Endoscopic Approaches to Rectal Neoplasia

48

John A. Dumot

Abbreviations

AIN	Anal intraepithelial neoplasia
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasound
G	Granular
NG	Nongranular
PP	Pit pattern
TEM	Transanal endoscopic microsurgery

48.1 Introduction

Flexible endoscopic examination of the rectum and colon is quite common and has advantages over the rigid trans-anal endoscopic examination and resection techniques. Flexible endoscopy allows examination of the entire colon and has become the most common gastroenterology procedure in the world. While there remains developed countries that do not promote routine colonoscopy for colorectal cancer screening, the technology is readily available in most medical centers. High definition imaging improves detection and visualization of the lesion margins. The majority of polyps can be easily removed during colonoscopy with routine cold or cautery snares. Removal of larger neoplasia previously referred for surgery is possible with advanced endoscopic techniques discussed in this chapter. An important concept in the endoscopic therapy of advanced colorectal neoplasia is recognition of lesion morphology, and important mucosal characteristics are summarized in this chapter.

Evacuation of the rectum with an enema preparation (tap water, isotonic saline, bisacodyl or sodium phosphate) is recommended before all limited endoscopic procedures to improve visualization for diagnostic purposes. A full bowel preparation and endoscopic evacuation of residue is required before therapy of rectal neoplasia to provide a clear site, reduce the risk of methane gas explosion when using electrocautery and minimize peritoneal soilage in case of perforation. After wide area endoscopic removal of advanced rectal neoplasia, most patients are monitored for a short period and then be discharged home provided there are no significant symptoms suggesting a complication. Limiting oral intake to fluids for the remainder of the day will allow a clear field for endoscopic intervention should delayed bleeding or perforation develop in the interim period. Patients with complicated resections should be monitored closely and receive periprocedural intravenous antibiotics if they experience abdominal pain or the bowel wall was compromised.

J.A. Dumot, DO, FASGE
Division of Gastroenterology and Hepatology,
Case Western Reserve University, University Hospitals of Cleveland, Cleveland, OH, USA

Digestive Health Institute, Ahuja Medical Center, Beachwood, OH, USA
e-mail: john.dumot@uhhospitals.org

H.R.H. Patel et al. (eds.), *Pelvic Cancer Surgery: Modern Breakthroughs and Future Advances*,
DOI 10.1007/978-1-4471-4258-4_48, © Springer-Verlag London 2015

48.2 Assessment of Rectal Lesions

Retroflexion of the endoscope to examine the anal verge is an important maneuver during rectal endoscopy. Visualization of the dentate line at the anal verge is accomplished with a fully angulated bending section of the flexible endoscope or colonoscope. Careful inspection of the most distal portion of the rectal vault can reveal hidden lesions and neoplasia at the squamocolumnar anal junction (Fig. 48.1). The technique should be performed with the lumen distended with air or carbon dioxide. The lowest rectal fold or valve is used as a target as the up/down wheel is moved counter clockwise to its fullest extent. Gentle torque is applied to the insertion tube as well as counter clockwise movement of the left/right wheel to complete the maneuver. The operator should gently insert or "give up" approximately 15 cm of the instrument to accomplish the maneuver. The operator should not struggle or force the instrument because perforations of the rectum can occur and do not seem to be related to experience of the physician. Fortunately these perforations are infrequent and rarely need surgical intervention [1]. Retroflexion in difficult situations with a narrow caliber rectum from chronic colitis, radiation therapy or altered surgical anatomy can be avoided and alternatively use careful visualization of the entire mucosa through the anal canal during slow withdrawal of the endoscope in a circular fashion (Fig. 48.1).

Advanced mucosal neoplasia usually refers to lesions with advanced histology (tubulovillous, villous or high grade dysplasia) and are generally ≥10 mm [2]. Large flat lesions or laterally spreading tumors can increase in size and extend over several mucosal folds before becoming invasive. However, smaller lesions can be invasive and the experienced endoscopist takes into account tactile as well as visual features before entertaining endoscopic removal. Mucosal lesion morphology is defined according to the Paris classification of neoplastic lesions [3, 4]. Type 0 lesions are superficial mucosal neoplasia classified as *protruding*, *flat elevated* or *flat* in general terms. Protruding lesions include pedunculated (0-Ip), subpedunculated (0-Isp) or sessile (0-Is). Flat elevated lesions have shoulders less than 2.5 mm and may be flat elevation of the mucosa (0-IIa) or a mixture of flat elevated and central depression (0-IIa + IIc) or flat elevated and raised broad based nodule (0-IIa + Is). Other formations include entirely flat lesions (0-IIb), depressed lesions (0-IIc) and excavated lesions (0-III). Type 1 lesions are polypoid carcinomas usually attached on a wide base. Type 2 lesions are ulcerated carcinomas and raised sharp margins. Type 3 lesions are ulcerated and have no definite limits. Type 4 lesions are non-ulcerated and diffusely infiltrating.

