Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

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Introduction

Endoscopic resection (ER) started with the introduction of snare polypectomy in the colon, esophagus, cardia, and stomach in Germany and in Japan at the end of the 1960s and beginning of 1970s [1]. In 1970, Deyhle, Seuberth, Jenny, and Demling performed the first colonic polypectomy [2]. In the following Classen and Demling form Erlangen, Germany, removed the first gastric polyp [3,4]. Other locations followed. In 1972, Seifert et al. removed for the first time a polyp due to neurofibromatosis from the upper esophagus [5]. Henke and Ottenjann resected an adenoma with focal cancer at the cardia in three sessions in 1973 [6]. Deyhle performed in 1974 the first “en bloc” resection of a minute early gastric cancer using a snare [7].

Polypectomy as the name says is useful for the removal of polyloid lesions. The technique frequently fails when a soft standard snare is applied to remove an only slightly elevated lesion. With the introduction of saline-assisted polypectomy in 1973 by Deyhle et al. after prior experiments in dogs, deep coagulation of the wall could be prevented and the removal of flat lesions facilitated [8]. This technique is nowadays the classic “endoscopic mucosal resection” (EMR) technique but was described in the following often as “strip biopsy,” especially in the Japanese literature and successfully applied in the removal of early gastric and colonic cancers [9–11].

There are mechanical alternatives to saline-assisted resection of mucosa. These include the use of a stiff monofilament snare to be pressed into the mucosa, the aspiration of mucosa into a tube with prograde or side opening and the aspiration of mucosa into a cap or plastic cylinder mounted onto the distal end of the endoscope [12,13]. The Nakajima tube uses the protrusion of mucosa itself to better grab it with the snare. In a further development by Inoue, the mucosa is aspirated into a special transparent plastic cap mounted onto the distal end of the endoscope. This cylinder is preloaded with a special fine asymmetrical snare placed into a narrow inner rim at the distal end of the cylinder and closed once the mucosal “mushroom” has been aspirated [13]. The third mechanical way is to aspirate the mucosa into a transparent cylinder with externally deployable rubber bands, ligate a pseudo-mushroom after mucosal aspiration, and to consecutively snare it off underneath the rubber band [14–17].

The search for techniques to resect even large mucosal areas with early gastric cancer and to get a thorough histopathologic diagnosis led to the development of “endoscopic submucosal dissection” (ESD) in Japan at the end of the 1990s [18–20].

The concept is based on a frehand needle-knife technique as applied in needle-knife sphincterotomy for difficult access to the biliary or pancreatic duct in ERCP. A large submucosal fluid cushion serves as protective layer when the lesion is first isolated by means of a circular cut outside a safety zone marked beforehand by fine coagulation dots placed around the margins of the lesion. After this circumcision, the lesion is separated from the muscularis propria at the level of the submucosa. This gives the technique the name of “submucosal dissection.” Various knives and special tools have been developed for this scope.

In the following section, the key steps for proper acquisition of EMB and ESD techniques as well as the prerequisites are explained. There is no doubt that a theoretical explanation of the techniques even when illustrated by images, schemes, and video sequences do not replace a one-to-one supervised preclinical and clinical teaching situation. However, we hope you will find some helpful tips for your daily practice.
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Endoscopic Learning Pyramid in 2011

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Figure 18.1 Endoscopic “learning pyramid” for stepwise clinical skills acquisition in gastrointestinal endoscopy and the possible complementary use of training simulators.

Endoscopic mucosal resection

EMR techniques to be considered

Common EMR techniques according to organs
- Colon:
  - Saline-assisted snare resection of flat lesions (classic “EMR”)
  - Resection of flat lesions using a stiff snare without prior injection
- Esophagus:
  - CapEMR
- Stomach:
  - Band and snare technique
  - Saline-assisted snare resection of flat lesions (classic “EMR”)
- Small intestine:
  - Saline-assisted snare resection of flat lesions (classic “EMR”)

Special EMR techniques not considered
- EMR via double channel endoscope “Pull and snare”
- EMR via Machuuchi tube
- Other rarely applied techniques

Procedures to be considered

EMR is carried out in the entire gastrointestinal tract according to the same principle. Preferred localizations are colo-rectum, stomach, esophagus, and small intestine. It can be part of any primarily diagnostic intervention in these organs, for example, within preventive colonoscopy. Accordingly, it can also be part of gastroscopy, enteroscopy, and ERCP procedures.

Prerequisite level of expertise for endoscopic mucosal resection

There is a large variety in the level of expertise needed for EMR depending on the lesion itself as well as the resection technique applied. Considering our learning pyramid of training, from the base to the most sophisticated techniques, EMR is today no longer considered an expert-only technique; EMR should to be started now at the second level and be taught together with injection and clip hemostasis after trainees have gathered sufficient experience in unsupervised gastroscopy and colonoscopy [21–24] (Figure 18.1). An exact number is not known, but 50 unsupervised colonoscopies plus 100 unsupervised gastroscopies could be a good starting point for the first supervised steps in EMR. The learner should begin with uncomplicated colo-rectal polyps of less than 2 cm, easy to reach, for example, in the rectum.

More sophisticated techniques and EMRs in difficult locations such as the duodenum, in the esophagus or stomach do require a by far higher level of expertise and a high competence in complication management.

Special considerations

The necessary skills for EMR are best obtained in an initial “hands-on” training course and subsequent clinical guidance of an experienced endoscopist. It is a prerequisite that the trainee is familiar with indications for EMR. He must know contraindications for endoscopic procedures in general and in particular for EMR. Specifically, the trainee has to be able to anticipate and to act upon procedure-related complications during and after EMR.

Specific technical and cognitive skills

EMR requires sufficient cognitive skills with regard to the
- Indication for EMR
- Ability to discriminate submucosal lesions and invasive cancers from mucosal pathologies
- Interpretation of non-invasive imaging results such as abdominal and endoscopic ultrasound (US; EUS), computed tomography (CT), or magnetic resonance imaging (MRI)
Adequate estimation of the time needed for elective therapeutic procedures
Knowledge of specific instrumentation or accessories that might be necessary during the procedure in order to organize logistics. Availability has to be checked best the day before the intervention
Evaluation of clinical signs and symptoms during the procedure and following the endoscopy, for example, abdominal pain due to bloating after colonoscopy versus an "acute abdomen" due to perforation
Available diagnostic measures and imaging techniques for the detection of procedure-related complications (e.g. CT-scan, US; plain abdominal X-ray film)
Management of complications endoscopic and non-endoscopic, for example, medical, minimal-invasive, or surgical
Evaluation of the histologic result. This is true for an uneventful course but also in case of complications that may lead to the necessity of endoscopic or differentiated more or less radical surgical management
Scheduling of endoscopic follow-up surveillance intervals according to the histologic result
Management of late complications such as strictures or local tumor recurrences, non-surgical, or surgical

Equipment for EMR
General considerations
The equipment for EMR depends on the individual lesion and anatomical situation. Criteria to select specific equipment include size, macroscopic appearance, and location of the target lesion, and may vary considerably. Furthermore, the resection technique applied and accessories used may play a role for the overall setting.
For localizations in the lower and upper GI-tract, standard colonscopes and gastroscopes are commonly used. However, for special localizations, for example, in the duodenum or at the greater or lesser curvature of the stomach, other endoscopes such as duodenoscopes may facilitate resection. In the rectum, a therapeutic or standard gastroscope may prove favorable as it is easier to maneuver than a long routine colonoscope. A double-channel gastroscope can provide an additional channel for suction and be advantageous, for example, for strongly vascularized lesions or resections over the hemorrhoidal plexus in the distal rectum. EMR in the jejunum is possible by means of a special enteroscope and serve as a substitute for surgery. A large channel therapeutic enteroscope, for example, a therapeutic double-balloon enteroscope (e.g., Fujinon EN450T5) is considered best because of adequate hemostasis possibilities. ERs of tumors of the papilla of Vater (Figure 18.2) require advanced skills in ERCP and have to be discussed separately. Special locations of ERs have been described, such as the pharynx and hypopharynx or in the common bile duct on the percutaneous–transhepatic route [25,26].

Equipment independent of the procedure
Adequate monitoring and supervision during sedation
Sedation should be carried out according to national guidelines. In cases of severe comorbidity or extremely complex interventions, general anesthesia should be considered. EMR procedures in large lesions or with technically difficult anatomical access may take considerable time, for example, 1–2 hours (Figure 18.3).

Endoscopic flush pump
A separate flush pump (e.g., “Endowasher” Griessat Endotechnik, Solingen, Germany) operated by a foot switch and coupled in by means of a Y-adapter or a special “jet channel” facilitates the removal of debris, blood, or mucus and seems essential to us for ER techniques. This way, the water pump can be operated without taking an instrument out of the accessory channel during irrigation (Figure 18.4).

