colorectal ESD, beginning with rectal and smaller lesions may be advisable [63].

Comparative Studies Between Endoscopic Mucosal Resection vs Endoscopic Submucosal Dissection of Colorectal Neoplasms

A number of non-randomized studies compared efficacy and safety profiles between EMR and ESD for management of colorectal polyps. In a meta-analysis of eight studies (2299 colorectal lesions) comparing EMR and ESD, the size of the tumor [odds ratio (OR) 7.38 (6.42–8.34)], en bloc resection [OR 6.84 (3.30–14.18)], and curative resection as confirmed by the absence of tumor cells on histological examination [OR 4.26 (3.77–6.57)] were higher, and the rate of recurrence [OR 0.08 (0.04–0.17)] was lower in the ESD group vs the EMR group [66]. On the other hand, in the ESD group, the procedure was longer, and the rates of additional surgery [OR 2.16 (1.16–4.03)] and perforation [OR 4.96 (2.79–8.85)] were higher. These data suggested that EMR should be the first-line intervention for large colorectal lesion, whereas ESD should be preferred when en bloc resection is intended (e.g., for lesions that are suspicious for submucosal involvement) at the cost of higher risk of procedural complications.

Resection at Challenging Locations

Anorectal Junction

Endoscopic resection at the anorectal junction is technically challenging due to several reasons: limited endoscopic visualization, the area just distal to dentate line is highly sensitive to pain, and the presence of underlying hemorrhoidal vessels. Therefore, surgery has been the mainstay management of large polyps involving anorectal junction at most centers.

Recently, Holt et al. described simple modification of the EMR technique which allows safe and effective treatment of advanced mucosal neoplasia that involves the anorectal junction [13]. Their modified EMR technique included (1) long-acting local anesthetics in the submucosal injectate, (2) endoscopic resection over the dentate line and hemorrhoidal columns, (3) prophylactic antibiotics for resection of lesions at high risk for bacteremia (such as lesions >40 mm in diameter located within 5 cm of the dentate line), (4) transparent cap to improve endoscopic access, and (5) use of a gastroscope. Complete adenoma clearance was achieved in 100 % of the 24 advanced polyps involving the anorectal junction (median lesion size 40 mm). Focal adenoma recurrence was seen in 22 % at first surveillance colonoscopy, and all were successfully treated endoscopically.

ESD is also feasible for rectal lesions extending to the anorectal junction. In a case series of 45 patients with rectal lesions extending to the dentate line, en bloc resection and R0 resection rates were 95.6 and 53.3 %, respectively [14]. No residual adenoma was observed at the first surveillance colonoscopy. The perforation rate was 4.4 % and post-procedural bleeding occurred in 2 % of cases. Other adverse events included high-grade fever (22 %), anal pain (26 %), and rectal stenosis. The authors also recommended prophylactic antibiotics in ESD for these lesions. Comparing ESD to surgical transanal resection of lesions close to the anorectal junction, en bloc resection with a negative resection margin was significantly higher in the ESD group (67 % [35/52] vs 42 % [14/33]) with lower recurrence rate and shorter hospital stay. Adverse events including rectal perforations ($n = 2$), minor delayed bleeding ($n = 1$), and subcutaneous emphysema ($n = 1$) in the ESD group were successfully managed conservatively [67].

Ileocecal Valve

Although representing a small proportion of colonic lesions, lesions involving the ileocecal valve (ICV) are technically challenging for endoscopic resection. Traditionally, these lesions are treated surgically at most centers. However, in specialized centers, endoscopic resection is feasible with very high technical success. In a recent prospective study of 53 patients with LST ≥20 mm involving the ICV, standard or cap-assisted colonoscopy using pediatric colonoscope was used for the EMR [15]. Complete adenoma clearance was achieved in 93 % of patients, and 81 % of patients ultimately avoided surgery. Adverse events were infrequent (6 % bleeding and no perforations or strictures).