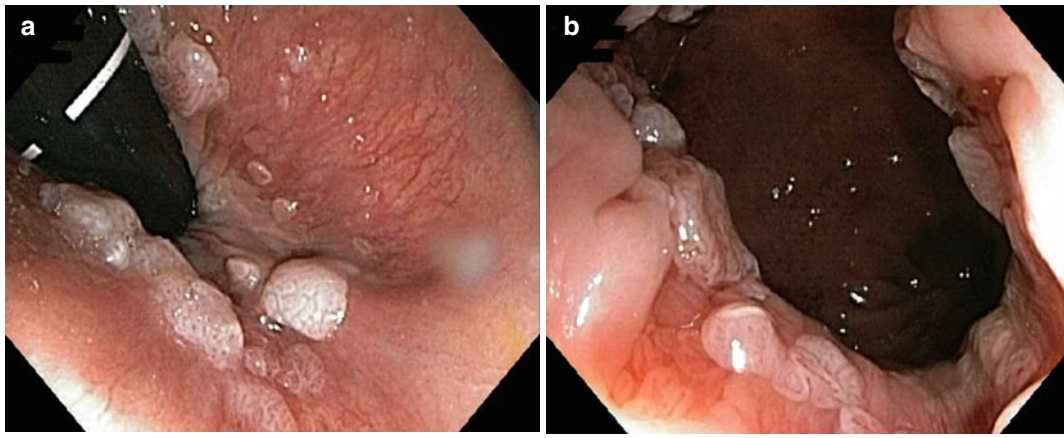

Fig. 48.1 Example of retroflexion view of anal brim. (**a**) Anal Intraepithelial Neoplasia (AIN) 0-IIa grade 2 with immunohistochemical stain for p16 positive favoring an HPV-related pathogenesis. (**b**) AIN lesion on withdrawal of the endoscope

The surface topography of the mucosal lesion is best characterized as granular (G, nodular) nongranular (NG, flat) or mixed. Morphology can be enhanced with dye spraying of indigo carmine 0.4 % or crystal violet 0.05 % solutions, which helps demarcate margins and mucosal patterns. Mucosal morphology is extremely important because it predicts submucosal invasion in advanced lesions. A uniformly 0-IIa G lesion has a very low risk of submucosal invasion (~1 %) compared to the highest risk 0-IIa + c NG lesions with submucosal invasion of 67 % (relative risk, 54; $P<0.001$) [5]. Depressed areas in neoplastic lesions are clearly associated with an increased risk of submucosal invasion [6, 7]. Other features of colorectal lesions include loss of lobulation within a large protruding nodule, fold convergence, demarcated depressed areas, stalk swelling and fullness should raise a suspicion of submucosal invasion [8].

Mucosal pit pattern (PP) are best described according to the Kudo system [9]. Mucosal PP are highlighted with high definition endoscopes and dye spray chromoendoscopy. Advanced imaging processing with light filters (narrow band imaging, Olympus Medical) or computer modulation of the image (intelligent color enhancement, Fujinon and i-scan, Pentax) can facilitate PP recognition without the dye spray using a virtual chromoendoscopy image. Type IV PP is the most common pattern and corresponds to a tubulovillous adenoma histology. Type III PP is seen with NG lesions and corresponds to tubular adenoma histology. Irregular PP are associated with intramucosal carcinoma or an invasive neoplasm. The Sano mucosal vascular patterns seen with narrow band imaging can further characterize advanced mucosal neoplasia using the capillary arrangements (regular brown mesh networks vs. irregular or complex branching and blind ending) to differentiate noninvasive and invasive lesions [10]. The relationship of PP with submucosal invasion appears to be more significant in sessile and superficial lesions more so than pedunculated lesions [8]. The use of PP recognition and micro vascular features are helpful in determining if a lesion is high risk for invasive disease but no features are uniformly reliable and there is considerable intraobserver variability with inexperienced operators. Therefore, proper tissue handling and histologic evaluation of resected lesions is imperative to guide subsequent care.

48.3 Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is helpful to assess the depth of invasion for mucosal lesions and confirm the presence, size and location of subepithelial lesions. Fine needle aspiration and core biopsy of lesions and lymph nodes are possible with EUS guidance. EUS is not necessary before endoscopic removal of lesions with favorable morphologic features discussed above but can be helpful in large, depressed or ulcerated lesions. Figure 48.2a shows a T1a wide base raised rectal neoplasm measuring 27 mm in width. The wall layers of the rectum are preserved and suggest a lack of invasion. True assessment of invasion is based on pathologic evaluation of the lesion looking for the extent of invasion into the lamina propria, vascular or lymphatic invasion and tumor grade in the resected specimen. Debate on the need to remove lesions en bloc is based on the difficulty assessing lateral margins and cautery artifact of deeper margins with piecemeal resection techniques discussed below and may be avoided with endoscopic submucosal dissection. EUS is very useful for characterizing intramural lesions in the rectum. Figure 48.2b, c shows a large submucosal lesion with a bulky intramural neoplasm of the deep muscularis propria characteristic of a gastrointestinal stromal tumor. Smaller intramural lesions are more commonly rectal carcinoid tumors. EUS is helpful in determining size but endoscopic resection method is a better predictor of complete pathologic response than EUS findings [11].

