Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

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Abstract

Up to 15% of colorectal polyps are amenable for conventional polypectomy. Advanced endoscopic resection techniques are introduced for the treatment of those polyps. They provide higher en bloc resection rates compared with conventional techniques, while helping patients to avoid the complications of surgery. Note that 20 mm is considered as the largest size of a polyp that can be resected by polypectomy or endoscopic mucosal resection (EMR) in an en bloc fashion. Endoscopic submucosal dissection (ESD) is recommended for polyps larger than 20 mm. Intramucosal carcinomas and carcinomas with limited submucosal invasion can also be resected with ESD. EMR is snare resection of a polyp following submucosal injection and elevation. ESD involves several steps such as marking, submucosal injection, incision, and dissection. Bleeding and perforation are the most common complications following advanced endoscopic procedures, which can be treated with coagulation and endoscopic clipping. En bloc resection rates range from 44.5 to 63% for EMR and from 87.9 to 96% for ESD. Recurrence rates following EMR and ESD are 7.4 to 17% and 0.9 to 2%, respectively. ESD is considered enough for the treatment of invasive carcinomas in the presence of submucosal invasion less than 1000 µm, absence of lymphovascular invasion, well–moderate histological differentiation, low-grade tumor budding, and negative resection margins.

Keywords

- colonic polyp
- endoscopic mucosal resection
- endoscopic submucosal dissection
- advanced endoscopic resection

Colorectal cancer is the third leading cause of cancer-related mortality both for women and men.[1] Increasing emphasis on screening and polypectomy have led to earlier identification and removal of precancerous lesions, which significantly decrease colorectal cancer incidence and mortality.[1,2] While most polyps can be resected with snare polypectomy, up to 15% of them are not suitable for conventional colonoscopic removal due to a variety of reasons such as large size, difficult location, or previous resection attempts.[3–5]

Prior studies have reported that 25 to 34% of colectomies are performed for endoscopically unresectable polyps.[5,6] We previously reported that only 8.4% of those polyps have malignant pathology.[7] Furthermore, colectomy for endoscopically unresectable polyps has been shown to be associated with morbidity and mortality rates of 14 to 21% and 0.7 to 1.5% in the postoperative period, respectively.[4,8,9]

First used in the treatment of gastric neoplasms,[10] advanced endoscopic techniques (e.g., endoscopic mucosal resection [EMR], endoscopic submucosal dissection [ESD], hybrid EMR/ESD) have been introduced for the resection of these complex colorectal polyps.[11,12] While the troublesome anatomy of the colon with its folds, flexures, relatively thinner wall, and narrower lumen (►**Fig. 1**) makes advanced endoscopic resections in the colon technically more challenging,[13] nevertheless, colonic EMR and ESD provide higher en bloc resection rates than conventional endoscopic resection, while allowing patients to avoid the morbidity and mortality of colectomy.[14–16]

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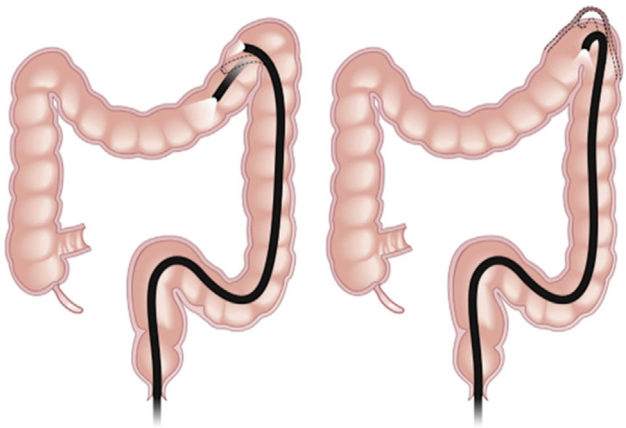

Fig. 1 Colonoscope manipulation in flexures (Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved).

Indications for EMR and ESD

The United States Multi-Society Task Force (USMSTF) on Colorectal Cancer guidelines' recommendation is to remove colorectal lesions < 10 mm with cold snare polypectomy, and consider EMR for nonpolypoid and serrated lesions sized 10 to 19 mm.[17] Note that 2 cm is considered as the largest size of a polyp that can be resected by polypectomy and EMR in an en bloc fashion.[18] For the treatment of nonpedunculated large-sized lesions (> 20 mm), both EMR and ESD can be used. However, achieving en bloc resection with EMR can be difficult,[17–19] and piecemeal resections are associated with reduced histopathological assessment quality and higher local recurrence rates.[19] Thus, for lesions larger than 20 mm, ESD is recommended.[18,19] In addition to large-sized polyps, any lesion that is difficult to resect in an en bloc fashion using conventional techniques or EMR (e.g., difficult location,[20] underlying fibrosis due to previous resection attempts[21]) can be a candidate for ESD. Similarly, residual, and recurrent lesions following EMR[21] can be resected with ESD.

From an oncological standpoint, in the presence of high suspicion for limited submucosal invasion (less than 1,000 µm), ESD should be preferred.[19] The prediction of malignancy can be made based on the morphological features of polyps, which is validated by several classification systems (e.g., Kudo,[22] Paris,[23] and Narrow-band Imaging International Colorectal Endoscopic[24]). While laterally spreading granular tumor (LST-G) with homogenous patterns can be resected with EMR, ESD should be considered for LST-G of mixed nodular type and laterally spreading nongranular tumors.[23] In the presence of a colorectal lesion with slight crypt distortion and intact vascular structures,[22,24] ESD can be considered, whereas for severely disrupted lesions, the risk of deep submucosal invasion is high and surgery should be the treatment of choice.[25] Rectal carcinoid tumors larger than 10 mm constitute an indication for ESD as well.[26]

Preprocedural Management

Preoperative assessment of patients with detailed medical history taking is a crucial step prior to the procedure. Anticoagulants should be stopped 5 to 7 days before the procedure.[27] If applicable, previous colonoscopy reports with colored images should be evaluated by the advanced endoscopist. Depending on the comorbidities of the patient and characteristics of the lesion, the procedure may be performed in the endoscopy suite or operating room.[28]

Mechanical bowel preparation is another critical step for proper visualization of the lesion and possible interventions. While osmotic agents, such as sodium phosphate solutions, might cause significant fluid and electrolyte changes, large-volume polyethylene glycol solutions are widely available and better tolerated by most patients.[29]