Organ-specific equipment
Colon
- Standard or pediatric colonscope
- Saline-assisted EMR
  - Injection needle 21G (0.7 mm) with saline ± epinephrine, for example, 1:250.000 and indigocarmine blue 0.002%
  - Different stiff snares of a size of 15–35 mm (standard snares have often a size of 20–25 mm)
  - Hemoclips for colonoscopic use (e.g., Olympus Optical, Tokyo, Japan; Boston Scientific, Natick, MA)
  - Polyp trap to be interposed into the endoscope suction at the level of the attachment to the endoscope light source
- Polyp retrieval net (e.g., Roth net, US Endoscopy, Mentor, OH, USA)

Esophagus
- High-resolution standard diameter adult gastroscope
- For CapEMR
  - Injection needle 21G (0.7 mm) with saline ± epinephrine, for example, 1:250.000 and indigocarmine blue 0.002%
  - Oblique or straight transparent cap with inner rim (Olympus Optical, Tokyo, Japan) adopted to the outer diameter of the endoscope (e.g., Cap No. 3 for many standard gastrosopes)
  - 25 mm multilamination asymmetrical snare (which fits all types of caps; Olympus Optical, Tokyo, Japan)
  - Hemoclips for use in the upper (or lower) GI tract (e.g., Olympus Optical, Tokyo, Japan; Boston Scientific, Natick, MA)
- For band and snare EMR technique
  - Ready available kit with multilamination cylinder equipped with six rubber bands and special hexagonal snare (Cook Medical, Winston-Salem, USA; Figure 18.7)
  - Alternatively, a variceal band ligation set plus standard snare in case of a single lesion
  - Polyp retrieval net (e.g., Roth net, US Endoscopy, Mentor, OH, USA) for retrieval from the gastric fundus
  - Polyp trap in case of the use of a large channel gastroscope to be considered (interposed between suction tube and endoscope)
Figure 18.2  (a, b) Endoscopic snare resection of a large 2.5 cm × 3 cm ampullary tumor using a side-viewing endoscope: 5 Fr polyurethane drainage still in place. EUS and EBCP with pancreatic and biliary sphincterotomy and bi-ductal stenting had been performed 2 weeks earlier to guarantee a safe ductal access even in case of complications.  

(c–e) Generous submucosal injection using a Carr-Locke spiral 25G injection needle (US Endoscopy, USA) and a saline/epinephrine solution (1:250,000) with 0.002% indigocarmine blue addition. (f) A complete lifting of the lesion is achieved as important diagnostic criterion for endoscopic respectability. (g–j) Piecemeal EMR is carried out using a 25 mm multifilament snare (Griessat Endotechnik Corp., Solingen, Germany). (k) Macropopically adenoma-free resection base as final result. (l, m) As last step, a new pancreatic and biliary drainage is implanted to prevent fluid retention.
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Figure 18.3 (a) Patient preparation: for long-lasting interventions such as complex ESDs, the use of a warming blanket may be advisable.

Stomach
- High-resolution standard diameter adult gastroscope
- Saline-assisted EMR
  - Injection needle 21G (0.7 mm) with saline ± epinephrine, for example, 1:250,000 and indigocarmine blue 0.002%
  - Different sizes of a size of 15–35 mm.
  - Hemoclips for use in the upper (or lower) GI tract (e.g., Olympus Optical, Tokyo, Japan; Boston Scientific, Natick, MA, USA)
  - Polyp trap to be interposed into the endoscope suction at the level of the attachment to the endoscope light source
  - Polyp retrieval net (e.g., Roth net, US Endoscopy, Mentor, OH, USA)
  - Polyp trap in case of the use of a large channel gastroscope to be considered (interposed between suction tube and endoscope)

Duodenum
- High-resolution gastroscope and therapeutic side-viewing duodenoscope.
  - Injection needle 21–23G (0.7–0.5 mm) with saline ± epinephrine, e.g., 1:250,000 and indigocarmine blue 0.002%
  - Different sizes of a size of 15–20 mm
  - Hemoclips for use in the upper (or lower) GI tract (e.g., Olympus Optical, Tokyo, Japan; Boston Scientific, Natick, MA, USA)
  - For a sideviewing duodenoscope, disposable (yellow) Olympus clips preferred
  - Polyp trap to be interposed into the endoscope suction at the level of the attachment to the endoscope light source
  - Polyp retrieval net (e.g., Roth net, US Endoscopy, Mentor, OH, USA)
  - Polyp trap in case of the use of a large channel gastroscope to be considered (interposed between suction tube and endoscope)

Jejunum and deep small intestine
- Therapeutic enteroscope, for example, therapeutic double-balloon enteroscope (e.g., Fujinon EN450T5)
- Pediatric colonoscope 175 cm for the first 30–50 cm of the jejunum often feasible. For interventions using a pediatric colonoscope or enteroscope of max. 200 cm standard colonoscopy equipment often works

Figure 18.4 (a) The system is connected to a Y-shaped side port at the instrumentation channel inlet or a complimentary water jet channel. (b) Helpful accessory for all endoscopic resection techniques: an "endowasher" pump with 3 L bag of rinsing solution.
Salvage accessories

- "Over-the-scope-clip," "bear trap" (OTSC; e.g., Ovesco, Tuebingen, Germany).
- Hemoclips DBE (Olympus Optical, Tokyo, Japan) or for the use in the lower GI tract (e.g., Boston Scientific, Natick, MA).
- Polyp trap to be interposed into the endoscope suction at the level of the attachment to the endoscope light source.
- Polyp retrieval net (e.g., Roth net, US Endoscopy, Mentor, OH) in case of retrieval after interdisposition in the fundus of the stomach.

Patient preparation

- Focus on informed consent
  - To justify EMR within a procedure, it has to be covered within the informed consent of the patient prior to the intervention. If EMR appears to be indicated during a primarily diagnostic intervention, the physician has to decide if he needs additional information for example, a rectal ultrasound or MRI of the lesser pelvis to exclude invasive growth or if it seems justified to proceed to resection within the same session. Furthermore, it has to be cleared if alternative treatment options have been discussed sufficiently and if the patient would be ready to accept that she/he needs hospitalization after a complex procedure. Especially in the upper GI tract without the necessity of a special preparation and easy and fast access, it is rather recommended to come back in a second session than to proceed to an invasive procedure without having discussed the next steps sufficiently with the patient.

Patient condition and alternative treatment options

- EMR in difficult locations or large lesions may require a long-lasting procedure. Fitness of the patient for prolonged sedation during this intervention and complication management has to be checked early. For special interventions anesthesia may be required for airway management. Furthermore, the intervention has to be seen in an interdisciplinary context and alternatives be balanced. Is this the best treatment option for the patient also in the eyes of his relatives, of a general surgeon, or an outside assessor in case of a litigation? Often, it is better to postpone an elective intervention if conditions are not optimal or patient and relatives not thoroughly convinced of the procedure.

Patient preparation

- The general preparation is according to the "carrier procedure," for example, gastroscopy or colonoscopy. Special medication such as anticoagulants should be discontinued according to national guidelines and individual recommendations, for example, of the attending cardiologist [27].

Key steps for proper technique in EMR (see Video 18.1)

Evaluation of the lesion

- EMR is focused on the removal of epithelial lesions. The first step to an exact evaluation of the lesion is optimal visualization. One should always inspect the entire lesion, including the proximal and lateral margins. Debris or stools should completely be flushed off the lesion and its proximity. Within the last decade, new technical features such as digital chromoendoscopy (NBI, FICE, 1-scan), zoom and high-resolution endoscopy (HRE) have added a significant diagnostic yield to standard video endoscopes [28]. Optical contrast such as NBI or FICE can help to better delineate the margins of the lesion and to evaluate the surface structure and the so-called “pit pattern” [29,30]. Already by optical appearance, an experienced endoscopist may correctly classify a lesion as suspicious or endoscopically treatable about 80% of the time [31]. However, especially in the upper GI tract and in the rectum, noninvasive imaging such as EUS, CT, or MRI may add significant information on local lymph node status and invasion depth. The value of submucosal (sm) injection as diagnostic tool will be discussed in the next section. In uncertain cases, clip marking 1–2 cm from the lesion, exact determination of the location, biopsies, and a second examination with more information may be a good alternative [32].

Marking

- In case of suspected or proven early malignant lesions, a prior marking including a safety zone of at least 3 mm from the lesion should be performed using thermo coagulation. The by far easiest tool to use is Argon plasma coagulation (e.g., 25 W, 0.3 L gas flow “forced coag” in the VIO generator; ERBE Medizintechnik, Tuebingen, Germany). Alternatives are, for example, the tip of a snare, however, with an increased risk of deeper injury of the wall.

Submucosal injection

- Submucosal injection can help in two senses as diagnostic tool. Using saline and epinephrine 1:100,000 alone for injection usually turns the mucosa pale with impaired vision, a reason some endoscopists did not like to use submucosal injection of flat polyps over the years. Adding indigo carmine blue to the injection solution (e.g., Indigo Carmin™, American Regent, Shirley, NY, 1.5–2 mL of a commercial 0.8% solution to a bag of 500 cc of saline) and epinephrine 1:250,000 turns the underground to a mid blue after submucosal injection while the lesion remains bright. This leads to wonderful images with a sharp delineation of even shallow lateral margins.