48.4 Endoscopic Resection Techniques

Most lesions limited to the mucosa and neuroendocrine tumors can be successfully removed with a diagnostic flexible endoscope using a variety of

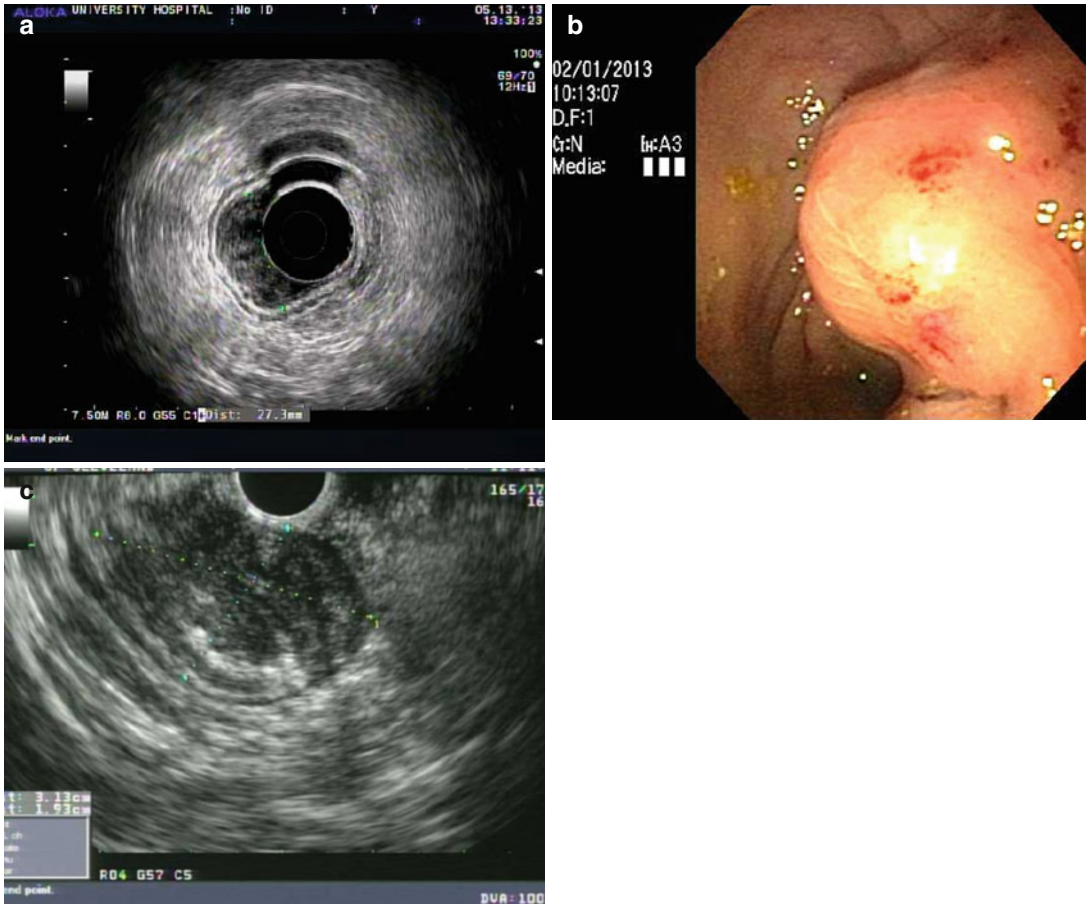

Fig. 48.2 Endoscopic ultrasound images. (**a**) T1a wide base raised rectal neoplasm measuring 27 mm in width. (**b**) A large submucosal lesion seen on routine endoscopy in the rectum. (**c**) The lesion measures 3.1 × 1.9 cm and fine needle aspiration revealed features of a gastrointestinal stromal tumor (GIST) with immunohistochemical stain positive CD 117

devices passed through the accessory channel. Treatment of rectal neoplasms with flexible endoscopes has several advantages over transanal endoscopic microsurgery (TEM). A diagnostic endoscope measures approximately 11 mm in diameter compared to the average operating rectoscope measuring 40 mm. Using the gastroscope provides a shorter device that improves control and reduces time and effort compared to the colonoscope length devices. Most patients having endoscopic resection do well with monitored anesthesia in the deep sedation state compared to general anesthesia for TEM. Candidate lesions for endoscopic resection are listed in Table 48.1. TEM is still the preferred choice for neoplasia with deep submucosal or muscularis propria invasion is suspected if patient characteristics dictate a local excision over traditional anterior resection because TEM allows full thickness resection and

Table 48.1 Rectal neoplasms amenable to endoscopic therapy

Epithelial neoplasms
Adenomatous polyps
Serrated adenomatous polyps
Malignant rectal polyp without stalk or submucosal invasion
Giant hyperplastic polyps
Subepithelial neoplasms
Rectal neuroendocrine (carcinoid) tumors

closure using proven microsurgical techniques. To date, endoscopic closure techniques are limited to smaller defects and are cumbersome to employ. TEM is also preferred for lesions involving a significant portion of the squamocolumnar junction in the anorectal lumen although ESD has been successful for early stage squamous cell carcinoma within the anal canal [12].

Informed consent should outline the decision to pursue endoscopic resection over surgical weighing the risk of incomplete resection and major complications of endoscopic approach to the immediate risks of full thickness surgical resection (leakage, infection, loss of bowel function and general anesthesia). The most common risk of endoscopic resection is delayed bleeding 2–12 days following resection. We schedule complex endoscopic procedures with monitored anesthesia assistance so that the endoscopist can solely focus on the resection task. Dedicated assistance with proper training must demonstrate patience and share the goal of complete resection at the time of the first procedure no matter how long it takes because subsequent sessions will encounter fibrosis at the resection site, which reduces the effect of future resections and increases the risk of perforation.

