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REVIEW

Technological review on endoscopic submucosal dissection: available equipment, recent developments and emerging techniques

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ABSTRACT
Endoscopic submucosal dissection (ESD) is widely practiced in Japan and the Eastern World and is rapidly expanding in western countries for the management of early malignancies of the upper and lower gastrointestinal tube. In addition, novel therapeutic applications deriving from ESD have emerged including the treatment of achalasia, of submucosal tumors, of diverticula, of strictures and of reflux disease. An ESD procedure necessitates not only skills and specific training, but also familiarization with a vast spectrum of devices (endoscopes, high-frequency generators and their settings, endoknives, hoods, irrigation devices) and techniques (such as countertraction, artificial ulcer closure), that render the procedure faster, more efficient and safer. This technological article gives an overview on current and novel equipment for an ESD and associated techniques.

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Introduction

Endoscopic submucosal dissection (ESD) is widely practiced in Japan and some Asian countries as a minimal invasive modality for 'en bloc' resection of superficial malignancies of the GI tract. Indications are early cancers exceeding 10 mm and widespread premalignant lesions in order to achieve a complete histo-pathologic analysis and reduce local recurrence to a minimum. The choice of suggesting an ESD treatment depends on several parameters such as the macroscopic aspect, the 'lifting' of the lesion, after submucosal injection, and the evaluation by means of high-resolution ultrasound. However, the value of this later modality in local staging had been overestimated in the past. Only the exact analysis of the resected specimen gives accurate information of the depth of infiltration, as well as of the lymphatic and vessel involvement. Additional treatments such as surgical resection or chemo-radiation have to be considered in a global setting and discussed in an oncology meeting. In an effort to further define which lesions are suitable for ESD, the European Society of Gastrointestinal Endoscopy (ESGE) recently published guidelines [1]. Consequently, partial or complete reimbursement of ESD procedures has been achieved in several European countries such as Germany, Belgium and Italy. However, the learning curve for ESD is long, making systematic training necessary [2]. In addition, ESD-derived techniques including endoscopic esophageal myotomy (POEM), submucosal tunneling endoscopic resection (STER) and laparoscopic endoscopic cooperative surgery (LECS) have broken the boundaries between medicine and surgery and are rapidly evolving into areas beyond the GI lumen. This paper gives an overview of recent procedural and technological developments in the field.

Equipment

Injection agents

Various liquids have been used for lifting. Hyaluronic acid solution (MucoUP, Johnson and Johnson, Tokyo, Japan) creates a long-lasting submucosal cushion. However, due to its high cost, it is not widely used. Another commonly used agent in Japan is Glyceol (Chugai Pharmaceutical, Tokyo, Japan), which consists of 10% glycerol and 5% fructose in normal saline, combined with a small amount of sodium hyaluronate. Hydroxypropyl methylcellulose ('artificial eye drops'), hydroxyethyl starch (Voluven[R]) and modified gelatin plasma substitutes (Geloplasma[R], Gelofusine[R]) are relatively inexpensive solutions, mostly used in non-Asian studies. Normal saline is inexpensive, and universally available, but the lifting is of short duration in the range of only 5 min, compared to, e.g., hydroxyethylic starch, with about 30 min

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mean elevation time [3]. NaCl 0.9% is commonly used with the Hybrid Knive (ERBE Elektromedizin, Tuebingen, Germany) due to the possibility of fast and repeated injections, as necessary. A small amount of Indigocarmine 0.2% (0.5 ml in 500 ml of solution) should be added to the injection solution, in order to better delineate the submucosal plane. For lesions close to the dentate line, lidocaine (1%) or ropivacaine (75 mg) [4] is added to the solution for local anesthesia.

Irrigation of the dissection plane

A water pump is an indispensable accessory since irrigation of the bleeding permits faster and accurate coagulation. The waterjet pump is connected either to the jet channel of the endoscope, to a modified valve at the biopsy channel or to a modified irrigation hood (Type KUME, Create Medic, Japan).

Lately, newly developed endoknives provide a multipurpose jet function designed for irrigation of the tip of the knife, of the operation field and for submucosal injection. In this case a second water pump can be connected to the accessory channel of the knife. However, if a second pump is not available, then a single pump may be used for both functions, by adding a three-way port.

