Endoscopic Treatment of Early Cancer of the Colon

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Abstract: Colorectal cancer is the fourth most common cancer diagnosis worldwide and the second leading cause of cancer death. In the United States, it is estimated that in 2015 there will be 132,700 new cases of colorectal cancer (representing 8.43% of all new cancer cases) and 49,700 deaths. Colonoscopy plays a fundamental role in the prevention and management of colorectal cancer patients and is used for both the diagnosis and treatment of early colorectal cancer and its precursors. Improvements in colonoscopy preparation, new techniques of adenoma detection, and recent progress in endoscopic imaging methods are providing higher-quality results and reducing the incidence and mortality of the disease. Traditionally, colonoscopy has been used to remove precursor lesions. Invasive cancer was treated by surgical resection with or without chemoradiotherapy. During the past decade, endoscopic resection techniques have advanced, and cancers confined to the mucosal and superficial submucosal layers can now be resected via flexible endoscopes. Therefore, it is important to understand the indications and limitations of endoscopic resection, determine whether the cancer can be curatively resected, and assess the risk of lymph node metastasis, which precludes endoscopic treatment.

Early colon cancer is defined as cancer that is confined to the mucosa or submucosa that does not invade the muscularis propria. Intramucosal cancer is virtually never associated with lymph node metastasis and can be curatively resected via colonoscopy. Once the submucosal layer is invaded, metastasized lymph node involvement is reported in 6% to 13% of cases.[1]

However, some cases of shallow submucosal invasion, especially invasion with a vertical depth of less than 1000 μm from the lower border of the muscularis mucosae, are still eligible for endoscopic treatment, depending on the lateral size, endoscopic features, and histopathologic findings.[2] Careful coordination among the therapeutic endoscopist, pathologist, and other members of the multidisciplinary team is critical to properly define which cases can be treated optimally via endoscopic measures, which would thus avoid surgery and its associated risks.