Lesions Over Scars or Lesions With Submucosal Fibrosis

Incomplete piecemeal endoscopic resection of large colon polyps may result in local recurrence with submucosal fibrosis making subsequent endoscopic polyp eradication more technically difficult. In a retrospective review of patients with non-lifting lesions from prior interventions, 96 % of adenomas were treated successfully and safely by a combination of endoscopic piecemeal resection followed by argon plasma coagulation (at a setting of 40–60 W, ERBE USA, Marietta, GA, USA) [68]. Similarly, Tsiamoulos et al. described "rescue therapy" for patients with fibrotic polyps (submucosal fibrosis >30 % of the entire lesion) using combination of piecemeal EMR and endoscopic mucosal ablation [69]. After piecemeal EMR, normal saline/adrenaline solution with/without sodium hyaluronate was injected into the submucosal layer of the fibrotic segments, and this was followed by high-power destruction (a mean argon plasma coagulation (APC) power setting of 55 W; ERBE ICC 200, APC 300, Germany) with short, sequential bursts of forced coagulation (flow 2 L/min) until there was no viable polyp tissue visible. Of 14 patients with 15 recurrent colon adenomas (mean polyp size 30 mm), complete polyp eradication was achieved in 82 % of patients and only 2 of 14 patients required surgery. No perforation or post-polypectomy syndrome was noted.

Adverse Events of Endoscopic Resection

The main adverse events associated with colonic polypectomy are bleeding and perforation. Bleeding is the most common serious adverse event with the overall rate of bleeding after EMR or ESD for large colorectal neoplasms between 1 and 10 % [70]. Risk factors of intraprocedural bleeding include larger lesions, Paris endoscopic classification of 0-IIa + Is, and lesion histology (tubulovillous or villous histology). Delayed bleeding is associated with proximal colon location, use of an electrosurgical current not controlled by a microprocessor, and intraprocedural bleeding [71•]. Prophylactic approaches to decrease the risk of bleeding for non-pedunculated polyps include epinephrine injection at the polypectomy site and prophylactic clipping closure. Epinephrine injection prior to polypectomy appeared to be effective in preventing immediate but not delayed post-polypectomy bleeding [72–74]. Prophylactic clipping of resection sites may reduce the risk of delayed post-polypectomy hemorrhage. In a retrospective study of 524 large colorectal lesions which were treated with EMR using low-power coagulation current, the delayed hemorrhage rate was 9.7 % in the "not clipped group" vs 1.8 % in the "fully clipped group" [75]. A randomized trial of clipping large polypectomy sites is warranted before prophylactic clip placement can be recommended for routine practice.

The EMR resection defect often contains blood vessels of various sizes which may cause subsequent post-EMR bleeding. However, a recent randomized trial showed that applying low-power coagulation with coagulation forceps to non-bleeding vessels in the EMR defect did not significantly decrease the incidence of post-EMR bleeding [76•]. A new method to control intraprocedural bleeding during EMR of large colonic lesions has been described. "Snare tip soft coagulation" technique used the tip of the polypectomy snare to apply soft coagulation (80 W) to sites of bleeding. The snare tip soft coagulation technique alone achieved effective hemostasis in 40 of 44 cases (91 %) of intraprocedural bleeding that occurred during wide-field colonic EMR [77].

Based on data from the Australian Colonic Endoscopic resection multicenter study including 1039 patients who underwent wide-field EMR for sessile colorectal polyps 20 mm or larger in size, clinically significant post-EMR bleeding (defined as any bleeding after EMR procedure necessitating emergency room presentation, hospitalization, or re-intervention) occurred in 6 % of cases and resolved spontaneously in 55 % of patients [78]. Factors increasing risk of intervention for hemostasis included (1) hourly or more frequent hematochezia (OR 36.7; $p = .001$), (2) American Society of Anesthesiologists class 2 or higher (OR 20.1; $p < .001$), and (3) transfusion (OR 18.7; $p = .003$). Thus, patients without identified risk factors can be managed conservatively and discharged to home. Patients responding to initial resuscitation can be observed, with a lower threshold for intervention in those with the identified risk factors.