Conventional Polypectomy

Standard or conventional polypectomy for mucosal lesions using a electrocautery snare is considered the major technical advance since the advent of flexible fiber optic imaging. Progression of the technique into wide area endoscopic mucosal resection (EMR) refers to piecemeal resection with a submucosal injection when the lesion cannot be completely grasped in total by a routine cautery snare. The submucosal injection was first described by Rosenberg before fulguration of rectal and sigmoid polyps with a transanal approach [13]. Injection into the submucosal plane has now become standard of care throughout the gastrointestinal tract with the advent of flexible endoscopic needle-tip catheters making polypectomy safer and easier. A more recent advance includes tinting the saline solution with a pigment such as indigo carmine to color the submucosal layer blue to improve visibility of that tissue plane (Fig. 48.3). Submucosal injection can obscure the peripheral margins of the lesion, therefore, marking the margins with the tip of the closed electrocautery snare can delineate the area to be resected prior to resection. On the other hand, identification of the margins in very subtle flat colorectal neoplasms is often improved after injection of indigo carmine tinted submucosal saline. We find the later to be more common with flat serrated adenomas due to their hyperplastic appearance.

A colloidal additive (succinylated gelatin or hyaluronic acid) can improve the sustainability of the submucosal injection and facilitate wide area piece meal resections compared to saline by reducing the number of injections, resections and procedure time [14]. Other agents such as artificial liquid tears (hypromellose 2.5 % solution) and intravenous volume expanders (hydroxyethyl starch) are more widely available with similar effect. In an excellent review of wide area endoscopic resection techniques of colonic neoplasia, Holt and Bourke recommend intravenous antibiotic prophylaxis and a long acting local anesthetic can be added to the injection solution for resection of advanced neoplasia of the anorectal junction [15].

In piecemeal resection of large polyps, elevate only a portion of the lesion to facilitate capture with the electrocautery snare. Choose the most difficult area first and reposition the patient if needed to achieve a 6 O'clock position with the endoscope. The addition of a friction fit cap to the endoscope tip allows capture of the tissue with application of suction. One cap technique uses a crescent-shaped snare perched at the outer rim and another technique uses a variceal band elastic ligature followed by routine snare cautery. A shorter version of the friction fit cap is commonly utilized to improve visualization during mucosal resection by maintaining a minimum focal length between the mucosa and the endoscope optical lens. Without the cap, positioning of the endoscope is more difficult to maintain endoscopic view especially in angulated and uneven topography. Invasive lesions are difficult to differentiate

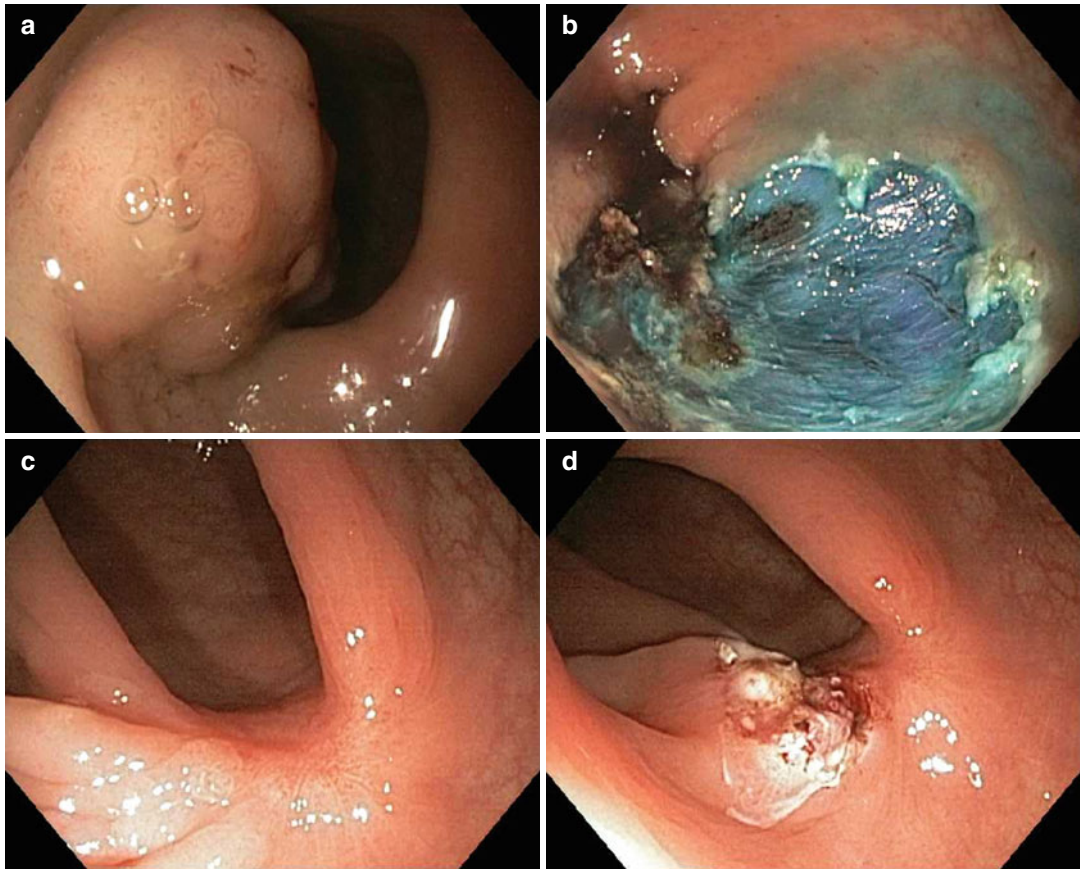

Fig. 48.3 Endoscopic mucosal resection. (**a**) A 40 mm adenoma 0-Isp granular lesion at the rectosigmoid junction. (**b**) EMR site cleared of all neoplasia and reveals blue residual submucosal layer. (**c**) EMR site healed at 3 months with central scar. (**d**) Biopsy and focal electrocautery treatment of any suspected residual adenoma; only hyperplastic change noted on specimens

from fibrous tissue from chronic mucosal prolapsed or prior interventions because both can limit the submucosal injection lift especially at the central portions of the lesion. These clinical situations may be best treated with further advancement in endoscopic submucosal dissection technique.