CO_2

Insufflation with CO_2 has become a prerequisite for most ESDs, allowing the use of fewer sedative medications and reducing the risk of compartment syndrome following perforation. CO_2 is strictly obligatory for POEM and STER procedures.

Hood

A transparent hood facilitates visualization during dissection by keeping the field 'open' during dissection. In addition, transient compression of a bleeding vessel can help during hemostasis. The choice of the hood depends on the diameter of the endoscope, the location of the lesion and endoscopist's preference. Attention should be paid to ensure that the cap is fixed tightly at the tip of the endoscope and if necessary stabilized with a sterile tape.

Endoscopes

Tables 1 and 2 present different endoscopes often used for ESD. The morphology of the lesion, its location, the type of endoknife, and the bleeding risk, influence the choice of instrument. The ideal endoscope should possess a high-definition image with close focus and magnification for easier determination of lateral margins and better characterization of the microvascular pattern. A large biopsy channel (>2.8 mm) is preferred by some endoscopists, since aspiration of blood or water becomes easier. A potential disadvantage of a large channel is the loss of precise control of instruments (e.g., endoknives, forceps) with small caliber due to inadvertent movement. Finally, a water jet channel is undoubtedly desirable for cleaning of oozing and debris

Table 1. Technical characteristics of gastroscopes suitable for ESD procedures.

Manufacturer	Olympus	Olympus	Olympus	Olympus	Pentax	Pentax	Pentax	Fujifilm	Fujifilm	Fujifilm
Model name	GIF-HQ290	GIF-HQ190	GIF-1TH190	GIF-2TH180	EG27-i10	EG29-i10	EG-3890TK	EZ-600ZW	EG-580RD	EG-530D
Field of view (degrees)	140	140	140	140	140	140	140	140	140	140
Depth of field (mm)	3–100	2–100	2–100	2–100	2 –100	2–100	4–100	1.5–100	3–100	3–100
Biopsy channel(s) (mm)	2.8	2.8	3.7	2.8/3.7	2.8	3.2	2.8 and 3.8	2.8	3.2	2.8/3.8
Angulation range (degrees)										
Up	210	210	210	210	210	210	180	210	210	210
Down	90	90	90	90	120	120	120	90	120	90
Right-Left	100	100	100	100	120	120	120	100	100	100
Distal end diameter (mm)	10.2	9.9	10	12.2	9.2	9.9	12.8	9.9	9.8	11.5
Water-jet	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Close focus	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Manual Zoom	Optical	Optical	No	No	No	No	No	Optical	Digital	No
Chromoendoscopy	NBI	NBI	NBI	NBI	i-scan	i-scan	no	FICE	FICE	No
Compatible processor	CV-290/CLV-190	CV-190/CVL-190	CV-190/CLV-190	CV-180/CLV180	EPK-i5000/i7000	EPK-i5000/i7000	EPK-100p	EPX-4450HD/3500HD	EPX-4450HD/3500HD	EPX-4450HD/3500HD

Featured endoscopes possess at least one major characteristic: latest image sensor, large biopsy channel or two channels. Disclaimer: this is not an extensive list. Some endoscopes are not available in all countries.

Table 2. Technical characteristics of latest coloscopes suitable for ESD procedures.

Manufacturer	Olympus	Olympus	Olympus	Pentax	Pentax	Fujifilm	Fujifilm	Fujifilm
Model name	CF-HQ290	CF-HQ190	PCF-H190	EC38-i10	EC34-i10	EC-600WL	EC-600LS	EC-600ZW/L
Field of view (degrees)	170	170	170	140	140	140	170	140
Depth of field (mm)	4–100	2–100	2–100	4–100	2–100	2–100	2–100	1.5–100
Biopsy channel(s) (mm)	3.7	3.7	3.2	3.8	3.8	3.8	3.8	3.8
Angulation range (degrees)								
Up	180	180	180	180	180	180	180	180
Down	180	180	180	180	180	180	180	180
Right-Left	160	160	160	160	160	160	160	160
Distal end diameter (mm)	13.2	13.2	11.7	13.2	11.5	12	11.5	12.8
Water-jet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Manual Zoom	Optical	Optical	No	Optical	Optical	No	No	Optical
Chromoendoscopy	NBI	NBI	NBI	i-scan	i-scan	FICE	FICE	FICE
Length (mm)	L:2005, I:1655	L:1680, I:1330	L:2005, I:1.655	L:2016, F:1816, M:1616	L:2016, F:1816, M:1616	L:1990, I:1820, M:1630	1630	L:1990, M:1630,
Compatible processor	CV-290/CLV-190SL/CLV-190	CV-190/CLV-190	CV-190/CLV-190	EPK-i5000	EPK-i5000	EPX-4450HD/3500HD	EPX-4450HD/3500HD	EPX-4450HD/3500HD