Perforation occurs in 0.8–1.3 % of colorectal EMR cases [10••, 79]. A meta-analysis reported that the overall rate of perforation for ESD was 4 % [57]. Most of perforations, if recognized intraprocedurally, are amenable to clip closure. Inadvertent deep resection through the muscularis propria during resection can result in immediate or delayed perforation. It is crucial to be able to identify the muscularis propria injury and close immediately during the same session. This defect appears as an unstained area within the resection site. However, it can be missed due to inadequate dye staining in these areas. Topical submucosal chromoendoscopy using blue dye is a novel technique that improves differentiation of the submucosa from deeper muscular layer. In a study by Holt et al., the authors irrigated the areas of non-staining in the EMR defect with the submucosal injectate by using the blunt tip of the injection catheter [80]. Of 147 EMRs performed, intraprocedural recognition of deep resection increased from four cases (2.8 %) to six cases (4.1 %) after topical submucosal chromoendoscopy, and these were successfully managed endoscopically.

Surveillance After Endoscopic Resection

Optimal follow-up interval following the initial endoscopic resection is still unclear. The Australian Colonic EMR study group recommended performing surveillance colonoscopies at 4 and 16 months following wide-field EMR for LST ≥20 mm [12]. In a recent meta-analysis, studies performing follow-up colonoscopy at regular intervals found that 76 % of recurrences were detected at 3 months and increased to 96 % at 6 months [11]. The authors proposed that 6 months may be the optimal initial follow-up interval. We perform surveillance colonoscopy in 4–6 months and again at 16 months after the initial endoscopic resection.

A recent meta-analysis showed that local recurrence after EMR of non-pedunculated colorectal lesions was 15 % [11]. Piecemeal resection is the most important risk factor for local recurrence [11, 81, 82]. Recurrence risks after piecemeal resection and en bloc resection were 20 and 3 %, respectively [11]. Other risk factors included granular-type LST, tumor size ≥40 mm, use of APC during EMR, and ≤10 years of experience in conventional endoscopic resection [82].

In a study of 252 large non-pedunculated adenomas (>20 mm), biopsy evidence of residual/recurrent adenomas was found in 7 % of macroscopically inconspicuous polypectomy scars [83]; therefore, biopsy sampling even from macroscopically normal appearing polypectomy scars should be performed in order to detect occult microscopic neoplastic residues. A normal macroscopic appearance of the polypectomy site plus negative scar biopsy specimens at the first colonoscopy follow-up is predictive of long-term adenoma eradication (relative risk 0.15; 95 % CI 0.035–0.618) [84].

"Clip artifact" is a microscopically non-neoplastic nodular area which is caused by prior clip closure of the EMR defects. It has been reported in one third of large clipped EMR sites and can be differentiated from residual adenoma by its endoscopic appearance. It is important to differentiate clip artifact from residual polyp because clip artifact does not require further endoscopic treatment [85].

Variation in Practice Regarding Management of Difficult Colorectal Polyps

Knowledge and recommendations for endoscopic resection of complex colorectal polyps vary among different physician specialties. In a survey study of gastroenterologists and surgeons, descriptions of the endoscopic appearance by using a standardized classification system (Paris classification) were accurate in 47.5 % of cases and gastroenterologists were more accurate than surgeons [86]. Moreover, surgeons were more likely to recommend surgical resection of difficult benign colorectal polyps (17 %) compared to gastroenterologists who were specialized in complex polypectomy (3 %) as well as those who were not specialized in complex polypectomy (13 %). Therefore, additional education and collaboration among all specialists are needed to ensure proper management of these lesions.