Endoscopic Submucosal Dissection

Endoscopic submucosal dissection (ESD) is a more tedious technique that utilizes small controlled incisions with the goal of en bloc resection for complete pathologic evaluation. ESD was originally developed for and revolutionized the treatment of early gastric neoplasms. Application of ESD to the colon was temporized by the high rate of perforation however, expert endoscopists were quick to apply those methods to colorectal neoplasms with excellent success using meticulous care. In an early series of 200 patients with laterally spreading tumors with favorable mucosal patterns throughout the colon and rectum treated by expert endoscopists, en bloc resections were achieved in 84 % and tumor free margin achieved in 70 % [16]. The mean size of the tumors was 35 ± 19 mm SD (range, 15–140 mm) and the final pathologic resection specimens revealed 51 adenomas, 99 intramucosal cancers, 22 invasive cancers with minute submucosal penetration T1sm1 (<1,000 μm) and 28

deep submucosal cancers T1sm2 (≥1,000 μm). Of the 180 patients (90 %) with a follow up examination, only one case of local recurrence was found and no lymph node or distant metastasis were found. In a large retrospective study by the same group, EMR was associated with a higher incomplete resection and recurrence rate than ESD [17]. The recurrence rate was 3 of 145 (3 %) lesions treated with ESD compared to 33 of 228 (14 %) treated with EMR ($p < 0.0001$). This favorable outcome was noted even though the lesions in the ESD group tended to be significantly larger than those in the EMR group. The rate of perforation was higher in the ESD group (1.3 % vs 6.2 %, p = NS), however all were managed conservatively without surgery. As their experience grew, the endoscopic mucosal pattern dictated their approach. Large laterally spreading G lesions were removed in piecemeal ideally with the largest nodule being resected first. NG lesions required ESD en bloc resection to due a significantly higher rate of submucosal invasion (NG 14 % vs. G 7 %; $P < 0.01$) [7]. Unfortunately, even with favorable histologic features after resection and clear early follow up examinations, one case of intramucosal cancer treated with piecemeal resection recurred as a submucosal-like cancer was found 1 cm from the original resection site 2.5 years later.

Equipment and materials for ESD are listed in Table 48.2. ESD characteristically is a two-step process: complete circumferential incision of the lesion followed by submucosal dissection of the plane beneath the lesion using short bursts of electrocautery to coagulate the tissue and blood vessels in the submucosal plane (Fig. 48.4). The peripheral incision is relatively easy and facilitated with injection of saline with indigo carmine blue dye solution (indigo carmine 80 mg per 500 ml saline). Colloid additive is usually not necessary for this step but improves the submucosal dissection process providing a sustained lift of the mucosa. Our unit prefers any commercially available artificial tears solution from the pharmacy. Adding epinephrine (1:100,000) is optional and may improve visualization by reducing intra procedural bleeding.

ESD is effective for removing submucosal lesions of the rectum less than 2 cm. Carcinoid lesions found incidentally on colonoscopy are usually asymptomatic and conventional approach is resection over observation in medically fit patients. Although EMR has been advocated for endoscopic removal with blind snare or band-ligation technique, ESD affords a reliable method for en bloc removal of lesions without invasion of the muscularis propria (Fig. 48.5).

ESD is clearly more technically demanding than EMR but both are associated with bleeding and perforation. Immediate bleeding is routinely encountered during ESD and controlled with a combination of epinephrine injection, hemostatic forceps and endoscopic clips. Factors independently associated with perforations include larger lesions, right sided colon lesions, less experienced endoscopist, and lack of hyaluronic acid in submucosal injection solution [18]. Endoscopic man-

Table 48.2 ESD devices and material

High definition endoscope or colonoscope
CO_2 insufflators—turn air setting to "OFF"
Electrosurgical generator with microprocessor control (ERBE, Tübingen, Germany or Olympus Medical, Tokyo, Japan)
Marginal resection setting—endocut effect 2, duration 1, at 30 W
Submucosal dissection setting—forced or spray coagulation 30 W
Coagulation forceps—soft coagulation effect 5 at 60–80 W
Sclerotherapy needle for injection of solution
Submucosal injection solution drawn up in 10 ml syringe:
Liquid artificial tears—5 ml
Saline—4 ml
Indigo carmine—1 ml
ESD knife options
Dual knife (Olympus KD-650U dual knife)
Insulated tip knife (Olympus KD-611L IT knife2)
Triangle tip knife (Olympus KD-640L TT knife)
Coagulation forceps (Olympus FD-411UR coagrasper)
Friction fit clear cap (e.g. Olympus D-201-type sized for endoscope)
Endoscopic hemostatic clips to control significant bleeding and closure of perforations
Epinephrine solution to control bleeding
Rat-tooth forceps and Roth net to retrieve tissue
Stiff bristle brush to clean knives of chard tissue
Pins and mat material to prepare tissue before fixation