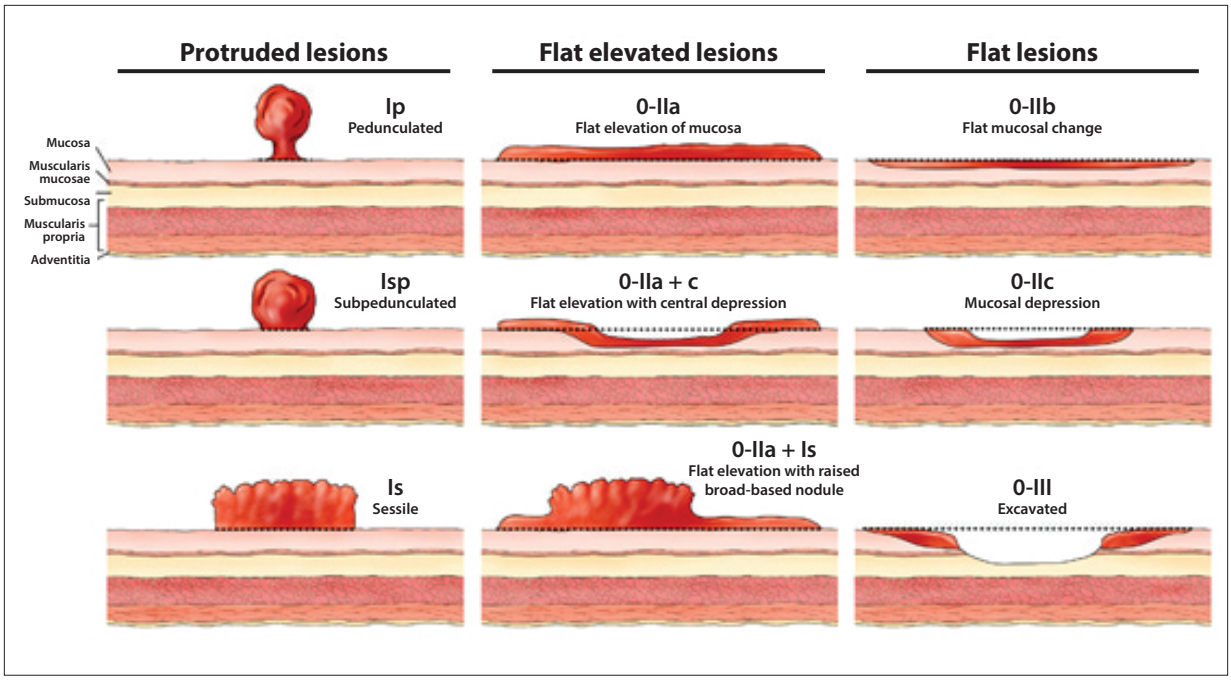

Figure 1. A schematic representation of the Paris classification for mucosal neoplasia. Lesion morphology helps in the evaluation of the risk of invasive disease and guides the approach to endoscopic resection. Advanced mucosal neoplasias are broadly divided into protruded, flat elevated, and flat morphologies. Protruded lesions rise more than 2.5 mm above the surrounding mucosa and include pedunculated (0-Ip), subpedunculated (0-Isp), and sessile (0-Is) lesions. Flat elevated lesions (0-IIa) rise less than 2.5 mm above the surrounding mucosa, and features such as central depression (0-IIa + c) or a broad-based nodule (0-IIa + Is) have been described. Flat lesions include barely perceptible elevation (0-IIb), depressed (0-IIc), and excavated (0-III) types.

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Endoscopic Diagnosis

If a colorectal lesion is detected via conventional endoscopy, careful lesion characterization—including the location, size, macroscopic type (Paris classification),[3] color, surface (pit) pattern, presence of fold conversion, and wall deformation—should be obtained. An initial overall assessment should be followed by a careful examination of any areas of concern (eg, a nodule or depression) to identify any features that might result in an incomplete endoscopic examination. Aggressive biopsy (more than 1-2 surface biopsies) and partial snare resection for histologic grading should be avoided because they might result in submucosal scarring and fibrosis, therefore compromising endoscopic removal.

Although endoscopic ultrasound (EUS) has traditionally been used to evaluate the depth of invasion and determine lymph node metastasis, with high sensitivity (80%-96%) and specificity (75%-98%) for the staging of T0 to T3 disease,[4] its role in assessing early colorectal cancer is limited. Modern high-resolution endoscopes, often used with dye spray (chromoendoscopy) or optical manipulation (eg, narrow-band imaging), enable highly accurate assessments of the depth of invasion without EUS.[4]

Macroscopic Classification

The Paris classification is a consensus classification of superficial gastrointestinal tract lesions that describes the shape of a neoplastic lesion. This classification was first devised in 2002 by a multidisciplinary group of experts and is widely accepted around the world.[3,5] According to the Paris classification, lesions are divided into polypoid (type 0-I) or nonpolypoid (type 0-IIa, IIb, or IIc) lesions. Type 0 to I lesions are subclassified as type 0 to Ip (pedunculated) and type 0 to Is (sessile) lesions. Type 0 to IIa lesions include those in which the height of the lesion does not exceed 2.5 mm, type 0 to IIb lesions are those that are truly flat, and type 0 to IIc lesions include slightly depressed lesions. Type 0 to III lesions comprise excavated-type lesions. Mixed-type lesions include type 0 to IIa + IIc, 0 to IIc + IIa, 0 to IIc + Is, and 0 to Is + IIc (Figure 1).

This classification system is important because it predicts the depth of invasion of a superficial cancer and also predicts the risk of lymph node metastasis. In general, lesions that are flat with ulceration or central depression below the mucosal surface most likely harbor invasive neoplasia.[3]