Settings and Equipment

The Setup of the Endoscopy Suite

The ideal setup should contain a colonoscope with a good bending range and water jet function to maintain a clear endoscopic view. To distend the colonic lumen, CO_2 insufflation is recommended given its association with less abdominal pain and bloating due to its rapid absorbance[16,30] (►**Fig. 2**). Electrosurgical unit with high-frequency generator and automatically controlled system is also required for incision and coagulation during EMR and ESD.[16]

Dissection Devices

A variety of snares and knives are available for endoscopic resections. Snares are mostly used during EMR and hybrid EMR/ESD procedures. A polypectomy snare consists of a wire loop attached to a long connector within a plastic sheath that is connected to a generator via an electrosurgical cautery cord. They are of different sizes and shapes (►**Fig. 3**), and the selection can be made based on lesion size, morphology, location, and personal preference.[21,31] While small snares (10–15 mm) are preferred for lesions in the right colon, larger snares (20–25 mm) can be used in the rectum.[31]

Electrosurgical knives are used for incision and dissection. There are three well-known groups of knives, namely, needle, insulated tip (IT), and forceps types[16] (►**Fig. 4**). The needle-type knives (e.g., needle knife, dual knife, flush knife [Olympus, USA]), as the name implies, have a small needle pointing out with ball-shaped processes at the tip. The ball-like tip provides a round surface for coagulation, which reduces the risk of perforation. IT knife also has a similar design with insulated ceramic ball-tip that reduces the perforation risk.[32] Forceps knives (e.g., steel blade knife, coagrasper [Olympus, USA]) are good for hemostasis and resection of lesions in difficult locations.

Procedural Technique

Submucosal Injection

To minimize the risk of inadvertent perforations and transmural thermal injuries during advanced endoscopic resections, adequate submucosal elevation is of utmost importance. By injecting a solution into the submucosal plane, a submucosal cushion is created, and the lesion is separated from the muscularis propria layer (►**Fig. 5**), which allows for

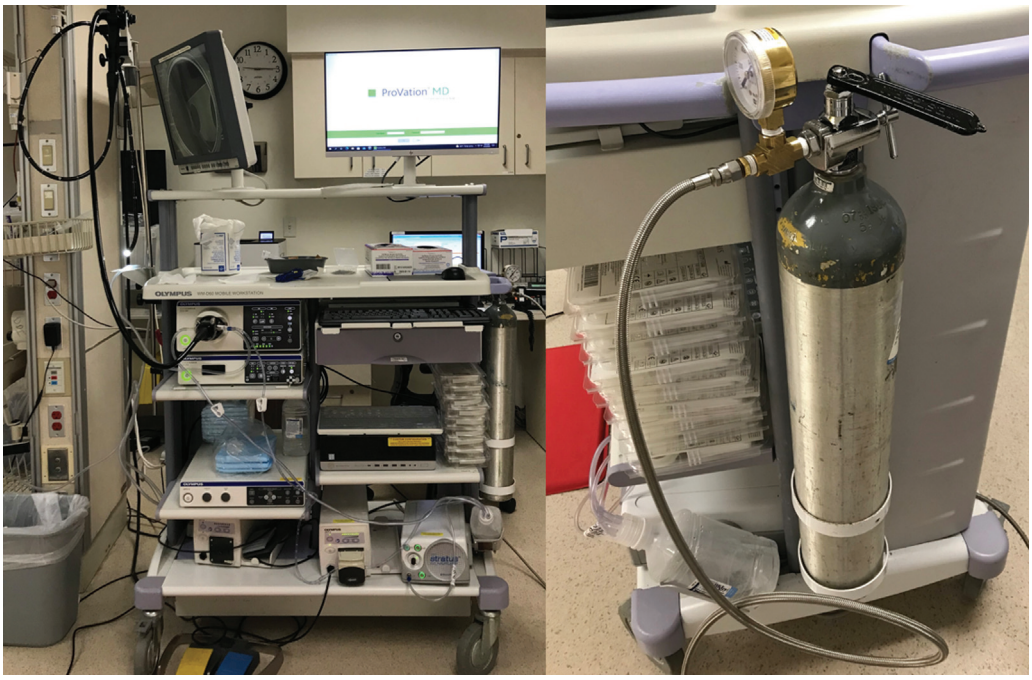

Fig. 2 Ideal setup should contain a colonoscope with a good bending range, CO_2 insufflation (on the right), and high-frequency generator.

more precise dissections by decreasing the tissue resistance within the transection plane.[33]

For submucosal injection, the needle should be inserted tangentially. As soon as the solution is injected into the submucosal plane, elevation is observed. Failure of a lesion to be lifted despite performing injection in the correct plane is called the "nonlifting sign" (►**Fig. 6**), which may indicate the presence of an underlying malignancy.[34] It might also be observed in the presence of fibrosis due to previous resection attempts.

Submucosal injection should be performed in such a way that the elevated lesion should not obstruct the view. If the polyp is situated on a fold, the injection should start proximally, so that the polyp would not fall backward away from the view.[21,27]

The ideal injection agent should be safe, inexpensive, and long-lasting. Injection solutions contain two common elements: a colloid (hyperosmolar) solution and an inert dye (e.g., indigo carmine or methylene blue) to facilitate visualization of tissue planes.[21] Alternatively, there are readily available solutions that do not require mixing. ORISE Gel Submucosal Lifting Agent (Boston Scientific, USA) and Eleview (Medtronic, USA) are Food and Drug Administration-approved injection solutions that can be used for this purpose. Additionally, diluted adrenalin (1 mL of 0.1% adrenalin) and hydroxyethyl starch solution mixed with methylene blue or other dyes can be used. Normal saline is not recommended as it dissipates quickly.[27]

Endoscopic Mucosal Resection

EMR consists of using snares for resection following the submucosal injection phase (►**Fig. 7**). For EMR, the lesion should be positioned at 5 to 6 o'clock. The goal during EMR is to achieve en bloc resection with 2 to 3 mm of negative mucosal margin.[31] Although not recommended, piecemeal resection can be performed when en bloc resection of the lesion is not possible.