- Furthermore, also the ease to separate layers at the level of the submucosa and the degree of adhesion serve as important diagnostic tools. In case of a clear “lifting” of the entire lesion, resection is almost always possible. A so-called “non-lifting sign” of the lesion with central adherence and lateral bulging, in the extreme case similar to a floating tire, always signals an increased perforation risk at resection. An insufficient or only moderate lifting is not always equivalent to malignant infiltration but may occur due to local scarring and prior inflammation, for example, in flat...
adenoma in the colon or prior incomplete attempts at resection. However, a “non lifting” even after generous fluid injection makes the lesion suspicious and should raise the question whether it is better to continue resection, send the patient to an expert, request additional information, or send the patient directly to the surgeon. We favor submucosal injection due to the reasons mentioned. However, for single instruments/techniques namely the “ligate and snare” technique using rubber bands for tissue ligation prior to resection, it seems that a larger tissue volume of mucosa can be accomplished with less injection edema in the submucosa. Furthermore, some authors prefer to not use submucosal injection in combination with a stiff monofilament snare [33,34].

An important practical point in submucosal injection is that in contrast to sclerotherapeutics where the needle is rather pressed into the tissue to avoid leakage of fluid, in case of EMR-ESD-injection, the target layer is the very superficial submucosa. Wall perforation of the needle leading to transmural leakage during further injection and the following resection procedure should be avoided. The needle is first advanced from the catheter and held about 1–2 mm over the mucosal surface. The assistant is asked to start injection. Only when fluid leaves the needle, it is advanced with a sharp “go” to just perforate the mucosa and then immediately pulled back 2–3 millimeters. This will lead to a typical submucosal blowing up of the mucosa. Trainers must be made aware that if the needle is deeply stuck into the tissue and nothing happens, the fluid is being injected beyond the organ wall. We use a standard 5 mm long 21G (0.7 mm) universal injection needle. However, shorter, 3 mm long needles are available for EMR purposes.

Resection techniques for EMR

In this chapter, we limit our discussion to the description in detail of the three most common EMR techniques applied. An overview on EMR and ESD techniques can be found in the current literature [27].

Lift and cut technique (“saline-assisted EMR”; “classic” snare EMR after prior submucosal injection)

Historical background and aim of this technique is to enable the resection of flat polyps in which a conventional snare would easily slip over the lesion (Figure 18.5). The technique is the most popular EMR technique applied especially for the removal of nonpedunculated colorectal polyps. Technically, submucosal saline injection provides a soft fluid cushion into which the snare can easily be pressed. A bulging of the mucosa to the interior of the snare provides a higher friction and better grip of the snare filaments when the snare is closed. This increases the tissue volume per cut. Resection proceeds often easier and faster after the first specimen has been removed. A clear step between the muscular resection base and the mucosal surface facilitates subsequent cuts. Following the first resection, the snare is placed, for example, with the left side into the mucosal defect and the right side is placed onto the lesion elevated by submucosal injection. Pressing the snare onto the ground and closing it slowly, the next piece of mucosa to the right is resected. This is repeated until the entire lesion as well as a lateral safety margin has been removed. The technique is therefore also called “piecemeal resection.” It is advisable to start at the lateral margins of the lesion, incorporating a “safety margin” of 2–3 mm in order to reduce the risk for local recurrences (Figure 18.5). The tissue removed can be pushed to the side and be collected by means of retrieval net (e.g., “Roth net,” US Endoscopy, Mentor, OH). Alternatively, but more traumatic and sometimes leading to a rupture of fragments is the retrieval by the snare itself or a wire basket for ERCP stone removal. The third possibility is to just suck off the fragments via the instrumentation channel and to collect them by means of a “pulp trap.” Care should be taken that the particles are not smashed and that they are placed in a sufficient quantity of formalin in an appropriate recipient (e.g., for urine samples with sealed trap).

CapEMR

CapEMR is an expert technique and should be applied by advanced endoscopists. It has been developed by Inoue et al. as a further development and logical consequence of the Makuuchi tube for the removal of early esophageal cancer in the beginning of the 1990 and has been one of the major achievements in EMR [13,35]. There is a straight and oblique version of the so-called “distal attachment cap” (Figure 18.6). Caps are provided in different diameters and are in the “classic version” composed of a hard plastic part with an inner rim at the distal end and a soft silicone ring to mount the cap on the endoscope. There are different variations, including a so-called “soft-cap” with larger diameter and flexible plastic cylinder. We usually recommend starting with a cap No. 3 and a standard HR gastroscope. For the beginner, a straight cap is easier to use. Gaining experience, many will prefer the oblique type as it provides larger resection pieces, better vision on the short side, and traumatizes less the underlying tissue. Having mounted an oblique cap onto the endoscope, one will see on the endoscopy video screen a round plastic tube with inner rim and rectangle being cut out. The purpose of this rectangle in the rim is to indicate the shortest part of the cylinder, while the oblique nose is on the opposite side. The cylinder has to be turned on the endoscope tip until the rectangle is exactly in front of the instrumentation channel (often in an 8 o’clock position). This is essential for a proper functioning of the oblique cap together with the asymmetrical snare (Figure 18.6). The cap is additionally fixed to the endoscope by means of a stripe of sterile soft adhesive (e.g., cut off from the lateral margin of an adhesive or as part of a fixation set for i.v. accesses) (Figures 18.6 and 18.8). This is necessary in order to not loosen the distal cap when retrieving the specimen after resection at the level of the mouth guard. We discourage from taking regular nonsterile “Scotch tape” used for dressings, etc., as it does not stay reliably on the neoprene end of the endoscope and is a potential carrier of hospital germs.

The cap resection technique implies the use of a special 25 mm asymmetrical multilament snare in the form of the head of a dolphin. The working mechanism includes a stopper integrated in the distal end of the Teflon sheath, the way one side of the snare is bulging while the other one stays in place. This mechanism allows the clockwise deposition of the soft snare into the inner rim of the distal attachment cap (see Video 18.1).
Figure 18.5 (a–e) Indigocarmine blue colorant for improved delineation of flat lesions and later resection margins. “Indigo” is added in a small quantity to the saline/epinephrine submucosal injection fluid (1:250,000; 1.5–2 mL of indigo into 500 cc of saline): flat laterally spreading colonic adenoma clearly visible for piecemeal resection of a lateral safety zone together with the lesion. (f, g) Complete clip adaptation of the margins in a patient at increased bleeding risk.

At first the endoscope is gently introduced into the upper esophagus. Pressing the rinsing and the suction button of the endoscope at the same time removes mucus from the inner side of the cylinder and leads to a clear vision. At first, a marking of the area to be resected is performed, e.g., using an argon plasma probe (25 W, “forced,” 0.5 sec pulses forced coag, ERBE VIO prograde probe), including a sufficient safety zone of adjacent inconspicuous tissue (minimum 2–3, recommended 5 mm).

In the case of a circumscript Barrett’s cancer, the surrounding Barrett’s epithelium may be resected at the same time or just the prominent part with secondary thermal ablation [36,37]. We personally prefer a clear histology over pure ablation after endoscopic inspection and focal biopsy and try to resect 1/3 to 2/3 of the circumference in a Barrett’s segment containing high-grade dysplasia or early cancer. In this case, an initial marking of the resection field is performed, extending at least 5 mm cranially and caudally of the Barrett’s segment into normal squamous or gastric cylindrical epithelium.

As a second step, the mucosa is generally lifted by submucosal injection using saline/epinephrine 1:250.000 and indigocarmine blue 0.002% in relatively large quantities (e.g., 300 cc during an examination and repeat injection). One should not be afraid of “overinjection” as passing by with the endoscope from cranially to caudally after a short time the fluid will rapidly disappear.

For deposition of the snare within the cylinder, the transparent hood is gently pushed against normal mucosa, for example, in the proximal esophagus, in order to not disturb the lesion itself until the snare is properly seated along the rim of the cylinder. The snare catheter with the snare closed is then advanced until it can be seen within the cylinder. The assistant has then to slowly open the snare.
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(a) (b)

(c) (d) (e)

(f) (g) (h)

Figure 18.6 (a) Cap resection (EMRc) for flat esophageal lesions: “distal attachment” caps (Olympus Optical, Tokyo, Japan) of various sizes with straight or oblique distal ends according to H. Innoe, Japan. (b) Clinical application in a patient with long-segment Barrett’s esophagus and multifocal HG-IEN. (c) After marking of the proximal and distal ends of the Barrett’s segment and generous submucosal injection (not shown), a transparent cap is mounted onto the distal end of the endoscope. We use size number 3 oblique with inner rim in combination with an HR standard endoscope, here applied in the proximal esophagus. The rectangle indicates the shortest point of the cylinder and should be aligned with the instrumentation channel. A snare catheter can be seen in the 9 o’clock position. The 25 mm asymmetrical snare consists of a special soft wire of 20 multifilaments and is placed into the inner rim of the cylinder, best in a clockwise direction. (d) Resection is started at the proximal end of the lesion including a 2–5 mm safety margin. The endoscope is rotated until the snare catheter directs towards the lesion. The end of the cylinder is then gently pressed tangentially against the mucosal surface and aspiration is activated. This way only mucosa distally to the cylinder is aspirated and the resection area better defined. When there is a “red out” and the cylinder completely fills the stent, the inner rim of the cylinder is closed and a mushroom-like area of mucosa is captured. After releasing the suction and gently pulling back the endoscope, the mucosa mushroom is released with the stent still closed and resection performed. (e) This can be repeated several times from cranially to caudally over the total length of the long Barrett’s segment. (f) Reaction of more than two-third of the circumference should be avoided at a time to prevent structuring. Fibrin-covered clean resection base is performed after 5 days. (g) Resection is continued in this case 2 weeks after the first resection but should preferably be carried out after complete healing, usually, 2–3 months after the first resection session. (h) Final result after 3 months with complete removal of the dysplastic area and all Barrett’s mucosa. (continued)
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Figure 18.6 (Cont.) (i) capEMR specimen up 3 cm, pinned on cork. (j) Specimen upside down in transport recipients filled with formalin. A second layer of cork is used to securely keep the specimen in the fluid and avoid insufficient fixation or drying.