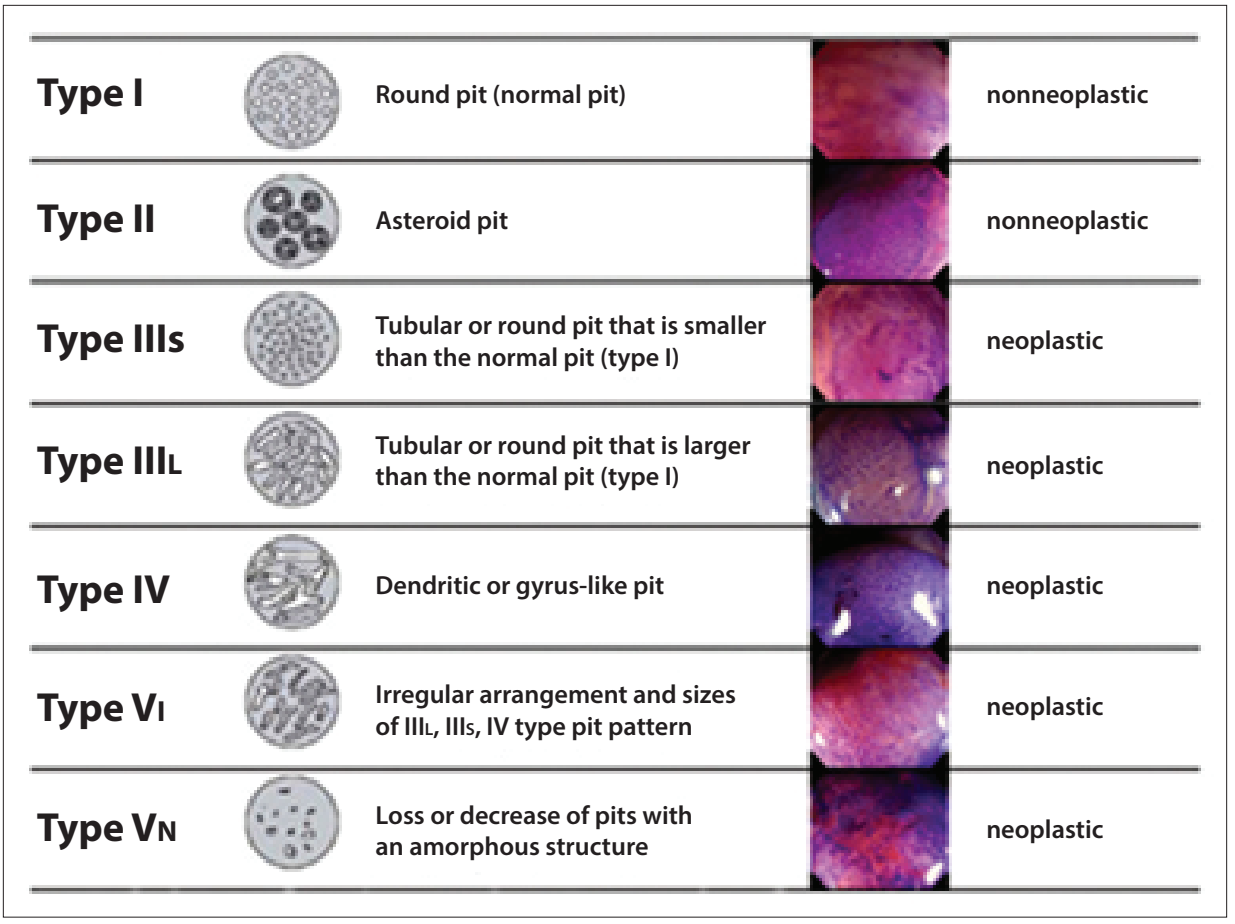

Figure 2. Kudo pit pattern classification of colorectal polyps.

Reproduced with permission from Takemura Y, Yoshida S, Tanaka S, et al. Quantitative analysis and development of a computer-aided system for identification of regular pit patterns of colorectal lesions. *Gastrointest Endosc*. 2010;72(5):1047-1051.

Pit Pattern

The opening to each crypt in the epithelium is known as a pit. Pits can be observed with optical manipulation (eg, narrow-band imaging) or when the surface of the colon is stained with dye (eg, indigo carmine). Kudo and colleagues classified pit patterns into 7 types to enable the differentiation of neoplasms as well as allow for histologic grading and depth evaluation of early cancers.[6] Type I includes round pits that are observed in normal mucosa. Type II includes stellate or papillary pits, which indicate hyperplasia. Type IIIs includes small tubular or round pits that are smaller than normal pits; these indicate neoplastic lesions, which occasionally include cancer that can be resected via endoscopy. Type IIIL includes tubular or roundish pits that are larger than normal pits. Type IV includes branch-like or gyrus-like pits, most of which are tubulovillous adenomas. Type Vi includes irregularly arranged pits that may be mucosal invasive or superficial submucosal invasive cancer, for which the proper treatment straddles the line between endoscopic and surgical therapy. Lastly, type Vn includes nonstructured pits, which indicate massive submucosal invasive cancer and require surgical resection with lymph node dissection (Figure 2).