A conventional EMR technique is the hot-snare resection, which utilizes electrocautery. This technique has been reported to be associated with thermal injury to the colonic wall, which might lead to delayed perforation in the postoperative period.[35] To decrease postprocedural complication while maintaining the same efficacy, cold-snare resection has been described. However, studies showed increased rates of specimen damage and positive margins with the use of cold-snare resection.[35,36]

Although not commonly used, modified EMR techniques, mainly cap-assisted EMR (C-EMR)[37] and underwater-EMR (U-EMR),[38] have been introduced to overcome the limitations of conventional techniques and achieve higher complete resection rates.[31] In C-EMR, the tissue is suctioned into the cap, snare is closed, and cautery is applied as the snare is closed.[31] In U-EMR, elevation of the lesion is achieved by water immersion, and the resection is done utilizing the snare.[31]

Endoscopic Submucosal Dissection

ESD involves several steps (►**Figs. 8** and **9**). First, the lesion is marked using the electrocautery. Following submucosal injection, circumferential incision (►**Fig. 10**) is performed starting from the proximal side of the lesion. Once half of the circumference is incised, submucosal dissection is performed in this half. Incision and dissection steps are repeated for the distal half of the lesion. Complete circumferential incision followed by dissection can also be performed. However, in this case, the injection solution might flow from the lesion, which might result in poor visualization of the submucosal space.[39] To facilitate submucosal dissection, a

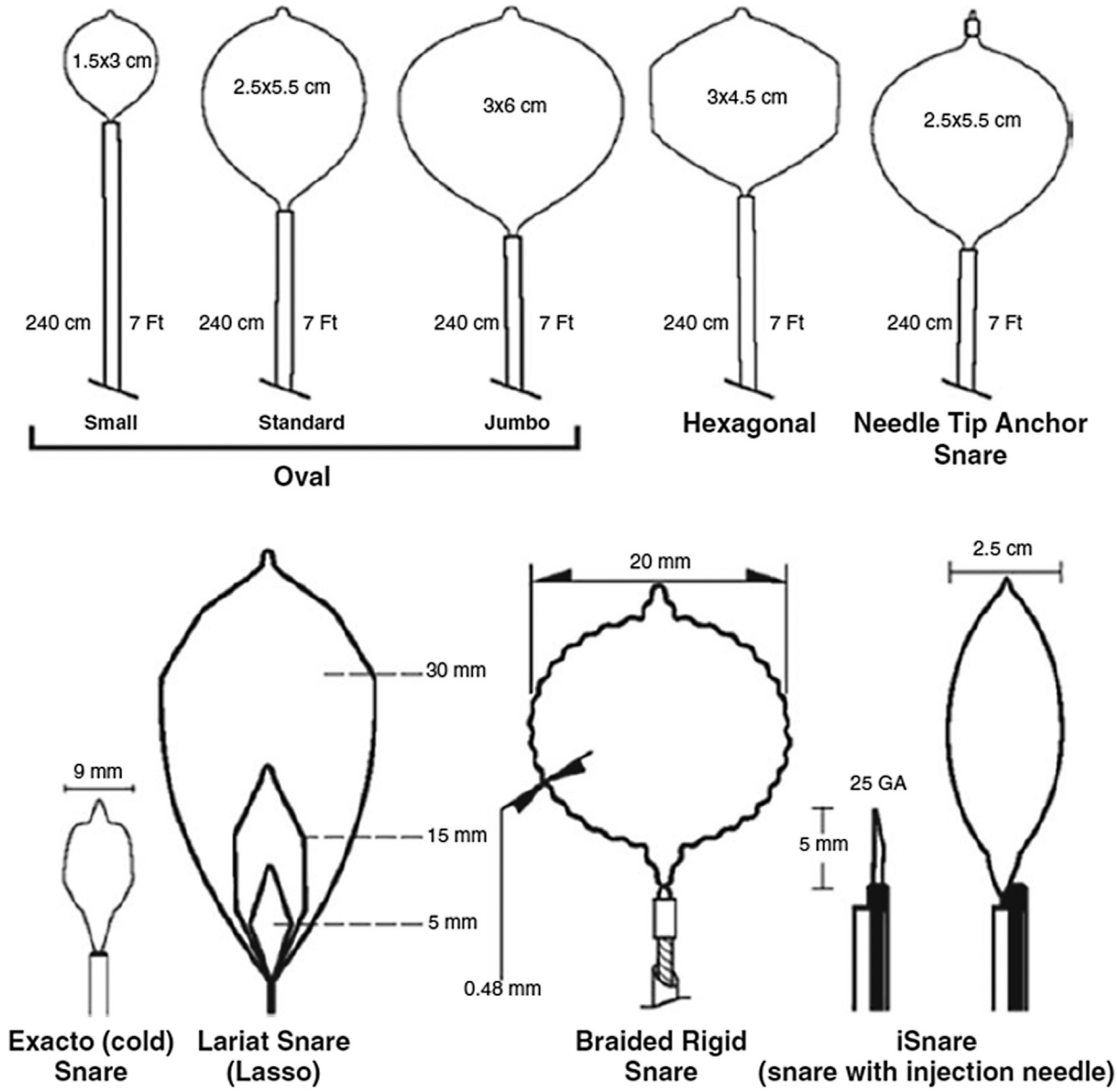

Fig. 3 Different snare types used for advanced endoscopic resection techniques.

transparent hood attached to the tip of the scope is required.[40] Traction can be helpful during the dissection stage, and many devices and techniques have been introduced for this purpose.[41]

In 2014, Yamamoto and colleagues[42] designed the "pocket-creation method" as a new strategy for ESD. In this technique, instead of making a circumferential incision in the mucosa, a minimal incision is made, followed by submucosal pocket creation. A meta-analysis revealed significantly higher en bloc and R0 resection rates with comparable adverse event rates associated with this technique.[43]

Hybrid EMR/ESD

ESD enables lesions to be resected regardless of their size,[18,19] but is technically challenging and time consuming. On the other hand, EMR is not a suitable option for large-sized lesions, lesions that are difficult to resect due to location, or previous attempts. The hybrid EMR/ESD technique is introduced to overcome the limitations of both the techniques,[44] and provides more reliable resections than EMR but quicker than ESD.

In hybrid EMR/ESD, following submucosal injection, incision and dissection steps are completed to a certain degree. Snare resection is performed following the dissection.[44,45]

Postprocedural Complications

Bleeding

Bleeding is one of the major complications of colorectal EMR and ESD, which can be observed intraprocedurally, immediately (within 24 hours), or delayed.[46] Studies have reported delayed bleeding rates of 1.4 to 3.5% for EMR and 1.5 to 2.8% for ESD.[13,47–49]

Large lesions (larger than 40 mm), lesions located in the proximal colon, patients on dual-antiplatelet therapy or heparin bridge therapy, and patients on hemodialysis have

Fig. 4 Different knives used for advanced endoscopic resection techniques. (**A**) Needle knife, (**B**) dual knife, (**C**) hook knife, (**D**) insulated tip (IT) knife, (**E**) steel blade (SB) knife, (**F**) coagrasper (Olympus, USA).