Resection itself is usually started at the cranial end of the Barrett’s epithelium or the respective lesion if not Barrett’s. The endoscope is rotated within the longitudinal axis in order to bring the instrumentation channel with the snare catheter close to the esophageal wall. Again resection is carried out by including in the first resection at least 2–3 mm if not more of normal appearing mucosa in order to be radical enough. The transparent cylinder is therefore placed in an oblique way onto the cranial end to be resected the way the snare catheter is close to the esophageal wall as possible. Aspiration is performed and the mucosa will stepwise creep into the transparent cylinder until there is a “red out” like in variceal band ligation. At this point, the endoscopist stays with his left index on the suction and has his right hand at the snare catheter above the instrumentation channel valve. The assistant now slowly closes the snare while the endoscopist advances the snare catheter into the instrumentation channel just as much as necessary to compensate shrinking of the Teflon tube by compression of the tissue under traction. The assistant has to close the snare to the maximum with the snare handle. A round to oblique area of mucosa is now caught like a mushroom in the snare. At this point, it is important to release the suction with the index of the left hand and to push the closed snare catheter about 2 cm forward out of the cylinder and shake it gently. This helps release possibly entrapped muscularis propria and avoids perforation. Now the entrapped piece of mucosa is cut through with blended current (e.g., “Endocut Q,” setting 2, ERBE VIO, or 60W setting 3 ERBE ICC 200). The created little “meat ball” of resected mucosa is then aspirated into the cylinder and the endoscope is withdrawn. With a standard gastroscope and 2.8 mm channel, a polyp trap at the level of the suction is usually not needed. Outside the patient, suction is released best over a sterile metal recipient filled with saline.

Figure 18.7 Commercial “Band and Snare” mucosal resection kit (“Douette”, Cook Medical, Winston-Salem, USA). A hexagonal monofilic snare (a) is used in combination with a special multiligation system (b) for repeated mucosal aspiration, rubber band ligation, and snare resection under the rubber band.
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and the specimen flushed out or if necessary caught by a pair of forceps without damaging it (see Video 18.1).

Time should not be wasted to take of the specimen at this point but rather to go back to the esophagus again and see if there is any bleeding or wall defect. Both should be fixed immediately in the case that either of this has occurred.

Multiple resections can be accomplished this way in the same session. The second resection should adjoin the first one caudally the way the transparent cylinder with the snare is placed precisely at the transition of prior resection base and mucosa to be resected. Again, the cylinder touches at the side of the snare catheter the muscularia propria and suction is applied. The snare should then slip exactly under the mucosal edge between muscularis resection base and mucosa in order to allow a seamless transition and enlargement of the resection. Even more than 10 particles can be taken out going from cranially to caudally, for example, in a Barrett’s esophagus and the resection street can be enlarged by a second or third directly adjacent track.

After resection, care should be given to hemostasis of small vessels using, for example, APC at a low gas flow or hemoclips.

Ligate and cut EMR-technique

A technically simple method to resect Barrett’s mucosa with HG-EIN in piecemeal fashion is the so-called “ligate and cut” technique [16,34]. Recent advances in refining the technique include the development of the “Duette” system (Cook Medical Bloomington, Indiana) [17,38]. A transparent cylinder with six rubber bands similar to the “sixshooter” variceal band ligation device is mounted on the distal end of the endoscope. In contrast to the variceal band ligator set, the EMR set has a different handle and contains a hexagonal snare that can be introduced into the instrumentation channel via an additional access port in the handle (Figure 18.7).

The technique is applied without prior injection. The mucosa is sucked into the cylinder and the band is fired. The snare is introduced and resection of the created ligation mushroom underneath the band is carried out. Immediately after the next band is placed adjacent to the previous resection site in order to avoid tissue bridges. Tang et al. from Dallas reported a successful removal of a 14 cm Barrett’s esophagus with HG-EIN in two sessions. However, in the second resection session alone, they applied 64 bands and 11 EMR/ligation kits, a considerable medical but also economic effort [38]. Wall perforations using the ligate and cut technique are rare [17,39].

Endoscopic submucosal dissection

ESD is composed of a sequence of different steps:

1. Identification and marking of the lesion with a sufficient lateral safety margin
2. Submucosal injection and tissue elevation
3. Circumcision of the lesion
4. Submucosal dissection, “en bloc” removal and subsequent retrieval of the lesion
5. Careful hemostasis and prophylactic occlusion of vessels at the resection base
6. Preparation of the specimen for histopathologic evaluation.

In the following, we will go through personal and technical prerequisites as well as the different steps of ESD.

Procedures to be considered for ESD

Procedures to be considered for ESD in the upper and lower GI tract are comparable to those of EMR, with the exception of the small intestine beyond the ligament of Treitz where ESD has not been described so far.

Skills for ESD and who should do it

Prerequisite level of expertise and skill for learning ESD

ESD is currently a technique for the “high-end” endoscopist requiring a long practice in interventional endoscopy and complication management. ESD originated in Japan and is a relatively new procedure in the Western world. The prerequisites and the learning curve to perform a “safe” and sufficiently fast ESD still have to be defined. ESD is a “freehand” needle-knife technique similar to needle-knife sphincterotomy when gaining access to the common bile duct in difficult ERCP situations. In the beginning, ESD is time-consuming and carries an increased complication risk, especially for perforation.

Special considerations for ESD

Initial steps in learning ESD should be accompanied by a training program and expert teaching. The training steps include a progressive approach to the technique in “ex vivo” pig stomachs. Training in live pigs is a useful next step to acquire ESD hemostasis skills and to train the technique in an environment with natural GI motility. For clinical practice, a close student–teacher relationship and sufficient phases of watching the procedure seem important before a student goes to unsupervised clinical ESD. Japanese say that at least 100 ESD procedures are required before the trainee reaches a sufficient speed and safety for standard “en bloc” resections. Systematic training programs will help to avoid pitfalls and lead to a successful spread of this undoubtedly fascinating technique.

Specific technical and cognitive skills for ESD

All statements given for EMR in section are also valid for ESD. Beside these points, the trainer should have the following personal prerequisites:

- Extensive experience in complication management in the upper and lower GI tract especially in adequate treatment of perforations and bleedings
- Several years of experience in interventional endoscopy including different EMR techniques for benign and early malignant lesions.

Equipment for ESD

General considerations on ESD equipment

The equipment for ESD depends much on the individual preferences and resection technique used [40]. For lesions located in the lower and upper GI tract standard gastrosopes and coloscopes may be used. However, our personal preference is a slim
therapeutic HR double channel gastroscope (Fujinon EG 530D Fujifilm Medical, Tokyo, Japan; Table 18.1) with the advantage of a large suction channel reserved exclusively for aspiration while the smaller channel takes the accessory, for example, the resection knife and is equipped with a Y-side-port for additional coaxial rinsing using a flush pump. We like the double channel instrument as it gives an optimal orientation and overview even in difficult situations. Especially, in a strongly vascularized environment as in the distal rectum, two different channels for rinsing and suction are a major advantage.

**Essential equipment for ESD**
- Upper GI tract, recto-sigmoid, left-sided colon
  - Respectively preferred instruments: double-channel gastroscope, standard gastroscope, standard, or pediatric colonoscope.

**Colo-rectum**
- Standard or pediatric colonoscope.

**Special equipment for ESD**
- R-scope or M-scope [Olympus Optical, Tokyo, Japan] as experimental articulating endoscopes with two elevators in order to allow up and down and left and right movements of instruments.

**Equipment independent of the procedure**
- Adequate monitoring and supervision during sedation
  - See section “EMR.”

**Endoscopic flush pump**
- See section “EMR.”

Figure 18.8 (a) Helpful accessories for endoscopic submucosal dissection (ESD): a high resolution double channel gastroscope (EG530D; Fujifilm, Tokyo, Japan) offers optimal suction and overview even in bleeding situations and can be used in the upper GI tract as well as in the recto-sigmoid. Two resection knives are inserted for demonstration only. (b–d) Transparent caps of different shapes and sizes significantly improve vision during ESD and offer a safe working space for resection knives. Furthermore, they mechanically help to separate mucosal layer and muscularis propria in analogy to surgical triangulation. (continued)
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Figure 18.8 (Cont.) (e–g) The cylinders should be fixed on the distal end using a sterile tape, for example, as used in dressing kits for IV accesses. This prevents a loss or displacement of the cap during the procedure.

Table 18.1 Typical technical features of different endoscopes (Fujinon EG 590 WR gastroscope, EC 590 ZW colonoscope, EG 530 D therapeutic double channel gastroscope) The EG 530 D (Figure 18.8 e,k) is the preferred standard endoscope for ESD with optimal rinsing and suction capabilities especially in the strongly vascularized distal rectum [40].