Kudo and colleagues[6] reported that small round pit patterns (type III) and nonpit patterns (type V) were common in depressed lesions and that these lesions had invaded the deeper layers more rapidly than protruding lesions.[7,8]

Capillary Pattern by Magnified Narrow-Band Imaging

The modified Sano system classifies lesions on the basis of their mucosal microvasculature as seen with optical enhancements such as narrow-band imaging (Olympus), i-scan image processing (Pentax), and Fujinon intelligent chromoendoscopy (Fujinon). This classification system is an alternative means of classifying the risk of submucosal invasion.[9]

The Sano classification system, which correlates highly with final histopathology, is useful for differentiating hyperplastic lesions (capillary pattern [CP]1), adenomatous lesions (CP2), advanced adenomatous lesions (CP3A), and invasive lesions requiring surgical therapy (CP3B).[10]

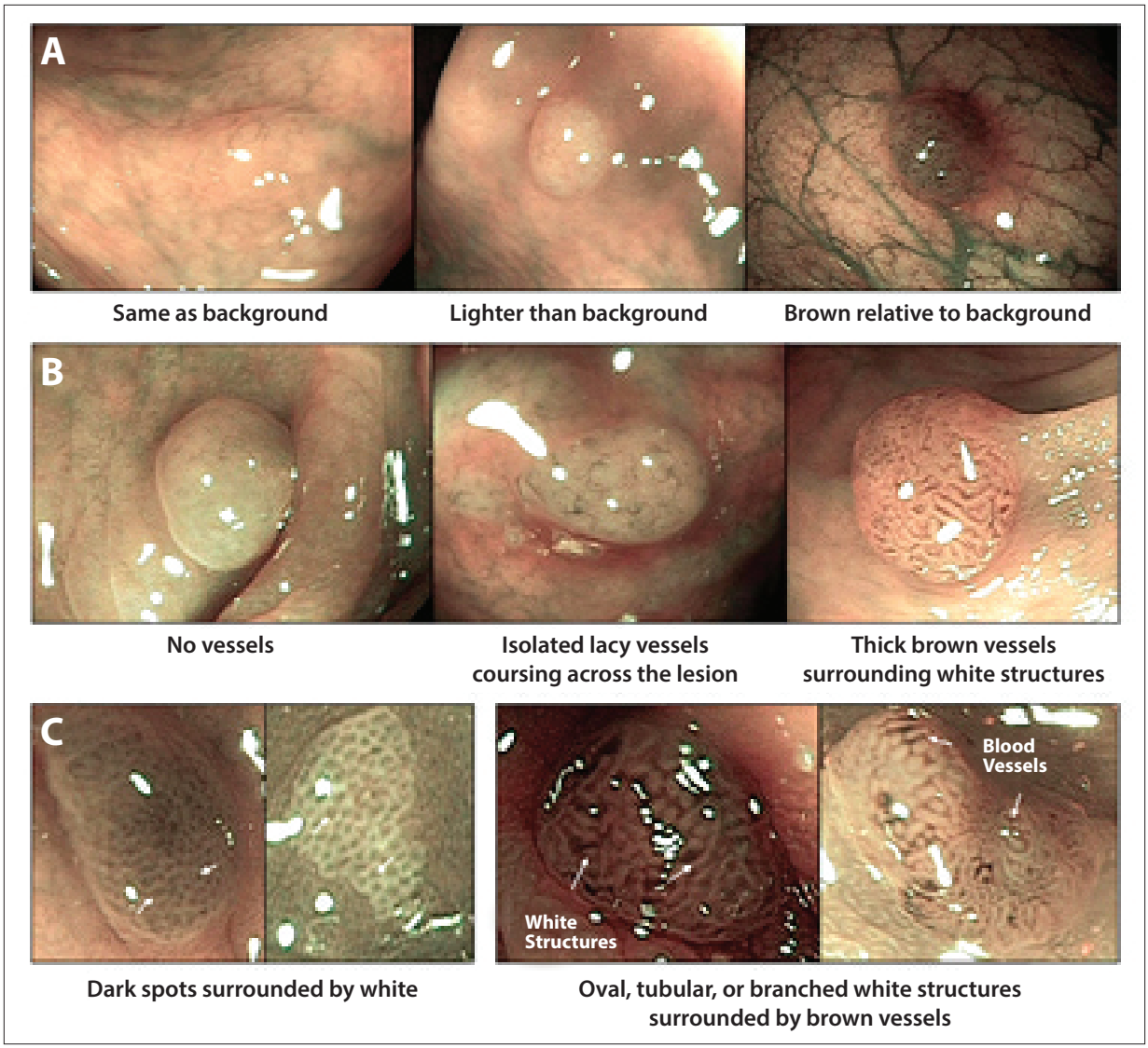

Figure 3. Examples highlighting typical features of the Narrow-Band Imaging International Colorectal Endoscopic criteria: color (**A**), vessels (**B**), and surface pattern (**C**).

Reproduced with permission from Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. *Gastroenterology*. 2012;143(3):599-607.e1.

Due to the wide variety of classification systems and technologies, there has been a recent effort to develop a consensus system for describing surface/pit features. This effort has resulted in the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification system, which closely mirrors the Sano system. The NICE classification system has been well validated as a reliable and accurate measure for neoplasia classification and depth assessment (Figure 3).[11]

It is critical to accurately determine the stage of a lesion prior to resection because specialized, resource-intensive techniques are necessary to ensure that resection is complete. Guidelines from the US National Comprehensive Cancer Center Network state that early colorectal cancers must be removed en bloc with detailed pathologic assessment of stage, margin positivity, and lymphovascular invasion.

Endoscopic Treatment

Endoscopic removal of early colorectal cancer may require advanced techniques and trained colonoscopists to achieve good results. Currently, there are many options available.

Snare Polypectomy

Snare polypectomy is chiefly used with pedunculated and sessile lesions that are 0.5 to 2.0 cm in diameter.[12] The most common adverse events resulting from this procedure are