Disclaimer: this is not an extensive list. Some endoscopes are not available in all countries.

during dissection. Endoscopes like the Olympus GIF-1TH190 (Japan), the Pentax EG29-i10 (Japan) and the Fuji EG580RD (Japan) combine high-definition imaging, closed focus, water jet capabilities and a large channel (3.7 and 3.8, respectively). The latest Fujifilm 600 series and Olympus HQ series provide a manual zoom option capable of impressive microvascular pattern analysis. However, not all endoscopic suites have the luxury to afford the price tag of a high-end endoscope and compromises are usually made. For standard endoscopes with a 2.8 channel but without water jet channel, the addition of a valve with a lateral water pump connection may overcome this default. Double-channel endoscopes provide the advantage of easier suction and may accelerate the procedure since the second channel can be used for insertion of an additional instrument (needle, clip or coagulation forceps). However, double-channel endoscopes often lack the image quality of latest series and have a wider distal end, which is not desirable when moving into tight spaces. A multibending double-channel endoscope by Olympus, also known as R Scope, offers additional flexure in front of the normal flexure [5]. However, its use in routine endoscopy has not been established yet.

Electrosurgical units

ESD requires a high-frequency generator with an automatically controlled system. Most published ESD cases have been performed with the ERBE ICC200, ERBE VIO 200/300 series or Olympus ESG-100. These units have a sensor that can control the power automatically and adjust to the circumstance achieving smoother and safer dissection. Table 3 illustrates suggested settings for ESD based on the authors' experience.

ERBE VIO200S and VIO200D

VIO200 devices offer the following modules: The ENDO CUT mode fractionates the cutting process into controlled cutting and coagulation intervals and is used for both incision and dissection. The operator can adapt the desired intensity of coagulation based on the thickness of the intestinal wall and the risk of bleeding (Effect 1: no coagulation, Effect 2: soft coagulation, Effect 3: fast coagulation, Effect 4: maximized coagulation; commonly set at 2–3) and the duration of the intervals. SOFT COAG is applied for marking and selective hemostasis with a hot biopsy forceps (80W). FORCED COAG is suitable for marking (20W) and hemostasis of smaller vessels with the cutting electrode of the endoknife (30–60 W). VIO200D has two additional modules not available to VIO200S: DRY CUT and SWIFT COAG. DRY CUT provides more cutting and coagulation effect than ENDO CUT and is used for both incision and dissection (Effect 2, 30 W). SWIFT COAG has a smaller cutting effect than DRY CUT, while its coagulation power is situated between that of FORCED COAG and DRY CUT. It can be used for dissection (effects 3–4, 50 W). VIO200D is supplied with a foot pedal that has an additional button for changing among the pre-saved settings.

Table 3. Electrocautery settings for tip-cutting endoknives (e.g., DualKnife).