Conclusions

Advanced endoscopic resection using EMR and ESD techniques allows curative treatment for difficult colorectal lesions and avoids the more invasive surgery in most cases. The choice of endoscopic management depends on lesion characteristics, local expertise, and patient factors. EMR and ESD should be performed by experts with experience in assessment of lesions, techniques, ancillary devices, recognizing and management of complications, and providing follow-up recommendations. Future research on modified techniques and instruments to improve endoscopic treatment outcomes is needed.

Compliance with Ethical Standards

Conflict of Interest Saowanee Ngamruengphong and Yamile Haito-Chavez declare that they have no conflicts of interest. Heiko Pohl reports personal fees from Interscope, outside the submitted work. Mouen A. Khashab is a consultant for Boston Scientific and Olympus.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Edwards BK, Noone AM, Mariotto AB, Simard EP, Boscoe FP, Henley SJ, et al. Annual Report to the Nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer. 2014;120(9):1290–314.
2. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012;366(8):687–96.
3. Loberg M, Kalager M, Holme O, Hoff G, Adami HO, Bretthauer M. Long-term colorectal-cancer mortality after adenoma removal. N Engl J Med. 2014;371(9):799–807.
4. Gallegos-Orozco JF, Gurudu SR. Complex colon polypectomy. Gastroenterol Hepatol (N Y). 2010;6(6):375–82.
5. Brigic A, Cahill RA, Bassett P, Clark SK, Kennedy RH. A prospective case controlled study of the short-term outcome following hemicolectomy for benign compared with malignant colonic polyps. Colorectal Dis. 2014;16(3):179–85.
6. Loungnarath R, Mutch MG, Birnbaum EH, Read TE, Fleshman JW. Laparoscopic colectomy using cancer principles is appropriate for colonoscopically unresectable adenomas of the colon. Dis Colon Rectum. 2010;53(7):1017–22.
7. van Westreenen HL, Ijpma FF, Wevers KP, Afzali H, Patijn GA. Reoperation after colorectal surgery is an independent predictor of the 1-year mortality rate. Dis Colon Rectum. 2011;54(11):1438–42.
8. Ahlenstiel G, Hourigan LF, Brown G, Zanati S, Williams SJ, Singh R, et al. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. Gastrointest Endosc. 2014;80(4):668–76.
9. Hassan C, Repici A, Sharma P, Correale L, Zullo A, Bretthauer M, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut. 2015.
10.•• Moss A, Bourke MJ, Williams SJ, Hourigan LF, Brown G, Tam W, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology. 2011;140(7):1909–18. **This is a prospective, multicenter, observational study of patients referred for EMR of large sessile colorectal polyps from the Australian Colonic Endoscopic (ACE) resection study group. The study included 479 patients with 514 lesions. The authors described procedural, clinical, and histologic outcomes, and identified predictors of EMR efficacy and recurrence of adenoma**.
11. Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy. 2014;46(5):388–402.
12. Moss A, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut. 2015;64(1):57–65.
13. Holt BA, Bassan MS, Sexton A, Williams SJ, Bourke MJ. Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). Gastrointest Endosc. 2014;79(1):119–26.
14. Imai K, Hotta K, Yamaguchi Y, Shinohara T, Ooka S, Shinoki K, et al. Safety and efficacy of endoscopic submucosal dissection of rectal tumors extending to the dentate line. Endoscopy. 2015;47(6):529–32.
15. Nanda KS, Tutticci N, Burgess NG, Sonson R, Williams SJ, Bourke MJ. Endoscopic mucosal resection of laterally spreading lesions involving the ileocecal valve: technique, risk factors for failure, and outcomes. Endoscopy. 2015.
16. 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.
17. Uraoka T, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut. 2006;55(11):1592–7.
18. Uraoka T, Saito Y, Ikematsu H, Yamamoto K, Sano Y. Sano's capillary pattern classification for narrow-band imaging of early colorectal lesions. Dig Endosc. 2011;23 Suppl 1:112–5.
19. Hayashi N, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, 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.
20. Christie JP. Polypectomy or colectomy? Management of 106 consecutively encountered colorectal polyps. Am Surg. 1988;54(2):93–9.
21. Binmoeller KF, Bohnacker S, Seifert H, Thonke F, Valdeyar H, Soehendra N. Endoscopic snare excision of "giant" colorectal polyps. Gastrointest Endosc. 1996;43(3):183–8.
22. Shia J, Klimstra DS. Intramucosal poorly differentiated colorectal carcinoma: can it be managed conservatively? Am J Surg Pathol. 2008;32(10):1586–8. **author reply 8–9**.
23. Saitoh Y, Inaba Y, Sasaki T, Sugiyama R, Sukegawa R, Fujiya M. The management of colorectal T1 carcinoma treated by endoscopic resection (EAST). Dig Endosc. 2015.
24. Choi PW, Yu CS, Jang SJ, Jung SH, Kim HC, Kim JC. Risk factors for lymph node metastasis in submucosal invasive colorectal cancer. World J Surg. 2008;32(9):2089–94.
25. Kawachi H, Eishi Y, Ueno H, Nemoto T, Fujimori T, Iwashita A, et al. A three-tier classification system based on the depth of submucosal invasion and budding/sprouting can improve the treatment strategy for T1 colorectal cancer: a retrospective multicenter study. Mod Pathol. 2015;28(6):872–9.
26. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum. 2002;45(2):200–6.
27. Suh JH, Han KS, Kim BC, Hong CW, Sohn DK, Chang HJ, et al. Predictors for lymph node metastasis in T1 colorectal cancer. Endoscopy. 2012;44(6):590–5.