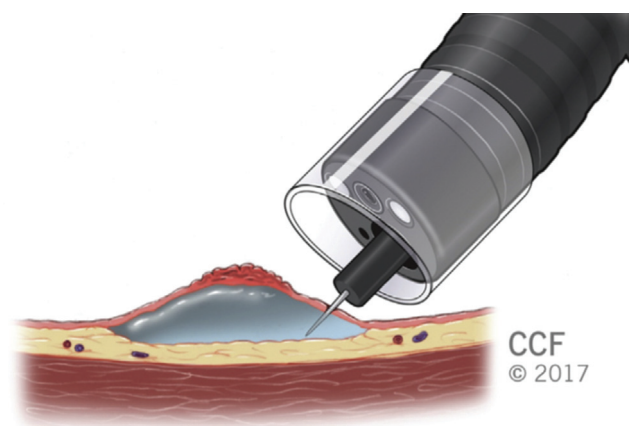

Fig. 5 Submucosal injection (Cleveland Clinic Center for Medical Art & Photography © 2017. All Rights Reserved).

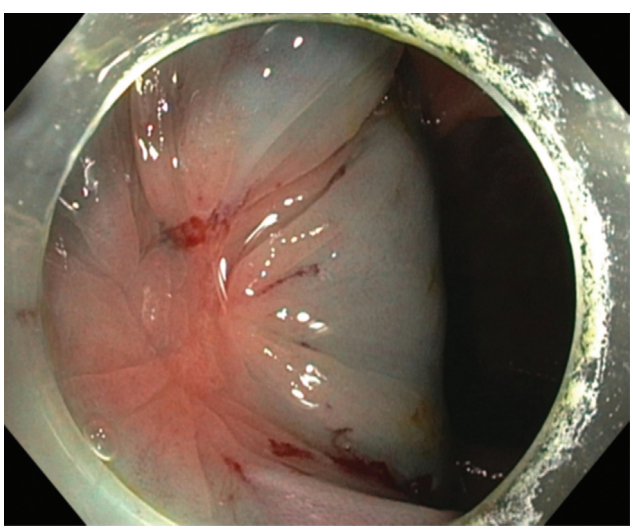

Fig. 6 Nonlifting sign. Injected solution does not elevate the lesion, but the normal submucosa around it. Endoscopically, a tuberance is seen outside the tumor.

increased risk for postprocedural bleeding.[46,50] Rectal and proximal colonic locations are reported to be independent risk factors for bleeding.[25,46]

The treatment of bleeding can be accomplished with coagulation or clipping. Minor bleeding from small vessels can be managed by contact coagulation with the tip of a snare or knife, whereas bleeding from larger vessels can be treated with hemostatic forceps[47] (►**Fig. 11**). While using the hemostatic forceps, application of electrocoagulation should be minimized to avoid thermal injury and subsequent delayed perforations.

Perforation

Given the thinner wall of the colon, and limited endoscopic maneuverability inside the colon, colonic procedures are associated with higher perforation rates than gastric procedures.[51] Perforation is the most concerning complication of colorectal EMR and ESD as it is associated with significant morbidity and mortality.[52] Depending on the timing of diagnosis, perforations are classified as early (diagnosed

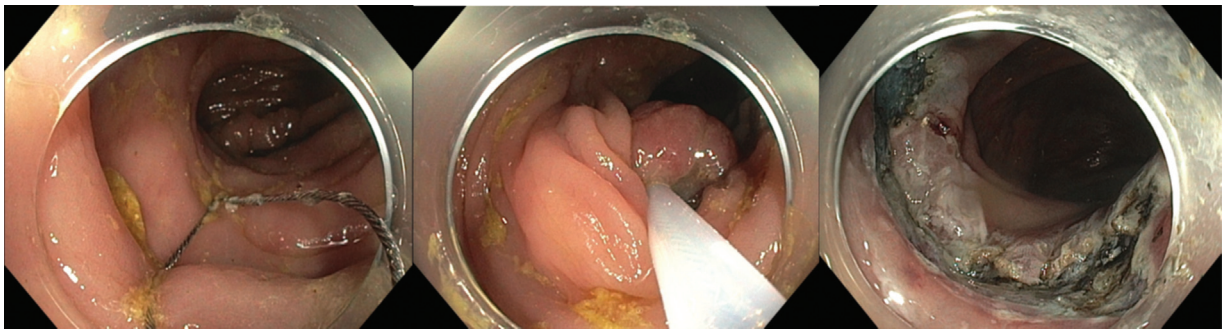

Fig. 7 Utilization of snare for endoscopic mucosal resection (EMR).

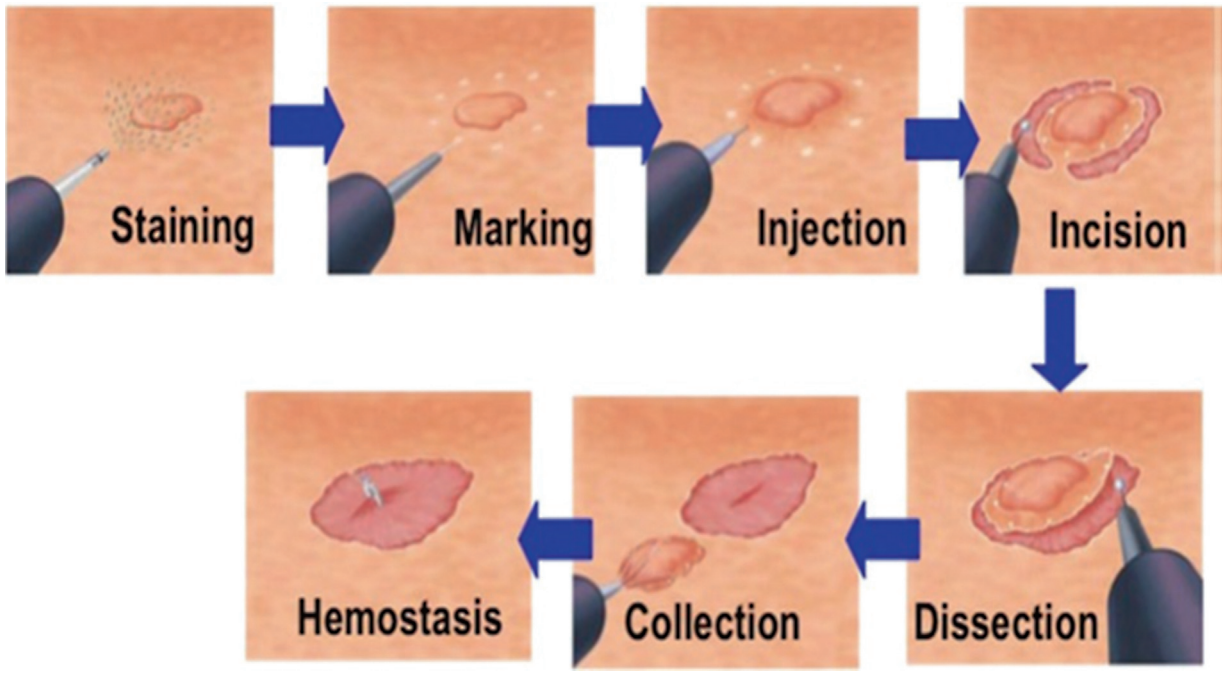

Fig. 8 Steps of endoscopic submucosal dissection (ESD).