<table>
<thead>
<tr>
<th>Endoscope denomination</th>
<th>Endoscope type</th>
<th>Distal end</th>
<th>Channel Ø</th>
<th>Bending</th>
</tr>
</thead>
<tbody>
<tr>
<td>EG 590 WR</td>
<td>Gastroscope</td>
<td>9.6 mm</td>
<td>2.8 mm</td>
<td>UD 210°/90°</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR 100°</td>
</tr>
<tr>
<td>EC 590 ZW</td>
<td>Colonoscope</td>
<td>12.8 mm</td>
<td>3.8 mm</td>
<td>UD 140°</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR 140°</td>
</tr>
<tr>
<td>EG 530 D</td>
<td>Therapeutic double-channel</td>
<td>11.5 mm</td>
<td>2.8 mm</td>
<td>UD 180°</td>
</tr>
<tr>
<td></td>
<td>gastroscope</td>
<td></td>
<td></td>
<td>LR 140°</td>
</tr>
</tbody>
</table>

UD, up/down; LR, left/right.
Viscous substances are preferably used in ESD for creation of a longer persisting fluid cushion compared to submucosal saline alone. As using syringes alone for application is cumbersome, the viscous fluid, for example, hydroxy ethyl starch (HAES 6%) is applied by means of commercial 30 cc balloon insufflation pressure manometer (a, b). An electric pump with a foot switch can be a helpful accessory alternative for submucosal fluid injection (c).

Positioning of the patient for ESD
ESD procedures can be prepared like other interventional upper and lower GI interventions. However, they can be long-standing procedures and take hours in large lesions or in case of unexpected events. At least in Germany, ESD is so far not yet an established outpatient procedure. We like to carry out ESD procedures in a left lateral position in a modern hospital bed after adequate hygienic coverage. This seems a good prevention against any kind of compression damage under deep and long sedation and is not a hygienic problem. In single, very long-standing cases even a warming cover can be helpful (Figure 18.3). After the procedure, the patient recovers in this bed, which may be exchanged then in the ward. We found it helpful to cover the part of the bed close to the assistant with a sterile drape. This provides a good
place for a short deposit of instruments when rapid exchanges of instruments are necessary, for example, in case of hemostasis. The other accessories are better stored on a separate height-adjustable table for the assistant.

**Antibiotics and PPI**

See section "EMR".

**Pre-interventional endosonography (EUS)**

For EUs of suspicious or early malignant lesions in the upper GI tract and rectum EUS is still the gold standard in order to have a status quo concerning regional lymph nodes and depth infiltration of the lesion [41–45]. See also "Evaluation of the lesion."

**Transparent distal endoscope cap for ESD**

A special cap at the distal endoscope end serves as transparent "cage" and provides a safe workspace in front of the endoscope. Tissue is kept at distance by means of this atraumatic plastic cylinder, and instruments can be pulled back into this "safety zone" without damaging the working channel. When "diving" with the endoscope underneath the lesion during resection at ESD, the cap serves as important window for local orientation. During initial circumcision, the cap helps to keep a constant distance to the tissue surface and to prevent slipping of the needle-knife into the depth of the cutting rim. There are different caps according to the preferences of the endoscopist (Figure 18.8). The most universal cap is in our experience a short 4 mm soft cylinder cap (Olympus Optical, Tokyo, Japan) as used for zoom endoscopy. It provides a broad field of vision and does not substantially prolong the bending section of the endoscope. Alternatively, a longer oblique distal attachment cap can be used as described for capEMR (endoscope dependent No. 3 or 4 oblique, Olympus Tokyo, Figure 18.8). The advantage lies in the rounded distal end of the cap on the outside, enabling an atraumatic work at the resection base without mechanical irritation. Unfortunately, the inner rim of the cap has to be removed by a scalpel to prevent instruments from getting caught on the rim. The third option is a funnel-like cap that eases tunneling under the lesion during ESD (Fujifilm Medical, Tokyo, Japan). However, this needs some experience with the technique as the field of vision is restricted. As mentioned above, all caps should be fixed to the tip of the endoscope by means of sterile tape.

**Injection substances for ESD**

Different modes of tissue elevation can be applied. Aspects of needle injection and the correct technique are described above. A constant cushion formation with just a few injection sites is desirable in order to avoid a leakage of fluid through mucosal needle perforations ("shower head effect"). Furthermore, a deep penetration of the needle into the muscle with transmural (e.g., peritoneal) spillage should to be avoided. Submucosal injection is usually performed using a sufficiently large sclerotherapy injection needle (21 G = 0.7 mm diameter, 3–5 mm long; Figure 18.10). Contrary to a smaller 23G standard needle, rapid injection of even large quantities of fluid becomes possible for the deposit of a sufficiently high local cushion, preventing escape of the fluid to the periphery. There is little experience with the use of a 19G (1 mm) needle. Although feasible in our experience, a leakage of fluid from needle perforation sites in the mucosa is disadvantageous. Furthermore, it is unclear whether initial excessive local pressure in the submucosa may lead to a transmural escape of fluid through muscle gaps.

**Needle injection for tissue elevation**

Conventional resection knives (Figure 18.11)

First ESDs had been performed with standard needle-knives often attached with tape on the distal end of the endoscope, leaving the instrumentation channel free [59,60]. A big step ahead was the development of the so-called "isolated tip knife" (IT knife) at the end of the 1990s (Olympus Optical, Tokyo, Japan) [19]. The advantage over a standard needle-knife was the protection of the muscle layer from the needle tip during dissection. A further development is the IT2-knife. The "IT2-knife" is equipped with an only hemispherical isolated white tip with...
Figure 18.10 Gastric ESD procedure supported by the use of an electric roller flush pump (Fujifilm, Tokyo, Japan). (a–c) After initial lifting of the lesion using a 21G standard needle connected to the pump, the fluid cushion can be re-established during the procedure by pressing the flush-knife catheter into the submucosa and subsequent pump activation.

"Mercedes"-star-like metal base with better lateral resection capabilities (Olympus Optical, Tokyo, Japan) [61,62]. The "hook-knife" is a miniature version of laparoscopic surgical hook-knife and can be rotated by the assistant. Resection of the mucosa as well as dissection of the submucosa is achieved by first "hooking" the tissue and then transection it by electrocautery. The assistant can steer the direction of the hook at the handle. This resection technique is considered the safest, for example, for resections in the colon and esophagus but probably also the most time consuming [63]. The flex-knife, developed by Yahagi, consists in a miniature monofilament snare resembling a broad nose at the tip of the Teflon catheter [18,64,65]. The triangular knife tries to combine hooking capabilities and enforced by means of a small triangular anchor at the tip of the knife [66]. To be mentioned also is the "dual-knife" (Olympus Optical, Tokyo, Japan) developed as along with the flex-knife by Naoshiya Yahagi, one of the pioneers in the field of ESD. The knife has a drop-like distal end, which allows easier coagulation of vessels and reduces the risk of a sharp damage to the muscle layer.

There is a little truth in the sentence "every expert has his own resection knife" as efficiency using a resection tool is closely related to personal experience. To that end, it is reasonable for trainees to gain exposure to a variety of available instruments during the early animal tissue work phases of training.

Resection knives with integrated fluid injection capability

Water jet technology and "hybrid-knife" (Figure 18.11)

In open surgery, a so-called "water-jet" technology is known over years but plays only a minor role today in surgical organ resection [67–72].

Within the last few years, this technique has been rediscovered for flexible endoscopy by many due to work by Kahler, Yahagi, Neuhaus, and Enderle [64,73,74]. Via an only 0.9-mm wide polyamide catheter (the "capillary"), creation of a submucosal fluid cushion is possible. The capillary does not even have to penetrate the submucosa. It is rather sufficient to just gently place it on the mucosal surface. By activation via a foot pedal, a pressure-controlled electronic pump drives the fluid through the catheter at a pressure of up to 100 bars. The just 60 μm wide flow penetrates the mucosa but is captured at the level of the submucosa as disruption of the muscularis propria would require much higher pressures than penetration of mucosal or submucosal tissue [75]. The system is integrated in a central bore of a needle-knife catheter and the device is called "hybrid-knife" (Erbe Elektromedizin, Tuebingen, Germany) [73]. This allows to elegantly first create a submucosal fluid cushion at a defined pressure and to then use the needle-knife as an electrosurgical tool for circumcision and dissection. Intermittent submucosal
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Figure 18.11 Eight different ESD cutting knives are shown. The IT Knife (a), Dual Knife (b) and Hex Knife (c) show an isolated respectively broadened tip to reduce the risk of inadvertent penetration of the knife. The Hook Knife (d) and Triangular Tip Knife (e) are used for ‘fishing’ and traction of submucosal fibres towards the knife before cutting them through which is considered a safety factor. The same is true for the Flush Knife (f) and the Hybrid Knife (g) which allows intermittent fluid injection for flushing of debris and re-establishment of the necessary submucosal fluid cushion during resection. The Mucosetome (h) somewhat resembles a mini-papillotome.

reinjection is simple. Disadvantages of the system are so far costs and the fact that this is a bit stiffer catheter compared to standard instruments. First preclinical and clinical results are promising [64,74,76,77].