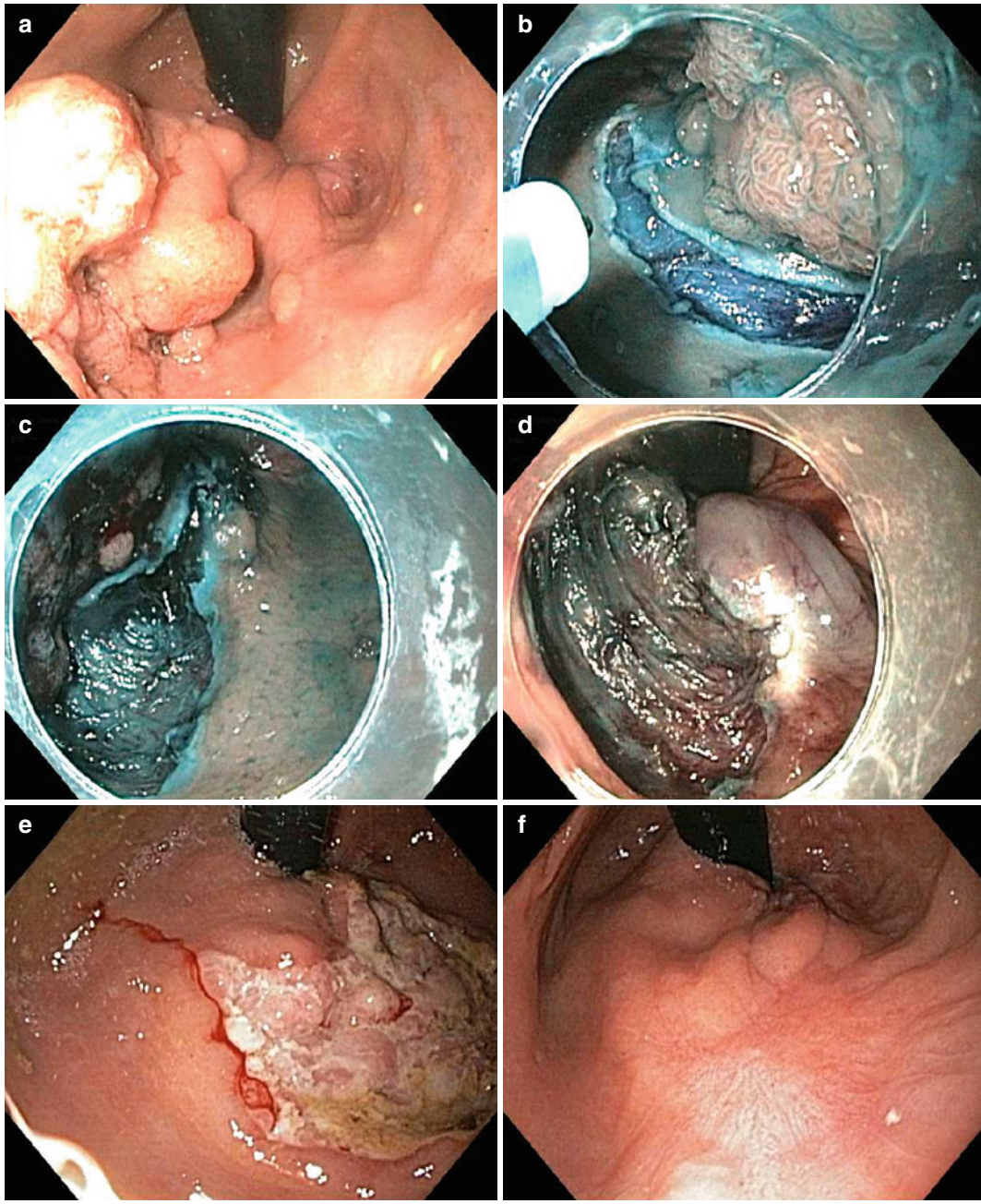

Fig. 48.4 Endoscopic submucosal dissection of a laterally spreading mucosal neoplasia. (**a**) A 50 mm distal rectal adenoma 0-IIa + Is granular lesion seen on retroflexion. (**b**) Circumferential incision of the margins with endoscopic knife after submucosal injection of indigo carmine tinted saline. (**c**) Submucosal layer injection expands layer for endoscopic dissection of the lesion base. (**d**) Final image of muscularis propria of the rectum after ESD. (**e**) Marginal bleeding noted at 10 days after ESD with granulation tissue covering ESD site. (**f**) Complete healing with central depression scar at 6 month follow up exam