intraprocedurally) and delayed (diagnosed after the completion of endoscopic resection) perforations. While intraprocedural perforations occur due to unintentional resections, delayed perforations are usually caused by thermal injury.[51] The incidences of perforation following EMR and ESD are 0 to 1.4% and 2 to 10.7%, respectively.[13,25,39,48,49]

The most common site for perforation is usually the sigmoid colon, followed by the cecum, ascending, transverse, and descending colon.[52] Additionally, larger lesions, submucosal fibrosis, female gender, advanced age, presence of diverticular disease, or Crohn's disease are shown to be associated with increased perforation risk.[51,52]

The most important step in the treatment of perforations is the diagnosis. The real-time evaluation of every resection site is crucial. Patients with perforations usually present with abdominal pain, which may or may not be accompanied by fever, tachycardia, and leukocytosis. X-ray and computed tomography scans can be used for diagnosis. However, the presence of the free air around the resection site is expected following advanced endoscopic resections, and does not always necessitate surgery. Most delayed perforations are diagnosed within 14 hours of the procedure, but some cases might be diagnosed even after 24 hours.[51] Therefore, high suspicion for perforation should be kept in mind in the presence of the abovementioned symptoms.

Historically, all perforations were managed with laparoscopy or laparotomy. With the advances in technology, less invasive techniques have been developed. Today, most perforations are handled by endoscopic closure techniques (e.g., clips, loops, suturing)[53] (►**Figs. 12** and **13**). While through-the-scope clips can be sufficient to handle small-sized perforations, over-the-scope-clips can be used to close larger defects.[54] Recently, a study from Cleveland Clinic[55] showed 86% success rate with the use of endoscopic clips for intraprocedural perforations, which is in line with the previous studies reporting success rates around 81%.[53,56] Endoscopic management of perforations is associated with less morbidity and mortality, and shorter length of hospital stay compared with surgery. However, surgery is needed in the presence of ongoing sepsis, signs of diffuse peritonitis, and failure of endoscopic management.[57]

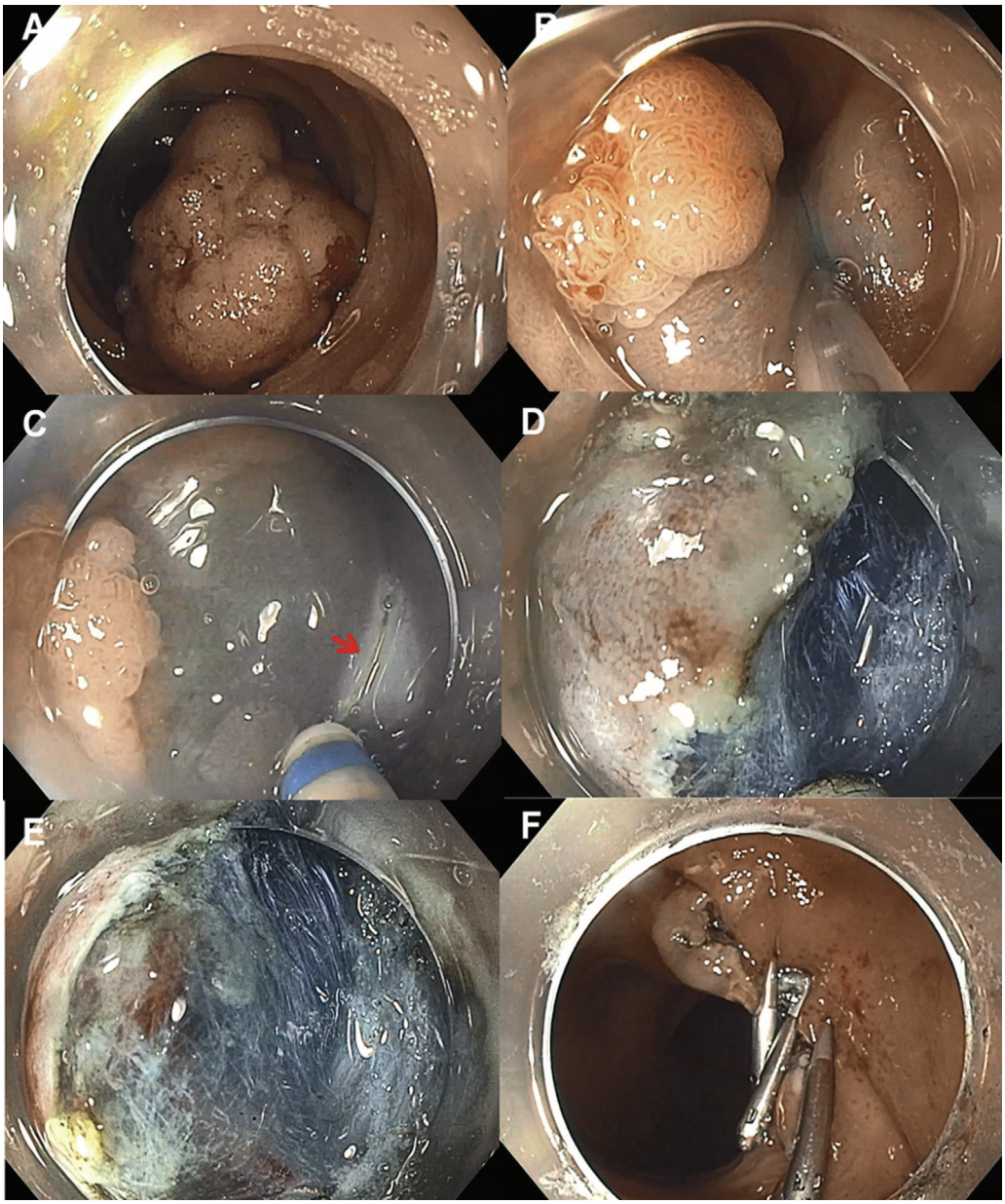

Fig. 9 (**A**) Operative steps of endoscopic submucosal dissection (ESD). (**B**) Lesion is visualized, submucosal injection is made, (**C**) incision is started, (**D** and **E**) dissection is continued in the submucosal plane, (**F**) and the defect is closed with endoclips.