28. Nakadoi K, Tanaka S, Kanao H, Terasaki M, Takata S, Oka S, et al. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. J Gastroenterol Hepatol. 2012;27(6):1057–62.
29. Oka S, Tanaka S, Nakadoi K, Kanao H, Chayama K. Risk analysis of submucosal invasive rectal carcinomas for lymph node metastasis to expand indication criteria for endoscopic resection. Dig Endosc. 2013;25 Suppl 2:21–5.
30. Seitz U, Bohnacker S, Seewald S, Thonke F, Brand B, Braiutigam T, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. Dis Colon Rectum. 2004;47(11):1789–96. **discussion 96–7**.
31. Yoda Y, Ikematsu H, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, et al. A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. Endoscopy. 2013;45(9):718–24.
32. Ikematsu H, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology. 2013;144(3):551–9. **quiz e14**.
33. Ahmad NA, Kochman ML, Long WB, Furth EE, Ginsberg GG. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. Gastrointest Endosc. 2002;55(3):390–6.
34. Uraoka T, Saito Y, Yamamoto K, Fujii T. Submucosal injection solution for gastrointestinal tract endoscopic mucosal resection and endoscopic submucosal dissection. Drug Des Devel Ther. 2009;2:131–8.
35. Yoshida N, Naito Y, Inada Y, Kugai M, Kamada K, Katada K, et al. Endoscopic mucosal resection with 0.13% hyaluronic acid solution for colorectal polyps less than 20 mm: a randomized controlled trial. J Gastroenterol Hepatol. 2012;27(8):1377–83.
36. Friedland S, Kothari S, Chen A, Park W, Banerjee S. Endoscopic mucosal resection with an over-the-counter hyaluronate preparation. Gastrointest Endosc. 2012;75(5):1040–4.
37. Moss A, Bourke MJ, Metz AJ. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. Am J Gastroenterol. 2010;105(11):2375–82.
38. Fasoulas K, Lazaraki G, Chatzimavroudis G, Paroutoglou G, Katsinelos T, Dimou E, et al. Endoscopic mucosal resection of giant laterally spreading tumors with submucosal injection of hydroxyethyl starch: comparative study with normal saline solution. Surg Laparosc Endosc Percutan Tech. 2012;22(3):272–8.
39. Facciorusso A, Di Maso M, Antonino M, Del Prete V, Panella C, Barone M, et al. Polidocanol injection decreases the bleeding rate after colon polypectomy: a propensity score analysis. Gastrointest Endosc. 2015.
40. Yandrapu H, Vennalaganti P, Parasa S, Rai T, Vennelaganti S, Kanakadandi V, et al. Normal saline versus other viscous solutions for submucosal injection during endoscopic mucosal resection (EMR) of colorectal polyps: a systematic review and meta-analysis. Gastrointest Endosc. 2015;81(5):AB372.
41. Nanda KS, Sonson RJ, Bourke MJ. Intramucosal injection: part of the spectrum of outcomes from submucosal injection during endoscopic resection. Gastrointest Endosc. 2014;80(4):733–5.
42. Soetikno R, Kaltenbach T. Dynamic submucosal injection technique. Gastrointest Endosc Clin N Am. 2010;20(3):497–502.
43. Kim HS, Kim TI, Kim WH, Kim YH, Kim HJ, Yang SK, et al. Risk factors for immediate postpolypectomy bleeding of the colon: a multicenter study. Am J Gastroenterol. 2006;101(6):1333–41.
44. Fry LC, Lazenby AJ, Mikolaenko I, Barranco B, Rickes S, Monkemuller K. Diagnostic quality of: polyps resected by snare polypectomy: does the type of electrosurgical current used matter? Am J Gastroenterol. 2006;101(9):2123–7.
45. Woodward T, Crook JE, Raimondo M, Wallace M. Improving complete EMR of colorectal neoplasia: a randomized trial comparing snares and injectate in the resection of large sessile colon polyps. Gastrointest Endosc. 2015;81(3):673–81.