gastrointestinal bleeding, colonic perforation, and local peritonitis.[13] Routine polypectomy should generally be avoided when an invasive lesion is suspected. Exceptions include pedunculated lesions in which the stalk and distinct margins can clearly be incised with a snare.

Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR), which was first described by Deyhle and colleagues in 1973,[14] is indicated for lesions confined to the mucosa or submucosa of the colon in which the risk of lymph node involvement is negligible. Lesions that are 2 cm or smaller can often be removed en bloc, whereas larger lesions may require endoscopic piecemeal mucosal resection (EPMR).

EMR combines the classic principles of conventional snare polypectomy with the addition of submucosal fluid injection. In difficult areas such as the ileocecal valve, the anorectal junction, or a proximal location on a fold, a cap attached to the tip of the colonoscope may be helpful to stabilize the position. Typically, a solution is injected into the submucosa via a sclerotherapy needle to raise the lesion for easier removal and to provide a cushion to protect the deeper layers of the bowel wall from mechanical or electrocautery damage. Normal saline is the most commonly used solution worldwide because of its low cost and ease of use. However, the submucosal cushion is relatively short-lived, and the mucosal elevation tends to be more diffuse. Given the short-lived nature of saline, endoscopists have developed multiple alternative agents to improve the duration of lifting, as well as chromoscopic agents to improve visualization of the submucosa. Agents commonly used to increase the lifting duration include hydroxypropyl methylcellulose, glycerol, starch volume expanders, and hypertonic saline. Epinephrine (1:100,000) can also be injected to reduce bleeding during the procedure. A diluted dye, such as inert indigo carmine or methylene blue, helps delineate the extent of the submucosal cushion and can be used to confirm whether the resection is in the correct plane. The inability to raise the base of a lesion after submucosal solution injection can indicate the presence of cancer invasion deep into the submucosa. Therefore, EMR should be attempted only if complete resection of neoplastic lesions is expected.[15] Unfortunately, obtaining multiple biopsy specimens, especially using electrocautery via a partial snare, can also cause nonlifting of the lesion and should thus be avoided.