Other Complications

Post-ESD coagulation syndrome/postpolypectomy electrocoagulation syndrome can be observed in around 4.8 to 14.2% of patients. Peritoneal inflammation occurs due to transmural thermal injury, and this syndrome usually presents with fever, abdominal pain, leukocytosis, and increased inflammatory markers after 24 to 48 hours of the initial procedure. Treatment is conservative with bowel rest, intravenous fluids, and antibiotics, with remission being expected within 24 hours. If symptoms do not improve within 24 to 96 hours of treatment, patients should be reevaluated for possible delayed perforation.[25,47,51]

Stenosis following ESD is a very rare complication. A study published from Japan[58] revealed 4 post-ESD stenosis out of 822 patients (0.49%). In this series, all cases were managed by endoscopic balloon dilation combined with steroid therapy. Surgery was not needed for any patient.

Outcomes

En Bloc and R0 Resection

En bloc resection refers to the resection of a polyp in one piece (►**Fig. 14**), whereas R0/complete resection is defined as histological disease-free margin polyp resection. Studies reported higher en bloc and R0 resection rates with ESD. EMR is associated with increased rate of piecemeal resections, hence local recurrence is observed more commonly after EMR.[19,25,46] En bloc resection rates range from 44.5 to 63% for EMR[48,59,60] and from 87.9 to 96% for ESD.[13,25,46,48,59] Similarly, R0 resection ranges for EMR and ESD are 42.3 to 65.5%[48,59] and 72 to

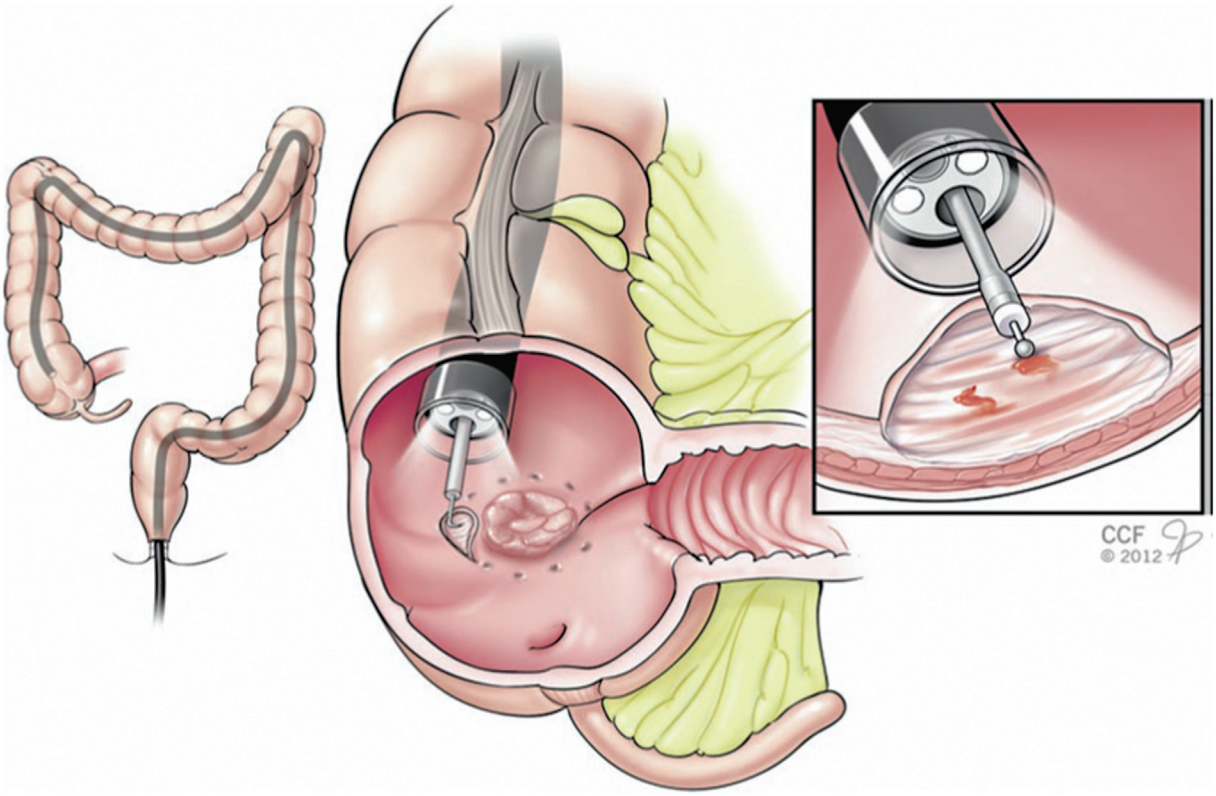

Fig. 10 Orientation for endoscopic submucosal dissection and dissection of the submucosal plane (Cleveland Clinic Center for Medical Art & Photography © 2012. All Rights Reserved).

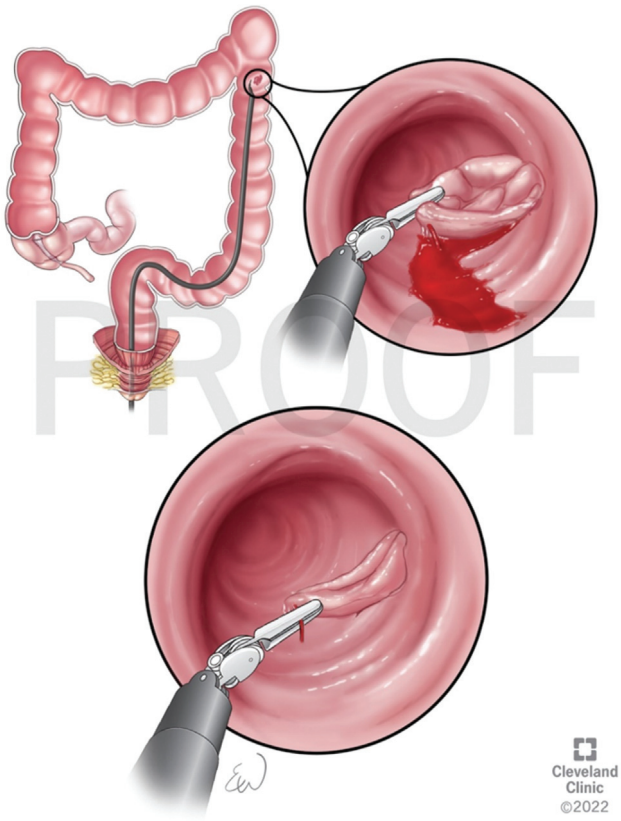

Fig. 11 Bleeding during endoscopic submucosal dissection (ESD) treated utilizing a coagulation forceps (Cleveland Clinic Center for Medical Art & Photography © 2022. All Rights Reserved).