46. Maple JT, Banerjee S, Barth BA, Bhat YM, Desilets DJ, Gottlieb KT, et al. Methods of luminal distention for colonoscopy. Gastrointest Endosc. 2013;77(4):519–25.
47. Wu J, Hu B. The role of carbon dioxide insufflation in colonoscopy: a systematic review and meta-analysis. Endoscopy. 2012;44(2): 128–36.
48. Bassan MS, Holt B, Moss A, Williams SJ, Sonson R, Bourke MJ. Carbon dioxide insufflation reduces number of postprocedure admissions after endoscopic resection of large colonic lesions: a prospective cohort study. Gastrointest Endosc. 2013;77(1):90–5.
49. Binmoeller KF, Weilert F, Shah J, Bhat Y, Kane S. “Underwater” EMR without submucosal injection for large sessile colorectal polyps (with video). Gastrointest Endosc. 2012;75(5):1086–91.
50. Binmoeller KF, Hamerski CM, Shah JN, Bhat YM, Kane SD, Garcia-Kennedy R. Attempted underwater en bloc resection for large (2–4 cm) colorectal laterally spreading tumors (with video). Gastrointest Endosc. 2015;81(3):713–8.
51. Kim HG, Thosani N, Banerjee S, Chen A, Friedland S. Underwater endoscopic mucosal resection for recurrences after previous piecemeal resection of colorectal polyps (with video). Gastrointest Endosc. 2014;80(6):1094–102.
52. Curcio G, Granata A, Ligresti D, Tarantino I, Barresi L, Liotta R, et al. Underwater colorectal EMR: remodeling endoscopic mucosal resection. Gastrointest Endosc. 2015;81(5):1238–42.
53. Wang AY, Flynn MM, Patrie JT, Cox DG, Bleibel W, Mann JA, et al. Underwater endoscopic mucosal resection of colorectal neoplasia is easily learned, efficacious, and safe. Surg Endosc. 2014;28(4):1348–54.
54. Tsiamoulos ZP, Saunders BP. A new accessory, endoscopic cuff, improves colonoscopic access for complex polyp resection and scar assessment in the sigmoid colon (with video). Gastrointest Endosc. 2012;76(6):1242–5.
55. Maple JT, Abu Dayyeh BK, Chauhan SS, Hwang JH, Komanduri S, Manfredi M, et al. Endoscopic submucosal dissection. Gastrointest Endosc. 2015;81(6):1311–25.
56. Bhatt A, Abe S, Kumaravel A, Vargo J, Saito Y. Indications and techniques for endoscopic submucosal dissection. Am J Gastroenterol. 2015;110(6):784–91.
57. Repici A, Hassan C, De Paula PD, Pagano N, Arezzo A, Zullo A, et al. Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review. Endoscopy. 2012;44(2): 137–50.
58. da Jung H, Youn YH, Kim JH, Park H. Endoscopic submucosal dissection for colorectal lateral spreading tumors larger than 10 cm: is it feasible? Gastrointest Endosc. 2015;81(3):614–20.
59. Toyonaga T, Man IM, Morita Y, Azuma T. Endoscopic submucosal dissection (ESD) versus simplified/hybrid ESD. Gastrointest Endosc Clin N Am. 2014;24(2):191–9.
60. Toyonaga T, Man IM, Morita Y, Sanuki T, Yoshida M, Kutsumi H, et al. The new resources of treatment for early stage colorectal tumors: EMR with small incision and simplified endoscopic submucosal dissection. Dig Endosc. 2009;21 Suppl 1:S31–7.
61. Iacopini F, Bella A, Costamagna G, Gotoda T, Saito Y, Elisei W, et al. Stepwise training in rectal and colonic endoscopic submucosal dissection with differentiated learning curves. Gastrointest Endosc. 2012;76(6):1188–96.
62. Probst A, Golger D, Anthuber M, Markl B, Messmann H. Endoscopic submucosal dissection in large sessile lesions of the rectosigmoid: learning curve in a European center. Endoscopy. 2012;44(7):660–7.