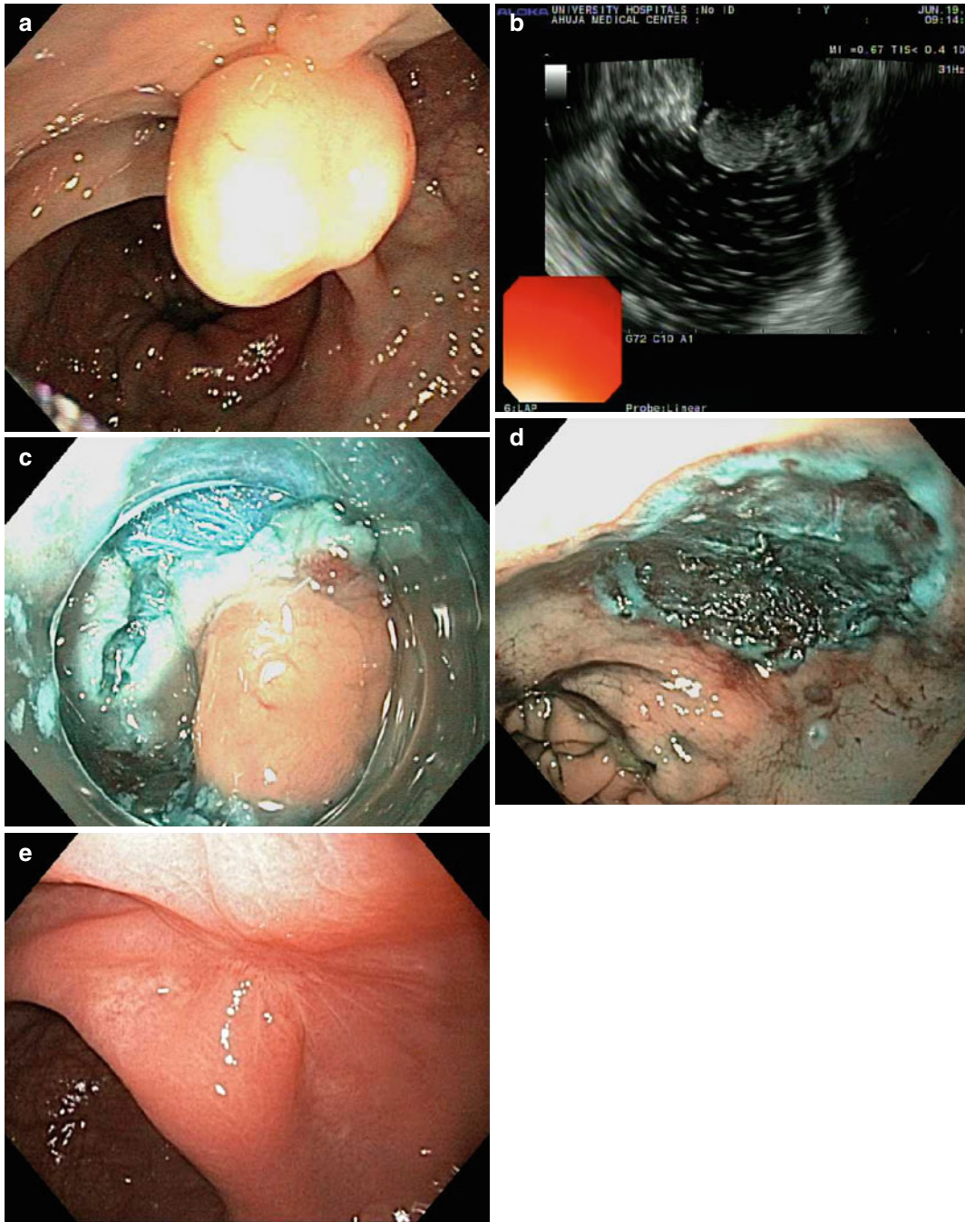

Fig. 48.5 Endoscopic submucosal dissection of a submucosal carcinoid tumor. (**a**) A submucosal lesion protrudes into the lumen at the rectosigmoid junction on the right lateral wall. (**b**) EUS reveals a hyperechoic lesion measuring 11 mm without. (**c**) Circumferential incision after submucosal injection precedes dissection of the deeper margin. (**d**) ESD site immediately following resection of the lesion en bloc. (**e**) ESD site at 3 months shows scar from prior resection

agement of perforations is possible in most cases provided they are recognized early and treated appropriately. Delayed or missed perforations can be devastating and difficult to manage without radiologic or surgical drainage. Recognition begins with inspection of the resection site for defects or penetration through the blue tinted submucosal tissue layer. Insufflation with carbon dioxide during endoscopy reduces the symptoms associated with pneumoperitoneum. Immediate decompression of a pneumoperitoneum with a large bore needle catheter may be necessary when cardiovascular compromise is noted. Attempts at endoscopic closure with hemostatic clips is usually successful with supportive care in a hospital setting. Multidisciplinary approach with administration of intravenous antibiotics, bowel rest and drainage of fluid collections is associated with good outcomes. Frank peritoneal soiling and large defects not amenable to endoscopic closure should be addressed surgically. Most endoscopic perforations of the rectal vault, either during retroflexion or endoscopic therapy can be managed conservatively because they usually occur below the peritoneal reflection.

48.5 Endoscopic Follow Up and Ablation Techniques

Endoscopic follow up exam at 6 weeks if resection is incomplete allows healing of the resected area and treatment of residual neoplasia with repeated applications of the resection techniques discussed above. Patients with lesions containing high grade dysplasia or intraepithelial carcinoma must be examined at 6 months and 12 month intervals due to the higher risk of recurrent and invasive neoplasia. Endoscopic ablation remains a viable option for residual neoplasia after endoscopic resection or when resection is not possible. Ablation without resection is inferior to resection techniques because it does not provide pathologic information and is generally less effective in terms of neoplasia recurrence. Argon plasma coagulation is the most common method of endoscopic ablation in the colon and rectum and most information about its use is based on small case series and limited controlled trials [19–21]. In a large retrospective series of difficult polyps, approximately one of four require ablation with the argon plasma coagulator to areas of non-lifting mucosa due to prior intervention [22]. In general, meticulous resection of lesion margins provides lower recurrence rates than routine use of argon plasma coagulation at the resection margins.

48.6 Summary

Informed consent for endoscopic resection must include delayed bleeding 2–12 days after resection, perforation requiring prolonged hospitalization or surgical intervention and incomplete resection of the neoplasia. In addition, although complete endoscopic en bloc or piecemeal resection of intraepithelial cancers (T1a) with favorable histologic findings is associated with good outcomes, late recurrences of submucosal cancers have been reported infrequently and should be considered in the balance of choosing endoscopic or surgical resection. Advanced endoscopic resection techniques begin with recognition of mucosal features associated with favorable noninvasive lesions compared to those with less favorable features with a higher rate of submucosal and lymph node invasion.