85%,[13,25,46,48,59] respectively. Imai et al[61] reported that using ESD, even for large neoplasms, it is possible to achieve high en bloc (94.9%) and R0 resection (79.7%) rates.

Recurrence

Compared with ESD, EMR has been proven to be associated with higher recurrence rates. Overall, recurrence rates after EMR range from 7.4 to 17%,[46,48,59,62] with increased recurrence rates being observed with piecemeal resections.[63,64] On the other hand, the recurrence rate after ESD is around 0.9 to 2%.[13,25,46,48,59]

The major risk factor for the recurrence happens to be piecemeal and non-R0 resections. Tanaka et al[47] suggested that piecemeal resection of lesions > 20 mm is an independent risk factor for recurrence, even following ESD. Lesion size is another predictor of recurrence.[63] Lesion characteristics or location are not associated with tumor recurrence.

What about Malignant Polyps?

The majority of dissected lesions are benign adenomas, while 10 to 20% are malignant lesions.[25] Intramucosal carcinomas and carcinomas with slight submucosal invasion can be treated with endoscopic resection, as soon as margin negativity is ensured.[18] Submucosal invasion > 1,000 µm, presence of lymphatic and vascular invasion, high-grade tumor budding, poor histological differentiation, and margin positivity increase the risk for lymph node metastasis and local recurrence.[65] Therefore, subsequent surgery should be

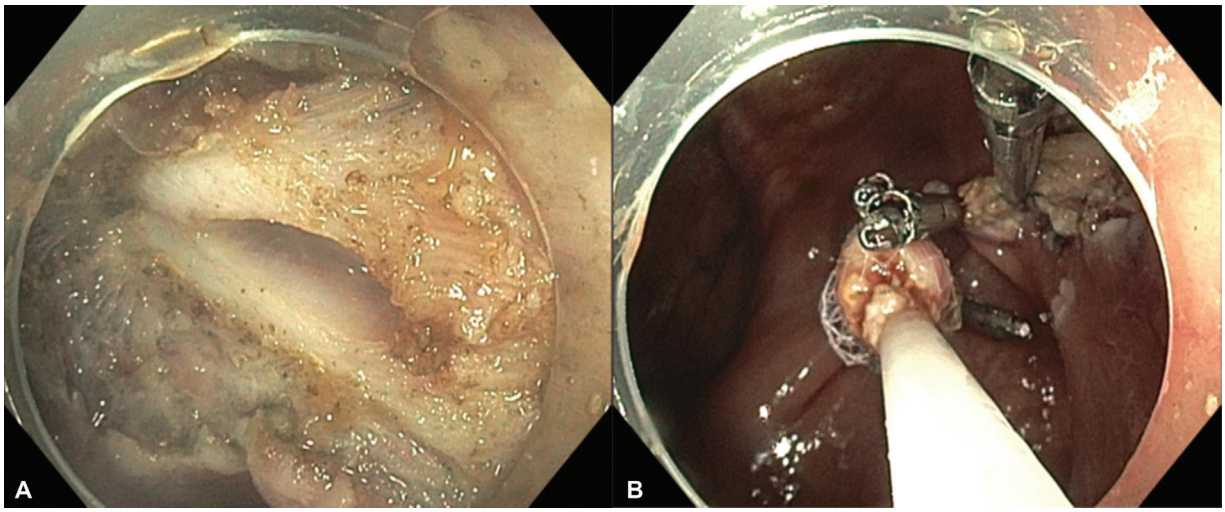

Fig. 12 (**A**) Defect in the colonic wall following endoscopic submucosal dissection (ESD), (**B**) placement of endoscopic clips for closure.

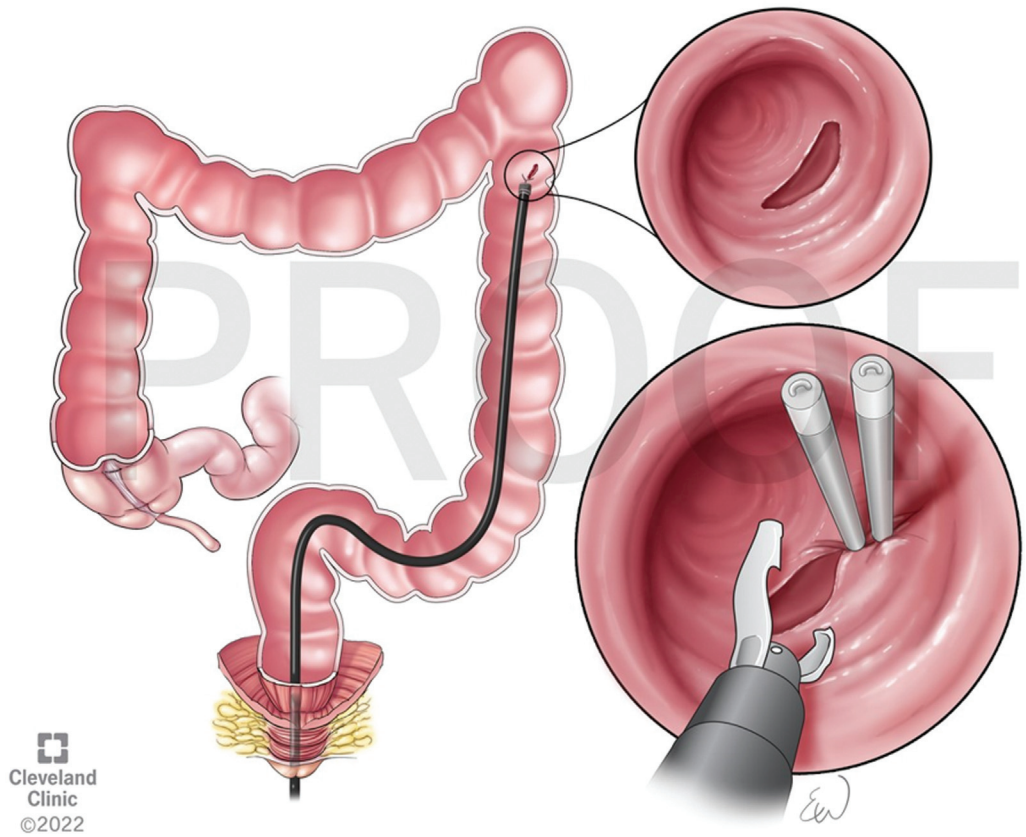

Fig. 13 Application of endoscopic clips for perforation (Cleveland Clinic Center for Medical Art & Photography © 2022. All Rights Reserved).