After lifting, the bulging lesion is captured in a snare and removed via cauterization with a high-frequency current. The choice of snare is also a matter of the endoscopist's preference; however, a stiff wire snare is generally preferred, as it allows the endoscopist to push the wire into the submucosal cushion and avoid slippage over the lesion. Recent randomized controlled trials suggest that combination snares that incorporate an injection needle may improve efficiency and the size of each piece that is resected.[16] A safety margin of 1 to 2 mm of normal mucosa should be included around the lesion. Every effort should be made to excise all neoplastic tissue with the snare. Small fibrotic areas, typically at the site of a prior biopsy or snare, can be removed with avulsion using cold biopsy forceps. When these methods fail, ablation of the lesion remnants with electrocautery can be used with caution. Specific techniques include argon plasma coagulation (APC) and low voltage electrocoagulation with the tip of the snare ("snare tip soft coagulation").[7,17]

Prophylactic closure of the defect with clips may prevent delayed bleeding and, theoretically, delayed perforation due to a cautery effect,[18] although randomized controlled trials are needed.

Technical success rates of EMR have been reported to be between 90% and 100%, with complication rates of 0% to 9%.[19] Bleeding is the most common intraprocedural complication and occurs in approximately 10% of all cases.[20] Epinephrine injection or coagulating forceps can be used to control acute hemorrhage. Oozing can be treated with APC or snare tip soft coagulation.[21] EMR is complicated by colonic perforation in approximately 1% to 2% of cases.[7] Endoscopic clip closure should be attempted, but if it is not possible or if peritonitis is observed, the patient should be referred to surgery. Clip closure is very effective when performed correctly; experimental data have shown that clip closure is as strong as the gold standard of handsewn interrupted surgical sutures.[22]

Estimates of short-term (2-6 months) residual/recurrence rates after EPMR are broad, ranging from 0% to 55%,[23] although the recurrence is usually small and easily treated with snare resection or ablation. Late recurrence (after 12 months) is less common, occurring in less than 5% in one study.[24] However, the studies in which these concerns were noted were limited by small numbers of patients, small lesions, and single-center or retrospective study designs.

In terms of accurate pathologic diagnosis and recurrence rates, EMR is thought to be better than EPMR[16]; however, for lesions 2 to 4 cm in size, there is likely an increased risk of complication when such a large lesion is removed in 1 piece.[7] The optimal technique to minimize the risk of residual neoplasia during EPMR is evolving. In general, the most important principle is to maximize the potential for complete eradication on the initial resection attempt. A recent multicenter prospective study conducted by Moss and colleagues[24] examined 1134 patients and reported early recurrent residual adenoma in 16% of cases (95% CI, 13.6%-18.7%), and on multivariate analysis, risk factors included increased lesion size (more than 40 mm), use of APC, and intraprocedural bleeding. Late recurrences