High-frequency generator	Settings			
	Incision	Dissection	Hemostasis with forceps	Marking
Olympus ESG-100	Pulse Cut Slow, 25–40W Forced Coag2, 30W	Pulse Cut Fast, 30W Forced Coag1, 40W Forced Coag2, 50W	Soft Coag, 80W	Forced Coag1, 20–30W Soft Coag, 50W
ERBE VIO200/300	ENDOCUT I or Q E1, D3, I3 DRY CUT, E2, 30W	ENDOCUT I or Q E2-3, D2, I 2-3 DRY CUT, E2, 30W FORCED COAG E2, 40W SPRAY COAG[a] E2, 60W SWIFT COAG, E2, 40–50W	SOFT COAG, E5, 80W SPRAY COAG[a], E2,10W SWIFT COAG, E2-4, 50W	SOFT COAG, E5, 50-80W, FORCED COAG, E2, 20W SWIFT COAG, E2, 50W
ERBE ICC200	ENDOCUT E2-3, 120W	ENDOCUT E2-3, 120W	SOFT COAG, 80W	FORCED COAG, 20W

Disclaimer: these settings represent the authors' suggestion and should be individualized according to the site of dissection, the type of lesion and available equipment. It is strongly advised to check the coagulation effect on healthy tissue and adapt the settings accordingly prior to use.
[a]SPRAY COAG is only available in ERBE VIO 300D series. E: Effect; D: duration; I: interval.

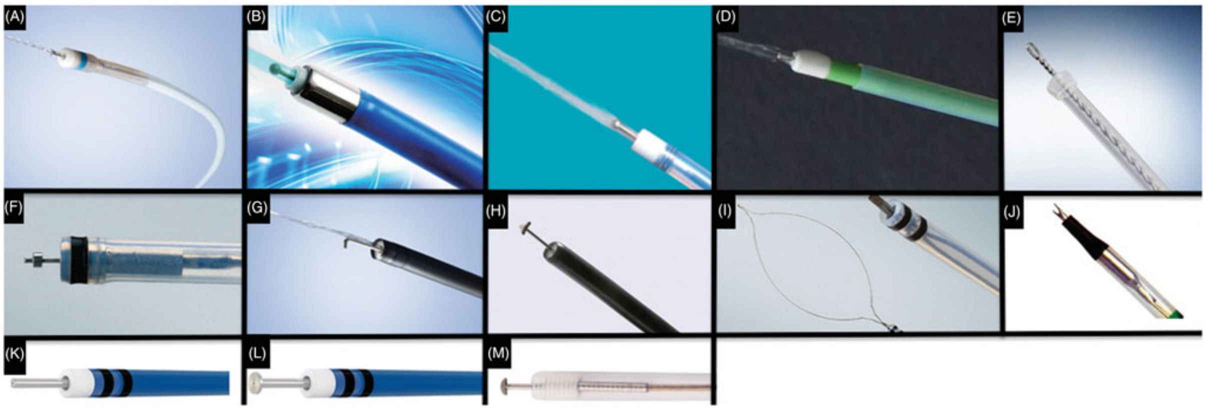

Figure 1. Tip cutting endoknives. (A) DualKnifeJ (B) B-Knife (C) Flush Knife BT (D) ESD AqaNife (E) FlexKnife (F) Splash M-Knife (G) HookKnifeJ (H) Triangle Tip Knife (I) Ksnare (J) Endo FK (K) Hybrid Knife I-type (L) Hybrid knife T-Type (M) Optimos.

ERBE VIO300D

This is an upgrade of the VIO200D series that offers the additional module of SPRAY COAG. This effect applies a non-contact coagulation effect (stronger than FORCED COAG) with low-penetration depth. It can be used for both submucosal dissection and hemostasis of diffuse bleeding.

ICC200

This unit has been replaced by the VIO series. Available modules for ESD are that of ENDOCUT, SOFT COAG and FORCED COAG.

Olympus ESG-100

ESG-100 has two settings for incision and/or dissection (Pulse Cut Fast and Slow). These modes alternate a cutting phase of 15 ms (Fast mode) or 800 ms (Slow mode). Coagulation modes include: ForcedCoag1, ForcedCoag2 and Soft Coag. ForcedCoag1 is a fast superficial pinpoint coagulation used for coagulation of small vessels with the tip of the knife. ForcedCoag2 is a cutting current used for dissection. An interesting feature is the presence of a third button at the footswitch that triggers the water jet.