performed in the presence of any of these factors. In our experience, 7.5% of patients had adenocarcinoma in the final pathology. Patients with good prognostic factors underwent surveillance, whereas patients with negative prognostic factors underwent subsequent surgeries. After a median follow-up of 21.2 months, we have not observed any recurrences.[66] Studies comparing colorectal cancer patients who underwent ESD preceding surgery versus surgery alone reported no difference in recurrence rates and concluded that ESD preceding surgery does not have negative impact on the oncological outcomes.[67,68]

Follow-Up

Today, there is no consensus on surveillance after advanced endoscopic resections. The follow-up plan should be individualized depending on the pathology results, quality of specimens, and individual risk factors. In general, authors

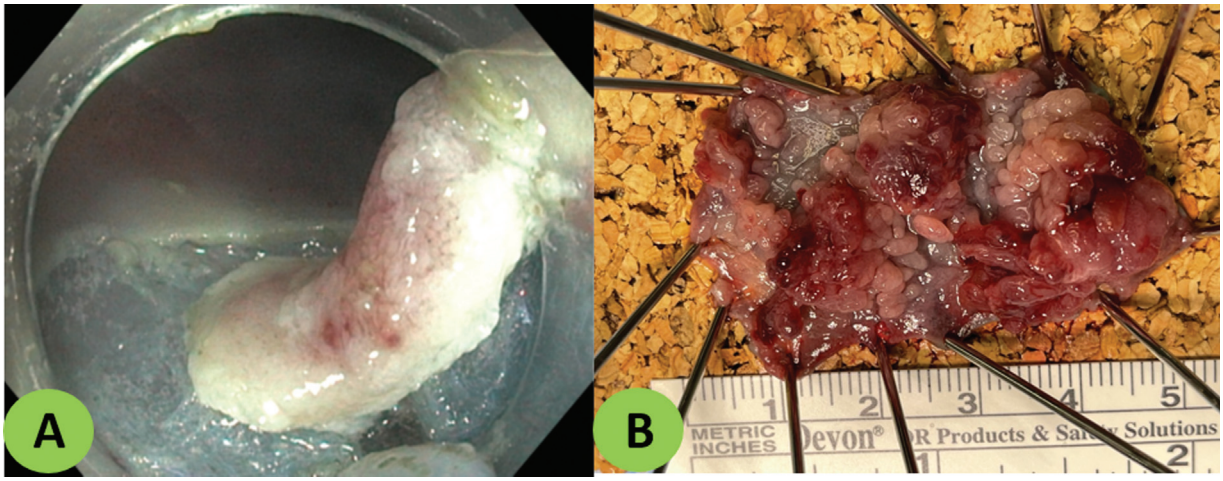

Fig. 14 (A) En bloc resection of a specimen, endoscopic view. (B) Specimen after en bloc resection.

recommend initial follow-up colonoscopy to be performed 3 to 6 months after resection to verify complete removal. If there are no suspicious findings, total colonoscopy for reassessment can be performed after a year.[19]

Conclusion

Increased emphasis on screening and polypectomy has led to significant decrease in colorectal cancer morbidity and mortality. Historically, surgery was the treatment of choice for polyps that were not able to be resected with conventional techniques. Today, advanced endoscopic techniques are used widely for the treatment of these lesions. They provide higher en bloc resection rates compared with conventional polypectomy, while helping patients avoid the morbidity and mortality associated with colectomy. EMR consists of lifting up the lesion with injection of a fluid into the submucosal space and using snares for resection. ESD has several steps including marking, submucosal injection, incision, and dissection. Each technique has their own limitations, and to choose between endoscopic resection modalities, one must be familiar with the techniques, their pitfalls, and outcomes. The capabilities of the institution and endoscopist are also important. Nevertheless, in general, ESD is associated with higher en bloc and R0 resection rates, and lower recurrence rates compared with EMR. Bleeding, perforation, and post-polypectomy coagulation syndrome can be observed following these procedures, and various techniques have been described for the treatment of these complications.

Pearls and Pitfalls

- With EMR and ESD, it is possible to achieve higher en bloc and R0 resection in the treatment of polyps that are not amenable to be resected using conventional polypectomy, while avoiding the complications of surgery.
- Polyps larger than 20 mm, in difficult locations, with underlying fibrosis due to previous resection attempts are candidates for ESD.
- The first step in both EMR and ESD is the submucosal injection. It provides submucosal cushion and allows surgeon to perform more precise dissections by decreasing the resistance in the transection plane.
- Nonlifting sign can represent underlying malignancy or fibrosis due to previous resection attempts.
- For EMR, following submucosal injection, snare resection of the lesion is performed.
- ESD consists of several steps, including marking, submucosal injection, incision, and dissection. For incision and dissection, several knives are present.
- Hybrid EMR/ESD uses submucosal injection, mucosal incision, and dissection of a certain degree, followed by snare resection.
- Bleeding and perforation are the most common complications following advanced endoscopic resections. During the procedure, any bleeding should be coagulated, and clips should be placed in the presence of perforation or suspicion for perforation.
- Compared with EMR, ESD is associated with higher en bloc and R0 resection, and lower recurrence rates.
- During endoscopic resections, it is important to recognize the signs of potential malignancy (e.g., surface patterns, nonlifting sign).
- Intramucosal carcinomas and malignancies with limited invasion to the submucosa can be resected endoscopically as soon as margin negativity is ensured. The presence of any poor prognostic factor necessitates subsequent surgical oncological resection.
- To verify complete removal of the lesion, a follow-up colonoscopy is recommended after 3 to 6 months.

Conflict of Interest
Dr. Emre Gorgun receives consultancy fees from Boston Scientific, DiLumen and Olympus.

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