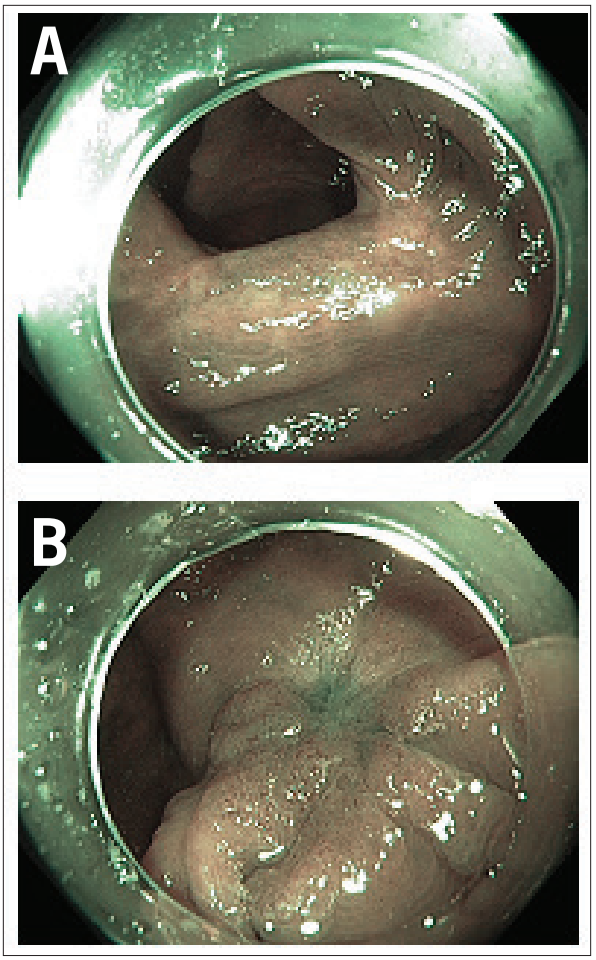

Figure 4. Visualization of a scar at an endoscopic mucosal resection site 3 months after the procedure showing no residual neoplasia (**A**) and residual adenoma (**B**).

were observed in only 4% (95% CI, 2.4%-6.2%). A small randomized study evaluating the use of prophylactic APC at piecemeal polypectomy sites where complete excision was thought to be achieved by the endoscopist produced a lower, statistically significant risk of recurrence in the APC group (1/10 vs 7/11; *P*=.02).[17] In a more recent, larger study of 479 patients with 514 colonic lesions that evaluated the safety and efficacy of EMR, the use of APC was an independent predictor of recurrence after EMR that was presumed to be effective. The authors of this study reported a 20% recurrence rate and did not prophylactically treat the polyp edges with APC, reserving APC for visible tissue that was not amenable to snare excision.[7] It is likely that the association between APC and higher recurrence is due to indication bias, not to the APC itself.

Regardless of the technique used, close surveillance is mandatory. To facilitate surveillance, tattooing should be considered at a location slightly away from the lesion. The optimal timing of endoscopic surveillance after EMR has not yet been determined, but guidelines recommend the first follow-up colonoscopy to be performed 2 to 6 months after the procedure, with both endoscopic and pathologic evaluations to ensure complete removal.[25,26] One retrospective study found that on the first follow-up surveillance endoscopy, a normal endoscopic appearance of the lesion site and negative scar biopsy specimens were predictive of long-term eradication in 97.9% of cases.[23] In a study by Shahid and colleagues, the use of high-definition endoscopes with narrow-band imaging and confocal endomicroscopy on the EMR scar was able to detect all residual neoplasia and could allow more targeted real-time therapy as well as avoidance of additional biopsy (Figure 4).[27]

Endoscopic Submucosal Dissection

The first attempt at endoscopic submucosal dissection (ESD) occurred in 1988. This procedure was developed for en-bloc resection of larger lesions without the use of snaring. In Japan, ESD quickly gained popularity and has become the preferred modality for the management of superficial lesions containing early cancer or high-grade dysplasia throughout the gastrointestinal tract.[28]

ESD is technically challenging in the colon because of less space, difficult positioning, a thin bowel wall (especially on the right side), and the presence of colonic folds.[29]

The principal target for ESD is an early, invasive lesion confined to the mucosa or superficial submucosa measuring greater than 20 mm in diameter. Lesions with shallow submucosal invasion and lesions measuring less than 20 mm but containing significant submucosal fibrosis precluding EMR can also be considered for ESD. Deep submucosal invasion is the main contraindication.[30]

In western countries, ESD has been adopted but in very limited cases as defined above.[31]

The typical ESD procedure begins with the determination of the tumor borders by chromoendoscopy with indigo carmine spraying for enhanced or magnified observation using narrow-band imaging. Marking around the tumor is not necessary in most cases because colorectal neoplasms typically have clear margins. If marking is necessary, marking dots should be placed 5 to 10 mm lateral to the margin of the lesion. A cap with a drainage hole at the 12 o'clock position should be used at the tip of the endoscope to help stabilize the position, and the use of carbon dioxide for insufflation is highly preferred because it is absorbed rapidly, causing less luminal distention and patient discomfort. In a study by Saito and colleagues that compared insufflation with carbon dioxide vs air during colorectal ESD in 70 patients, the researchers demonstrated that carbon dioxide was associated with lower operation time as well as lower dose of midazolam (90 ± 57 min vs 100 ± 80 min, 5.6 ± 4.9 mg vs 9.7 ± 5.9 mg, respectively; *P*=.005).[32]