Flush-knife

The so-called “flush-knife” (Fujifilm, Tokyo, Japan) is an interesting alternative to the hybrid-knife and consists of two components. The needle-knife itself exists in different lengths from 1 to 4 mm available in 0.5 mm graduations. We use exclusively the 1 and 1.5 mm knives. The chrome-plated needle is contrary to the hybrid-knife rounded at its tip and has a supple Teflon catheter with a broad base of 2.7 mm compared to the short nose of the knife. This gives a nice guideway during circumcision, reducing the risk of deeper penetration of the knife during circumcision like a jigsaw [78]. For rectum, esophagus, and colon, we use mostly the 1 mm knife, and for the stomach, we use the 1.5 mm knife [78]. The short length and rounded tip of the knife is responsible for the high safety and precise dissection of the knife. The flush-knife comes together with a roller pump activated by a foot switch and variable in rotation speed (Figure 18.10). A side connection at the level of the handle allows to couple-in fluid that is directed to the catheter tip. Pressing the catheter intermittently into the submucosa and activating the pump rebuilds effectively a decreasing
fluid cushion (Figure 18.10). However, initial conventional needle injection is advisable in our experience. Activating the pump intermittently also helps to better identify bleeding sources at the resection base with only limited flushing volume compared to flushing with the endowasher through the endoscope itself. An advantage of the flush-knife/pump combination is the reasonable price. A direct comparison of flush-knife and hybrid-knife does not exist yet.

The “ball-tip flush-knife” (Fujifilm, Tokyo, Japan) is needle-knife similar to the flush-knife with a broad catheter and short knife that is enlarged at the tip to a ball for better coagulation and questionably a reduced perforation risk. However, this may be at the cost of the very fine and clean resection capabilities of the original straight knife.

**Electrosurgical settings**

Concerning electrosurgery, there are big variations as well in the literature in regard to the settings used. While circumcision is mostly performed with a pure or blended cutting, current dissection is, at least in Japan, often carried out with pure coagulation current. Electrosurgical settings vary for different accessories and may not be comparable for generators of different companies.

We use a “VIO 300” generator (Erbe Elektromedizin, Tübingen, Germany) in combination with a 1 mm flush-knife (Fujifilm, Tokyo, Japan) for the circumcision with the following settings: “Endocut Q,” pulse duration 1, pulse length 1, effect 2 or 1. For coagulation with this knife, “Swift Coag” 30 W. For dissection under a strongly vascularized lesion, for example, in the distal rectum, “Forced Coag” 50 W setting 2 is often well suited. By changing

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**Figure 18.12** Steps of endoscopic en bloc resection using submucosal dissection technique (ESD). (a, b) A large, 8 cm × 6 cm, laterally spreading tumor in the mid and upper rectum is shown from a prograde and retroflexed position (LST-NG type; Paris IIa+c, tubulovillous adenoma with multifocal HG-IEN). (c) After circular marking of the lesion with small coagulation dots, injection of a large 300 cc fluid cushion helps to establish a more than 1 cm submucosal fluid cushion as safe dissection plane. Figures (d)–(i) show the stepwise ESD resection process preserving a single specimen until reaching the upper end of the subtotal circumcision of the lesion. (continued)
between cutting and coagulation current, a smooth resection is possible with effective coagulation of vessels up to 1 mm and rapid dissection using just one knife. Using a "coagulation forceps" (e.g., "Coag Gaser," Olympus Optical, Tokyo, Japan) with a larger contact area, a higher power setting may be necessary (e.g., "Soft Coag," effect 5, 30–60 W). It is important to keep always in mind that excessive coagulation may lead to late necroses even after 24–72 hours with secondary perforation. Basically, a stepwise testing of the coagulation capabilities of one’s own generator seems essential, and it is always helpful to take some time to compare coagulation depth of different instruments at various settings on a piece of meat, for example, beef or pig liver, even though this cannot be directly transferred to "in vivo settings." The trainee needs to understand the general principles of electrosurgical generators, a topic covered in detail in another chapter in this book and become well versed in the specific settings required for dissection and coagulation of bleeding vessels.

Using the 1–1.5 mm flush-knife at the abovementioned settings, we do not use any coagulation forceps anymore. In case of big vessels, we carefully start fulgurization at a distance of 1 mm from the vessel and close to the overlaying lesion as the vessel will shrink. If after shrinkage of the vessel this has to be performed at a distance too close to the muscular layer, and if one has to continue to coagulate due to ongoing bleeding, then retraction of the vessel into the muscular layer or creation of a coagulation defect in the muscle layer may occur. To avoid this, a short-arm (green or yellow) hemoclip should be applied at the penetration site of the vessel at the muscular layer.
Novel dissection tools are in preclinical and first clinical testing, such as flexible "Maryland Dissector," which applies gentle mechanical lateral force by opening its long jaws similar to the same named surgical tool. It may as well be used for the application of the electrocautery of vessels [79]. Other instruments and devices tested are, for example, submucosal balloon dissection or an automatic submucosal circumcision ("Circular Cutter," Apollo Endosurgery, Austin, TX, USA). These developments, which introduce traditional surgical techniques and principles into the realm of luminal ER, may be an indicator of trends leading in the not too distant future to the entity of the *Endoscopic Interventionalist*, a new hybrid endoscopic specialist who encompasses the skill sets of today’s traditional gastroenterologists and minimally invasive surgeons [80–82].

### Procedural steps of endoscopic submucosal dissection (Figures 18.10; 18.12–18.15)

There is a big variety of ESD techniques depending often on the individual preferences of the physician and personal level of expertise. There are common features of the technique such as marking of the lesion, creating a preferably stable submucosal fluid cushion, circumcision of the lesion outside the safety zone, and markings and separation of the mucosal layer from the muscularis propria at the level of the submucosa in a single piece. ESD is therefore composed of a sequence of different steps:

1. Identification and marking of the lesion with a sufficient lateral safety margin
2. Submucosal injection and tissue elevation
3. Circumcision of the lesion

![Endoscopic mucosal resection and endoscopic submucosal dissection](image)

*Figure 18.13* Endoscopic “en bloc” resection in submucosal dissection technique (ESD) of a wide spread flat polyp in the distal rectum reaching down the anal channel to the dentate line (a). Injection of lidocain 1% at the dentate line as well as repeat large-volume submucosal needle injection of an HAES 9%epinephrine/indigocarmine blue solution (b–g) under the proximal lesion is effected before and during the resection process in combination with an IT2 knife (Olympus Optical, Tokyo, Japan) (h). (continued)
Figure 18.13 (Cont.) Resection site with about 60–85% of the circumference resected in the distal rectum and anal channel over the hemorrhoidal plexus (j, k, l). Macropathologic and histopathologic aspects of the 7.7 cm × 3.6 cm specimen showing a tubulovillous adenoma with LGD (m, n). Resection site 6 months after resection with a white scar (o, p). Massive shrinkage of the formerly large resection area to about 1.5 cm × 1.5 cm with clips in situ can be seen with compensatory extension of the remaining healthy mucosa due to the storage function of the rectal ampulla. This would not have taken place with a 100% circular resection without retaining healthy mucosa.

4 Submucosal dissection, “en bloc” removal and subsequent retrieval of the lesion
5 Careful hemostasis and prophylactic occlusion of vessels at the resection base
6 Preparation of the specimen for histopathologic evaluation.

Submucosal injection
See p. 218 section ‘Needle injection for tissue elevation’

Circumcision
Care should be given that even distant parts of the lesion are sufficiently lifted by submucosal injection before proceeding to circumcision. One can imagine that with point-shaped needle injection, the fluid distributes in a circular or oval shape. To sufficiently reach and elevate the center of the lesion from an injection at the level of the peripheral markings, the same area will be lifted in a centripedal direction. Japanese carefully avoid central needle perforation of the tumor in order not to potentially seed tumor cells into the depth, therefore, to the submucosa or even to the muscularis propria.

After complete elevation of the lesion, one should uninterruptedly proceed to circumcision. It is advisable to start circumcision always at the most difficult part of the lesion, which is often the most distant one. In the ano-rectum, it is often the cranial and left-lateral side of the lesion. The importance of the markings is usually realized when it comes to circumcision. The cut is performed about 1–2 mm outside the markings. Placing the endoscope gently on top of the elevated mucosa with the transparent cap, the field of vision is often that close to the mucosa one will only see the next marking point as pathfinder for the right direction and to
Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

avoid to get lost toward the periphery or worse toward the lesion. Circumcision should be in every case be completed before one proceeds to submucosal dissection, even if there is often a nice bulging of the isolated central mucosal island, having performed only part of the circumcision. Otherwise, one risks to undermine the lateral margins under-tunneling the specimen with incomplete circumcision, or one has difficulties to free the specimen at the end due to a lack of submucosal fluid cushion at the end of the dissection. Often, it is necessary to circle a second time around the circumcision in order to completely transect tissue bridges.

A lateral submucosal dissection of the “normal” surrounding peripheral mucosa for about 5 mm helps to nicely form a broad rim at the circumcision as the freed mucosa tends to retract due to contraction of the muscularis mucosa after liberation from the submucosa. Care should further be given that the fluid cushion is not too much depressed by the cap and force of the endoscope. This may result in a superficial cut into the muscle layer. The shorter the knife is and the broader the catheter, the less is the risk of damage when using a needle-knife. We usually perform circumcision with the 1 mm flush-knife in the distal stomach with the 1.5 mm flush-knife at the EC settings described above. An alternative concerning safety is the use of a hook-knife.