63. Shiga H, Endo K, Kuroha M, Kakuta Y, Takahashi S, Kinouchi Y, et al. Endoscopic submucosal dissection for colorectal neoplasia during the clinical learning curve. Surg Endosc. 2014;28(7):2120–8.
64. Sakamoto T, Saito Y, Fukunaga S, Nakajima T, Matsuda T. Learning curve associated with colorectal endoscopic submucosal dissection for endoscopists experienced in gastric endoscopic submucosal dissection. Dis Colon Rectum. 2011;54(10):1307–12.
65. Hori K, Uraoka T, Harada K, Higashi R, Kawahara Y, Okada H, et al. Predictive factors for technically difficult endoscopic submucosal dissection in the colorectum. Endoscopy. 2014;46(10):862–70.
66. Fujiya M, Tanaka K, Dokoshi T, Tominaga M, Ueno N, Inaba Y, et al. Efficacy and adverse events of EMR and endoscopic submucosal dissection for the treatment of colon neoplasms: a meta-analysis of studies comparing EMR and endoscopic submucosal dissection. Gastrointest Endosc. 2015;81(3):583–95.
67. Kiriyama S, Saito Y, Matsuda T, Nakajima T, Mashimo Y, Joeng HK, et al. Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumor: a retrospective study. J Gastroenterol Hepatol. 2011;26(6):1028–33.
68. Friedland S, Shelton A, Kothari S, Kochar R, Chen A, Banerjee S. Endoscopic management of nonlifting colon polyps. Diagn Ther Endosc. 2013;2013:412936.
69. Tsiamoulos ZP, Bourikas LA, Saunders BP. Endoscopic mucosal ablation: a new argon plasma coagulation/injection technique to assist complete resection of recurrent, fibrotic colon polyps (with video). Gastrointest Endosc. 2012;75(2):400–4.
70. Anderloni A, Jovani M, Hassan C, Repici A. Advances, problems, and complications of polypectomy. Clin Exp Gastroenterol. 2014;7:285–96.
71.• Burgess NG, Metz AJ, Williams SJ, Singh R, Tam W, Hourigan LF, 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. **This study analysed data from 1172 patients with large sessile colonic polyps to identify factors associated with intraprocedural bleeding or post-endoscopic bleeding following endoscopic mucosal resection of large sessile colonic polyps**.
72. Hsieh YH, Lin HJ, Tseng GY, Perng CL, Li AF, Chang FY, et al. Is submucosal epinephrine injection necessary before polypectomy? A prospective, comparative study. Hepatogastroenterology. 2001;48(41):1379–82.
73. Dobrowolski S, Dobosz M, Babicki A, Dymecki D, Hac S. Prophylactic submucosal saline-adrenaline injection in colonoscopic polypectomy: prospective randomized study. Surg Endosc. 2004;18(6):990–3.
74. Corte CJ, Burger DC, Horgan G, Bailey AA, East JE. Postpolypectomy haemorrhage following removal of large polyps using mechanical haemostasis or epinephrine: a meta-analysis. U Eur Gastroenterol J. 2014;2(2):123–30.