Endoknives

Several ESD knives are available based on the location of lesion (esophagus, stomach, colon, rectum), the aspect of the lesion (sessile, flat, submucosal), the level of fibrosis and the axis of the knife in relation to the dissection plan (parallel or vertical to the lesion). Endoknives may be divided in three basic categories. *Tip cutting knives* have a needle-knife extremity that can be used for marking, cutting, dissection and hemostasis (Figure 1). *Blunt-tip knifes* consist of an insulated tip that prevents coagulation of the muscle layer (Figure 2). Although not suitable for marking, submucosal dissection may be faster. Most recently, *scissor-type knives* have emerged (Figure 3) and have been used for all steps of ESD at various locations. However, their use is not yet wide spread.

Tip cutting knifes

DualKnife (Olympus, Japan) was developed by Yahagi. It features a tiny non-insulated dome-shaped electrode at the tip of the knife of 1.5 mm (for the esophagus and colon) or 2 mm (for stomach), with two different working lengths of 1.6 or 2.3 m. The knife length can be fixed in two positions: retracted or extended. In the retracted position, the length of

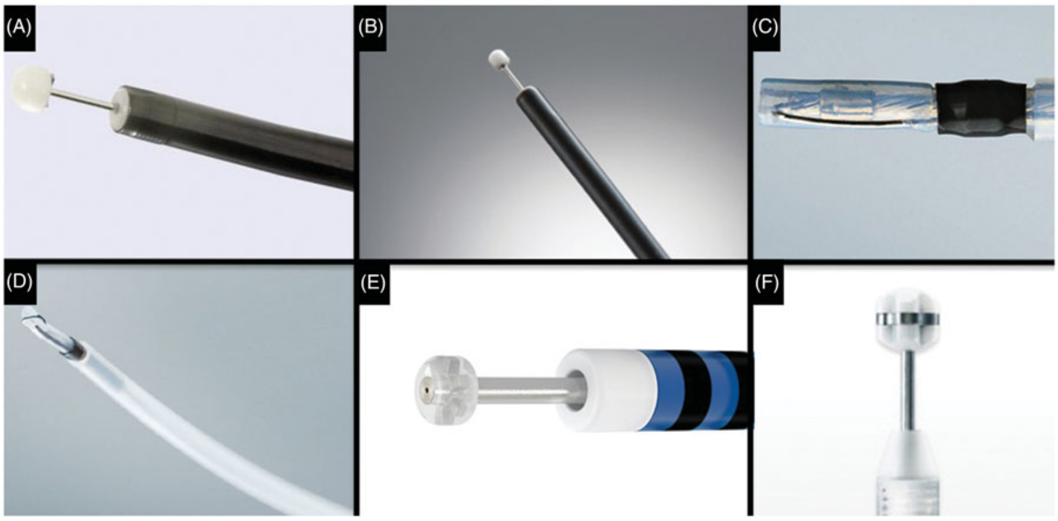

Figure 2. Blunt tip knives. (A) IT2 Knife (B) IT nano (C) Mucosectom (D) Swanblade (E) Hybrid Knife O-Type (F) Safe Knife V.