Typically, a submucosal injection is administered in the area that needs to be incised to create a fluid cushion, which increases the safety of the procedure. After the injection, a small initial mucosal incision is made, and the lesion is dissected from the deep layers of the bowel wall by using electrocautery knives. A mucosal incision is made in front of the tumor with a short needle knife. Only the needle portion should be used for the incision, keeping the tip of the sheath touching the surface of the mucosa without pushing the sheath into the submucosal layer. The endocut mode of the electrosurgical unit is commonly used for the mucosal incision. Technologies recently implemented in newer electrosurgical units are markedly increasing patient safety and causing fewer complications. Multiple modes are available that could be used for ESD depending on different characteristics of lesions. The electrosurgical units ICC 200 and VIO 300 D (Erbe) are equipped with sensors that detect the changing signals from the cutting device and tissue interaction and automatically control output and maintain quality of cutting. The cutting mode is comprised of Endocut IQ mode, dry cut, and swift coagulation, whereas the coagulation mode incorporates forced, soft, and spray coagulation. For successful ESD, it is extremely important to understand and properly use electrosurgical units.[33]

After repeated submucosal injection, it is essential to maintain a submucosal dissection plane through the submucosal layer while avoiding injury to the muscularis propria. When thick vessels are observed, a prophylactic hemostatic maneuver should be carried out using coagulation forceps with soft coagulation. A smooth dissection with less hemorrhage can be performed by maintaining the appropriate depth of dissection at the layer with fewer vessels and fibrotic tissue. Furthermore, a surrounding incision is then made, and submucosal dissection is performed while lifting up the dissected part of the tumor with the edge of the transparent cap at the tip of the endoscope. Gravity should be utilized (by manipulating the patient's position) to retract the mucosal layer and improve access into the submucosa.

Major complications of ESD include bleeding and perforation. In a prospective multicenter study of 1111 colorectal ESD procedures, perforations occurred in 54 cases (4.9%), and postoperative bleeding occurred in 17 cases (1.5%).[20] If a perforation is seen during the submucosal dissection stage of ESD, it should be clipped using standard clipping devices or over-the-scope clips. Importantly, prompt recognition of a perforation during the ESD procedure allows for immediate successful endoscopic therapy in the vast majority of cases, although surgery is indicated for large perforations or generalized peritonitis. Proper supportive measures are essential for cases with perforations and include antibiotics, needle decompression of tension pneumoperitoneum if necessary, and abstention from eating.[34]

Delayed bleeding is defined as bleeding that develops after the completion of the procedure and occurs due to a rupture in the exposed vessels. Therefore, post-ESD ulcers should be observed cautiously. If exposed vessels are identified, they can be coagulated via hemostatic forceps or APC. If the vessels are large, clipping is a useful measure to prevent delayed bleeding.[35]

Typically, follow-up after ESD is based on the status of the margins. If the margins are negative, recurrence rates are very low, and surveillance can be deferred for at least 1 year. If the margins are positive but there is otherwise no indication for surgical resection, then follow-up can be performed in 3 to 6 months.

The main tradeoffs between EMR and ESD are procedure time and risk (which favor EMR) and en-bloc excision (which has a lower recurrence when associated with ESD). The rate of en-bloc resection for large colorectal tumors using ESD in Japan and several other Asian and Western countries was reported to be as high as 80.0% to 98.9%, depending on the endoscopist's experience and technical difficulties. In a recent study by Lee and colleagues, the overall en-bloc resection rate was 97.5% and the curative resection rate was 91.2% among 1000 ESD procedures.[36] Given these tradeoffs, it is likely that ESD should be reserved only for lesions in which curative resection requires en-bloc removal.

Conclusion

Endoscopic methods have advanced to the point where nearly all noninvasive neoplasia (including polypoid, flat, and lateral-spreading lesions) can be removed endoscopically by physicians trained in EMR and/or ESD. This has now also extended to superficially invasive colorectal cancer, but great attention to resection technique and proper case selection are needed. Areas for future research include randomized controlled trials comparing EMR and ESD, optimizing surveillance based on the risk of recurrence, education to expand knowledge of the capabilities of EMR and ESD and thus avoid unnecessary surgery, and training of physicians in EMR and ESD techniques to expand the availability of these procedures.

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