Key Points

- Endoscopists should utilize high definition imaging and dye staining to recognize margins of lesions and characteristic mucosal patterns associated with invasive and noninvasive neoplasms.
- Careful endoscopic examination of the rectal vault and rectosigmoid junction requires an adequate bowel preparation, comfortable patient, and a very flexible endoscope. Addition of a clear friction-fit cap can greatly increase visibility and stability of the endoscope tip for inspection and therapy.
- Endoscopic resection is facilitated by injection of various saline-based dye

containing solution, such as indigo carmine, into the submucosal layer to delineate lesion margins and facilitate endoscopic resection.

- A non-lifting sign found when the submucosal injection does not elevate the lesion and characteristic of neoplastic invasion or scar formation due to prior interventions.
- Advanced endoscopic submucosal dissection resection techniques use colloid laden solutions injected into the submucosal layer for the initial endoscopic circumferential incision followed by submucosal dissection for complete en bloc resection, which improves histologic evaluation and reduces local recurrences.
- Endoscopic submucosal dissection is technically more challenging and associated with higher rates of bleeding and perforation compared to piecemeal endoscopic snare resection.
- Endoscopic submucosal dissection required a dedicated team willing to commit to careful patient selection, prolonged treatment sessions with meticulous attention to intra procedural details.
- Residual neoplasia found at the margins or base of endoscopic resection sites should be ablated using electrocautery such as argon plasma coagulation.
- Careful endoscopic follow-up examination in 6–12 weeks is required to assure complete early remission from neoplasia. Repeated endoscopic examinations are necessary due to late recurrences in and around the endoscopic resection site.
- Proper informed consent should always include the possibility of a surgical alternative and frank discussion of the expected number of endoscopic exams.

References

1. Quallick MR, Brown WR. Rectal perforation during colonoscopic retroflexion: a large, prospective experience in an academic center. Gastrointest Endosc. 2009;69:960–3.
2. Rotondano G, Bianco MA, Buffoli F, et al. The Cooperative Italian FLIN Study Group : prevalence and clinico-pathologic features of colorectal laterally spreading tumors. Endoscopy. 2011;43:856–61.
3. Paris Workshop Participants. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. Gastrointest Endosc. 2003;58:S3–S43
4. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy. 2005;37:570–8.
5. Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterol. 2011;140:1909–18.
6. Hurlstone DP, Sanders DS, Cross SS, et al. Colonoscopic resection of lateral spreading tumours: a prospective analysis of endoscopic mucosal resection. Gut. 2004;53:1334–9.
7. Uraoka T, Saito Y, Matsuda T, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut. 2006;55:1592–7.
8. Ikehara H, Saito Y, Matsuda T, et al. Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy. J Gastroenterol Hepatol. 2010;25:905–12.
9. Kudo S, Hirota S, Nakajima T, et al. Colorectal tumours and pit pattern. J Clin Pathol. 1994;47:880–5.
10. Katagiri A, Fu KI, Sano Y, et al. Narrow band imaging with magnifying colonoscopy as diagnostic tool for predicting histology of early colorectal neoplasia. Aliment Pharmacol Ther. 2008;27:1269–74.
11. Son HJ, Sohn DK, Hong CW, et al. Factors associated with complete local excision of small rectal carcinoid tumor. Int J Color Dis. 2013;28:57–61.
12. Chou YP, Saito Y, Matsuda T, et al. Novel diagnostic methods for early-stage squamous cell carcinoma of the anal canal successfully resected by endoscopic submucosal dissection. Endoscopy. 2009;41:E283–5.
13. Rosenberg N. Submucosal saline wheal as a safety factor in fulguration of rectal and sigmoidal polypi. Arch Surg. 1955;70:120–2.
14. Moss A, Bourke MJ, Metz, et al. A randomized double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. Am J Gastroenterol. 2010;105:2375–82.

15. Holt BA, Bourke MJ. Wide field endoscopic resection for advanced colonic mucosal neoplasia: current status and future directions. Clin Gastroenterol Hepatol. 2012;10:969–79.
16. Saito Y, Uraoka T, Matsuda T, et al. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc. 2007;66:966–73.
17. Saito Y, Fukuzawa M, Matsuda T, et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc. 2010;24:343–52.
18. Lee EJ, Lee JB, Choi YS, et al. Clinical risk factors for perforation during endoscopic submucosal dissection (ESD) for large sized, nonpedunculated colorectal tumors. Surg Endosc. 2012;26:1587–94.
19. Brooker JC, Saunders BP, Shah SG, et al. Treatment with argon plasma coagulation reduces recurrence after piecemeal resection of large sessile colon polyps: a randomized trial and recommendations. Gastrointest Endosc. 2002;55:371–5.
20. Regula J, Wronska E, Polkowski M, et al. Argon plasma coagulation after piecemeal polypectomy of sessile colorectal adenomas: long-term follow-up study. Endoscopy. 2003;35:212–8.
21. Mannath J, Subramanian V, Singh R, et al. Polyp recurrence after endoscopic mucosal resection of sessile and flat colonic adenomas. Dig Dis Sci. 2011; 56:2389–95.
22. Buchner AM, Guarner-Argente C, Ginsberg GG. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. Gastrointest Endosc. 2012;76:255–63.