Submucosal dissection

Before switching from circumcision to submucosal dissection, it is often considerable to first reinject in order to have an optimal circumferential resection was performed using a 1.5 mm short resection knife (Flush Knife, Fujifilm, Tokyo, Japan). (f–j) After marking and repeat submucosal injection, a U-shaped circumcision was performed including a 1 cm safety zone at the proximal and distal ends of the Barrett’s segment. (continued)
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Figure 18.14 (Cont.) (k-n) Step submucosal dissection from cranial to caudal with a clean resection base at the end. (o) Esophageal resection specimen pinned on cork histopathologically confirmed the initial diagnosis (multifocal HG-IEN; R0 within specimen). Local status after 3 months with a circumscript residual Barrett’s area (p), and after 6 months with complete removal (q).

Fluid cushion. Submucosal dissection is carried out in parallel to the mucosal layer often in a semilunar fashion. Vessels have to be respected and are better first coagulated than cut through with secondary coagulation. Depending on the diameter of the vessel, this is best be achieved by:
- Switching the foot pedal from “cut” to “coag” current
- Withdrawing the knife and switching to a coagulation grasper
- Placing a short-arm clip close to or at the exit of the vessel from the muscular layer.

The latter is usually avoided because of a possible accidental mechanical removal of the clip by the endoscope. Furthermore, the metal of the clip is conductant and the clip impairs vision and free maneuverability of the endoscope. Last but not least, the clip has later to be removed in order to get a “clean” scar for further follow-up inspection and biopsies.

After a short course of 7–10 mm, the lesion can be lifted and tunneled by the cap. This helps to stretch the submucosal tissue and ease resection. The function simulates traction forces applied during “triangulation” in laparoscopic surgical dissection.

Retrieval of the specimen
Attention should be paid especially in large resections not to destroy the specimen during retrieval. This is especially the case for large specimen in the stomach or rectum. In the rectum, this can be facilitated by first removing the flexible endoscope and introducing a rigid proctoscope for adults (e.g., 16–18 mm). After removal of the obturator, the proctoscope is held by an assistant and the flexible endoscope is reintroduced via the proctoscope. The specimen can now be pulled into the proctoscope and can be easily removed. For retrieval, a large braided snare or a stone extraction basket can be using moderate force at the handle when closing.

In the stomach, retrieval of big specimen can be facilitated by first introducing a flexible overtube (US Endoscopy, Mentor, OH; Figure 18.14). The specimen is first stretched and about 1/3rd grabbed by a snare. Removal of the specimen is then performed with slow and constant traction, fixing the catheter at the level of the instrumentation channel cap. The specimen is then first put temporarily in a recipient with sufficient saline (e.g., a metal basin accommodating 250–500 cc of saline).
Figure 18.15 Limits of endoscopic resection at the gastroesophageal junction. (a): Widespread "en bloc" resection using ESD of a 3 cm early cancer Siewert Type II extending to the distal esophagus and proximal stomach in a patient repeatedly refusing surgery. In analogy to the case in Figure (a), a 16.5 cm × 10 cm specimen is resected including 7 cm of the tubular esophagus, the cardia and proximal stomach (c–i). (continued)
Inspection of the resection base and occlusion of vessels
Careful inspection of the resection base should be performed directly after temporary deposit of the specimen in saline. Protruding resected vessels, sometimes still pulsating, should be checked for sufficient occlusion. In doubtful cases, coagulation with a coag grasper or clip application in vessels of more than 1.5 mm is advisable.

Preparation of the specimen for histopathologic evaluation
After a short immersion in saline, the specimen is pinned on cork. A pair of splinter tweezers as used in hand surgery and conventional fixing pins are well suited for this purpose, if not available usual 21 G cannulas (Figure 18.16). Cork as used in pin boards does a good job for this purpose. A rectangular piece of cork about 1 1/2 to 2-folds, the size of the estimated ER area, is cut from the board and placed on a disposable underlay. At first, the specimen is orientated with the epithelial surface upward. Pinning is performed about 1–1.5 mm from the margin, holding the specimen at the border with the tip of the forceps and avoiding damage by excessive compression. After the first pin is placed, the specimen is not (!) stretched out, placing the next pin at the opposite side, as this would lead to a disruption of the margins and impaired histopathologic evaluation. The margin of the specimen is instead caught about 5 mm away from the first needle and pulled laterally. The second fixation pin is placed 2–3 mm at the side of the first one. This way the whole specimen is stretched out like a tambourine (Figure 18.16.d). As the next step, the size of the specimen, if possible also of the lesion should be determined and documented. We found it the most hygienic way to use a pair of stainless steel compasses with locking possibility and to first determine the greatest longitudinal diameter. This distance is then transferred from the compasses to a metal ruler as used for engineering drawings and the size read off. The same is done for the largest perpendicular diameter. We usually perform then a photo documentation of the specimen with a ruler at the side. For fixation and transportation, the specimen is then placed upside-down in a recipient filled with usual buffered formalin 4%, the way it swins on the surface. Excessive cork material can be shortened before if necessary by a pair of scissors or a scalpel, avoiding getting injured by the needles. The piece of cork with the pinned specimen is slightly kept under water, charging it with a second cork plate or cork surpluses on top. The recipient is then covered at least by a stretched latex glove in case the lab is next door or safely sealed for further transportation (Figure 18.16.e).

In addition to standard histopathological documentation, the pathologist should be asked for macropathologic documentation, and in the case of submucosal infiltration of a tumor, the pathologist needs to report the precise vertical infiltration depth in microns.

**Post-EMR and post-ESD management**

**Control endoscopy**
We routinely inspect resection bases the next day after upper GI ESDs even in asymptomatic patients, for the purpose of detecting bleeding or other complications. However, first analyses indicate that this practice might be unnecessary [83].
Figure 18.16 Tools for adequate preparation of a mucosal specimen for histopathology: the specimen should be spread out and pinned on cork in order to facilitate lateral evaluation of the resection margins. A pair of splinter tweezers (a) is used in hand surgery and conventional fixing pins (b) are well suited for fixation of the specimen on a piece of cork. The pins are applied one-by-one in a circular fashion to avoid laceration of the specimen (see text) (d). A pair of compasses (c) is well suited to transfer the size of the lesion to a metal spacer (e). The lesion is then placed upside-down into a robust recipient with formalin for transfer to the pathologist. The fixed specimen shows a broad lateral safety zone important for histopathological evaluation (f).
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(a) (b)

Figure 18.17  (a) An over-the-scope clip (OTSC; Ovesco, Tuebingen, Germany) can be helpful salvage tool in ESD.

Risk of secondary bleeding

In case of a clinically uneventful procedure and postinterventional course, a second-look endoscopy is usually not necessary after EMR in colonic lesions. For EMR in the esophagus and stomach, it may clearly depend on the complexity of the procedure. However, as in ulcer hemostasis, a second look endoscopy might be unnecessary [83]. A recent retrospective analysis after ER of 434 gastric epithelial neoplasms (386 early gastric cancers and 68 gastric adenomas) showed an overall postinterventional bleeding rate of 5.7%. However, 2.8% and 2.5% occurred before or after a scheduled second day gastroscopy. All cases occurred within 14 days after the procedure.

Peri-interventional antibiotics and PPIs

Peri-interventional antibiotics are not routinely administered or supported by any data [84–86]. However, in complex procedures and in case of suspected intercurrent perforation or microperforation, an antibiotic prophylaxis should be given [85,87]. Established substances are a second- or third-generation cephalosporine (e.g., ceftriaxone 2 g/3 × die i.v.) plus metronidazole (3 × 500 mg i.v.) or ampicillin plus sulfadactam (e.g., 1g plus 0.5 g, 3 ×/die i.v.). The duration has to be decided on the clinical course and ranges from 1 to 5 days. We routinely place patients undergoing upper GI ESD on PPI medication to prevent delayed bleeding. Data supporting the role of PPI is limited.

Management of complications

Acute procedure-related complications

Procedure-related complications are defined as being clinically evident within 1 week after the procedure. Complications in total are rare but are more frequent in ESD than in EMR. The most common ones are bleeding, perforation, and sequelae associated with perforation. Sequela of open or covered perforation may be air leakage and infection. Gastric perforation is often associated with pneumoperitoneum and peritonitis, duodenal perforations often with retroperitoneal emphysema, and secondary peritonitis. Biliary leakages due to perforations in the second or third part of the duodenum are feared by surgeons. Other intrainterventional complications may involve cardiorespiratory depression (hypotension, arrhythmia, hypoxemia) and may be procedure- or sedation-induced.

Perforation

The incidence of intrainterventional gastric perforation ranges from 1–6% in gastric ESD and is described in a much lower percentage in gastric EMR (0.2%), maybe due to smaller lesions resected endoscopically at the time of EMR compared to nowadays.

Minami et al. from the National Cancer Center Hospital in Tokyo, Japan, followed 121 of 2460 patients (4.9%) who underwent gastric EMR between 1987 to 2004 with perforation during the procedure [88]. The initial four patients were treated with emergency surgery, the subsequent 117 patients with endoclips. Endoscopic closure with endoclips was successful in 115 patients (98.3%), only two patients had to undergo emergency surgery. Patients with perforation during gastric EMR treated with endoscopic closure had a recovery rate similar to that of the nonperforation cases. The authors conclude that gastric perforation during ER can be conservatively treated by complete endoscopic closure with endoclips in the hands of experienced endoscopists [88]. A new promising tool is the so-called "Over-the-scope-clip" (OTSC, "Bear-Trap", Ovesco Tuebingen, Germany; Figure 18.17) [89,90–93]. The nitinol macroclip comes already mounted on a transparent plastic cylinder and is fired similar to a variceal band ligator. However, the perforation site is actively pulled into the cylinder by means of grasper forceps as aspiration alone would be inefficient due to the air leak within the defect. First clinical applications for perforation closure, severe bleedings, and chronic fistulae are promising [94–96].