75. Liaquat H, Rohn E, Rex DK. Prophylactic clip closure reduced the risk of delayed postpolypectomy hemorrhage: experience in 277 clipped large sessile or flat colorectal lesions and 247 control lesions. Gastrointest Endosc. 2013;77(3):401–7.
76.• Bahin FF, Naidoo M, Williams SJ, Hourigan LF, Ormonde DG, Raftopoulos SC, et al. Prophylactic endoscopic coagulation to prevent bleeding after wide-field endoscopic mucosal resection of large sessile colon polyps. Clin Gastroenterol Hepatol. 2015;13(4):724–30 e1-2. **This is a prospective randomized controlled trial investigating the impact of prophylactic endoscopic coagulation (PEC) and risk of postendoscopic mucosal resection bleeding. The study randomly assigned patients with LST > 20 mm to groups receiving PEC (n = 172) or no additional therapy (n = 175, controls). They found that PEC does not significantly decrease the incidence of CSPEB after EMR**.
77. Fahrtash-Bahin F, Holt BA, Jayasekeran V, Williams SJ, Sonson R, Bourke MJ. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). Gastrointest Endosc. 2013;78(1):158–63 e1.
78. Burgess NG, Williams SJ, Hourigan LF, Brown GJ, Zanati SA, Singh R, et al. A management algorithm based on delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol. 2014;12(9):1525–33.
79. Nakajima T, Saito Y, Tanaka S, Iishi H, Kudo SE, Ikematsu H, et al. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc. 2013;27(9):3262–70.
80. Holt BA, Jayasekeran V, Sonson R, Bourke MJ. 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.
81. Woodward TA, Heckman MG, Cleveland P, De Melo S, Raimondo M, Wallace M. Predictors of complete endoscopic mucosal resection of flat and depressed gastrointestinal neoplasia of the colon. Am J Gastroenterol. 2012;107(5):650–4.
82. Oka S, Tanaka S, Saito Y, Iishi H, Kudo SE, Ikematsu H, et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol. 2015;110(5):697–707.
83. Knabe M, Pohl J, Gerges C, Ell C, Neuhaus H, Schumacher B. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. Am J Gastroenterol. 2014;109(2):183–9.
84. Khashab M, Eid E, Rusche M, Rex DK. Incidence and predictors of "late" recurrences after endoscopic piecemeal resection of large sessile adenomas. Gastrointest Endosc. 2009;70(2):344–9.
85. Sreepati G, Vemulapalli KC, Rex DK. Clip artifact after closure of large colorectal EMR sites: incidence and recognition. Gastrointest Endosc. 2015.
86. Aziz Aadam A, Wani S, Kahi C, Kaltenbach T, Oh Y, Edmundowicz S, et al. Physician assessment and management of complex colon polyps: a multicenter video-based survey study. Am J Gastroenterol. 2014;109(9):1312–24.