Hemorrhage- and procedure-related mortality

With the development of more aggressive interventional techniques in between traditional GI endoscopy and minimally invasive surgery such as ESD and NOTES, hemorrhage needs a
Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

Figure 18.18  (a–i) WHAT NOT TO DO: Difficult piecemeal snare resection of a flat rectal polyp (LST-GT) as one of the main causes for a later local recurrence into or aside a scar. This situation should be avoided especially in lesions at elevated risk for HG-IEN or mucosal cancer such as rectal polyps larger than 3 cm.

Late and secondary complications

Stricture formation

When more than 75% of the circumference is resected in a tubular GI structure, especially in the esophagus, pylorus, sigmoid, or anus, secondary stricture formation may occur (Figure 18.14 m) [103]. Stricture formation often initiates between 10 and 20 days after resection. However, at least in our opinion, an individual’s tendency to stricture formation plays a relevant role. Treatment consists of balloon dilation or bouginage and should be started early as soon as tissue retraction starts to become symptomatic. A sufficient diameter of 18–20 mm should be sought. In the case of esophageal strictures placement of a temporary self-expanding covered metal stent after the first bouginage sessions is a possible treatment alternative [47,104,105].

new definition. Acute bleeding during ESD cutting through a vessel due to insufficient coagulation cannot primarily be regarded as complication unless it cannot be treated endoscopically comparable to a surgical ligature during an operation. Only bleedings that cannot be stopped or hemorrhages with a consequent drop of hemoglobin more than 2 g/dL in addition to patients with relevant clinical signs of acute hemorrhage (shock, hematochezia, etc.) should be considered to be a complication. Data from large multicenter studies from Japan or South Korea including over 1000 patients are unfortunately all of retrospective nature [97–101]. Acute and delayed bleeding rates given are between 0.5% and 15.6% for acute bleeding during the first 48 hours and the same for delayed bleedings occurring at the most within the first 14 days after the procedure. In three large trials, cited procedure-related mortality was 0% [99,101,102].
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When to use EMR and when ESD?

This question has to be answered individually and no general rule is applicable. In case of a known or suspected malignant lesion, transection of the tumor should be avoided and “en bloc” resection for adequate histological evaluation should clearly be favored. Furthermore, a clearly lower local recurrence rate favors ESD over EMR even in benign lesions. However, ESD is still a new technique in the “Western World” and not yet a standard. We will have to learn it step by step and will have to take care that proper training is provided [106] (Figure 18.18).

Training and first steps in ESD

At present, endoscopic skills are mostly acquired under supervision by an experienced colleague while examining a patient. The usual method of teaching is similar to that of a craft apprenticeship. The trainees start gradually, at first only observing the examination and the handling of the equipment by the endoscopist and assistance. More complex procedures follow simple ones starting, for example, with gastroscopy, recto-proctoscopy, and colonoscopy. First interventional procedures include, for example, PEG implantation, then polypectomy. This kind of clinical learning we described in the past as a “learning pyramid” (Figure 18.1) [21–24,82].
Learning certain new techniques in the course of clinical practice as opposed to during formal fellowship training may be possible. However, it requires a very slow approach in multiple little steps under close clinical surveillance. Under the pressure of maximized efficiency in today’s clinical medicine, this way of learning is often not very realistic anymore. This may induce several consequences. Or, there is no real change in skills acquisition over years and an endoscopist, for example, working in private practice will just continue to perform procedures as he learned them during his clinical training at the hospital for the rest of his professional career. The second extreme is that one sees a new technique in advertisement or heard from a colleague about it and just orders the kit and tries it for the first time in the next more or less suitable case. The slightly nicer version is to see it during a live video transmission and to do it for the first time with assistance of the local sales representative. The best practical setting is to visit a department with a high frequency in the specific procedure and see it performed in the morning and train it in an EASIE simulator in the afternoon under the guidance of an experienced endoscopist for several days (Figure 18.19). Any therapeutic intervention a learner may approach in endoscopy should at the same time be accompanied by a training program on how to manage unintended outcomes and complications. Main complications in any ER technique are bleeding and perforation. Training in EMR and ESD will therefore always has to include hemostasis training. The degree of skill and expertise and amount of time required to gain necessary proficiency for such complicated and high-risk procedures as ESD make it extremely difficult to pick up in the course of a busy practice without a concerted effort and devotion of considerable time to the endeavor.

Systematic training studies for ESD do not exist so far up to our knowledge. We are currently registering the learning curves in ESD for ESD-novices of different prior levels of experience. We think that training in ESD includes obviously building up a sufficient theoretical background of the procedure and starting with the resection of a defined area of tissue in a pig stomach “in vitro” in the EASIE simulator. The next step is “in vivo” resection in the stomach of live pigs. Parallel first clinical steps are made beginning with marking the surrounding of the lesion carefully with APC dots at a distance of 2–3 mm from each other and from the lesion plus submucosal injection. The next step after at least 10 successful ESDs in the simulator without perforation is to perform short sections of circumcision under supervision. Training in the pig stomach and animal model should continue while first sections of dissection and complete circumcision in the patient are performed under supervision. This means that an experienced colleague is in the room and acts, for example, on the computer with intermittent following of the procedure and immediate intervention in case of problems. Japanese say that it takes about 100 ESDs before an ESD-novice has gained sufficient experience and has reached a satisfying speed for most standard situations. ESD is performed probably with the lowest risk in the gastric antrum to the greater curvature or anterior/posterior wall. Also, the distal rectum is a good location to start with. However, the distal rectum below the peritoneal fold is just theoretically without risk. We find that it requires most attention to not damage the wall and to occlude even small defects immediately in order to not risk free air in the surroundings and pain or fever of the patient. It should be emphasized that the width of the fluid cushion and the shortness of the needle-knife are important safety factors. The less experience one has, the shorter the knife should be, in our eyes preferably a 1 mm “flush-knife” and a large cushion of hydroxyethyl starch should be used.

As emphasized above, for the future structured training courses at expert centers including a clinical demonstration of the technique in the morning and lectures and “hands-on” training in pig stomach models and finally animal training as step 2 should become mandatory for a safe introduction of this fascinating technique in the Western world.

Conclusions and perspectives

EMR has developed to a standard technique for the removal of laterally spreading premalignant polyps in the Western world and has changed from an experts-only technique to one of the essential techniques to train after diagnostic gastroscopy/salmoneoscopy and parallel to or right after hemostasis techniques. ESD is currently the experts-only technique and will probably remain for the next years as it requires a high level of manual dexterity and experience in complication management as well as the oncologically correct treatment of early malignant GI lesions. The learning curve of ESD in the Western world is not known yet. However, growing experience in the West as well as in its locus of origin Japan and recently Korea will lead to far steeper learning curves. New developments as short-knife allowing injection and resection at the same time will further reduce resection times and complication risk. Special cases and locations of ERs have been described, such as ESD in the pharynx and hypopharynx or in the common bile duct on the percutaneous transhepatic route with special instrumentation [23,26]. ESD is a fascinating technique as is its concept of “en bloc resection” as oncologically correct treatment for high-risk or early malignant lesions is with no doubt convincing. Proper training will be one of the key issues for a successful spread of this promising technique.

Nonstandard Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>APC</td>
<td>Argon plasma coagulation</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DBE</td>
<td>Double-balloon enteroscopy/enteroscope</td>
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<tr>
<td>EC</td>
<td>Electrocoagulation</td>
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<tr>
<td>EGD</td>
<td>Endoscopic gastroscopy/dual endoscopy</td>
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<td>ESMR</td>
<td>Endoscopic mucosal resection</td>
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<tr>
<td>ESD</td>
<td>Endoscopic submucosal dissection</td>
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<tr>
<td>EUS</td>
<td>Endoscopic ultrasound</td>
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<tr>
<td>FAP</td>
<td>Familial adenomatous polyposis</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
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<tr>
<td>HG-IEN</td>
<td>High-grade intraepithelial neoplasia (synonymous to “high-grade dysplasia”)</td>
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<tr>
<td>HR</td>
<td>High resolution</td>
</tr>
<tr>
<td>LG-IEN</td>
<td>Low-grade intraepithelial neoplasia (synonymous to “low-grade dysplasia”)</td>
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MRI Magnetic resonance imaging
NOTES Natural orifice transluminal endoscopic surgery
PEG Percutaneous endoscopically controlled/assisted gastrostomy implantation
PPI Proton pump inhibitor
sm Submucosal

Videos

Video 18.1 Key principles of successful cap EMR technique
Video 18.2 Endoscopic submucosal dissection
Video 1.3 Use of simulator to teach what not to do: improper submucosal lift in EMR leads to perforation on purpose
Video 23.4 Closure of gastrointestinal perforations
Video 30.1 Ampulectomy
Video 30.4 Management of immediate bleeding during cap EMR
Video 30.5 Detection and endoscopic management of mucosal tear complicating upper endoscopy

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Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection


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