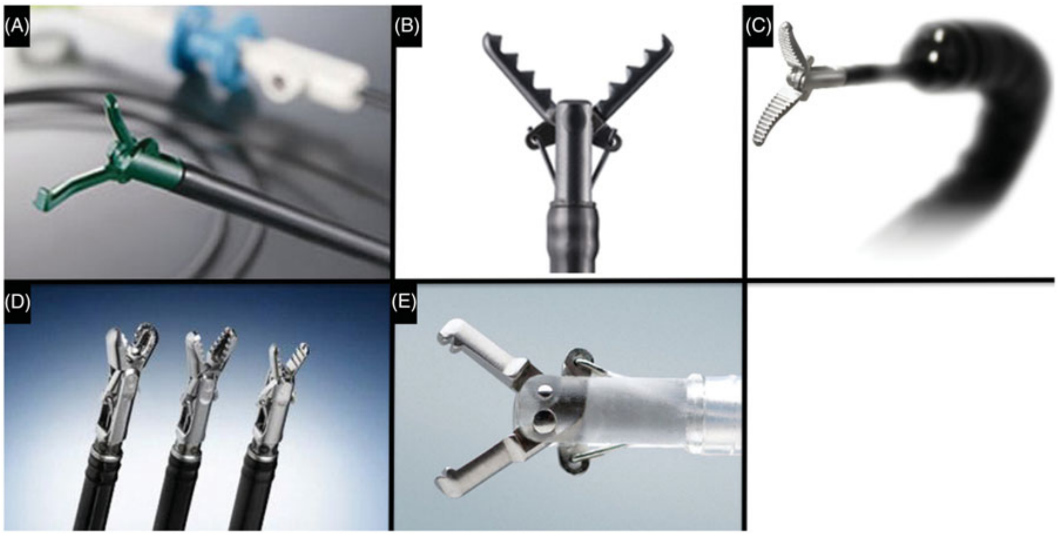

Figure 3. Scissor Type knives and coagulation forceps (A) SB Knife (B) Clutch Cutter (C) Maryland (D) Coagrasper (E) HemoStat-Y.

the exposed tip measures 0.3 mm. A new version with water jet function is currently available (DualKnifeJ).

FlexKnife (Olympus) was developed by Yahagi. This knife features a braided 0.8 mm cutting knife with a looped tip adjusted to different lengths, suitable for marking, incision and dissection. The distal end of the sheath, which functions as a stopper, was designed to prevent perforation by allowing better control of the cutting depth.

Flush Knife (Fujifilm, Japan) was developed by Toyonaga. There are 13 variations of this knife according to the length of the needle knife (1, 1.5, 2, 2.5 or 3 mm), with the presence or absence of a ball tip and the length of the catheter (1.8 and 2.3 m). The main advantage of this knife is the water-jet capability (thus the name 'flush'), which is designed to clean the operation field, the tip of the knife and most importantly reestablish the submucosal fluid cushion in the submucosa. It is often used in combination with viscous substances such as hydroxyethyl starch 6%.

HookKnife (Olympus) was developed by Oyama and Kikuchi. This knife has an L-shaped cutting wire, designed to hook tissue and pull it away, to minimize the risk of damage of the muscle layer. The orientation of the hook is changed by rotating the handle. It is particularly useful for fibrotic areas, and when the endoscope is positioned in front of and against the lesion [6]. A new version with a jet function will be soon available (HookKnifeJ).

Triangle Tip Knife (Olympus) was developed by Inoue and Kudo. This knife features a conductive triangle tip. Its design is suitable for marking, incision and dissection. It became popular with the introduction of POEM since it facilitates grasping and dissection of muscular fibers. However, it is less commonly used for ESD procedures due to the larger size of the tip.

Hybrid Knife (ERBE). This is a multifunction knife that can be used for marking, incision, dissection and most importantly submucosal injection. This later feature is provided by a central capillary within the knife that can serve as an ultrafine 120-µm water jet when coupled with a foot pedal-activated, computerized jet lavage unit (ERBEJET 2 System, ERBE). Three versions are commercialized: The I-Type (needle type with adjustable length), the T-Type (with a disc-shaped non insulated tip) and the O-Type (presenting an insulated hemispherical, dome-like tip similar to the IT2 Knife). Attention should be paid when used with spray coagulation, since carbonized tissue may obstruct the water-jet canal.

B-Knife (Xemex, Zeon Medical, Japan). This is a ball-tip bipolar knife with a water-jet function that does not require a counter-electrode plate. Burning of the muscularis propria layer is considered to be less with this knife than with other monopolar knives [7].

ESD AqaNife (Ovesco, Germany). This is a needle-type knife with a straight needle and a ceramic sheath. The needle length is available in 1.5, 2, 2.5 and 3 mm. It incorporates a flushing channel for irrigation and submucosal injection.

Splash M-Knife (Pentax). This is tip-cutting knife with jet function. The blade contains a metal disk that is used to hook tissue and provide clear marking.

Optimos (Taewoong, South Korea). The Optimos knife has a 1.9 mm wide and 2.5 mm long anchor-shaped tip which can be rotated with the help of a dedicated button. It has a water-jet function and it can be used for all steps of ESD [8].

Endo FK (Kachu Technology, South Korea). EndoFK is a multifunction knife that can be used for all steps of an ESD procedure [9]. It consists of two interchangeable knives, a fixed flexible snare similar to the FlexKnife and a forked knife, which form a single working unit, and has an inlet for material injection or saline irrigation during the procedure. The knives can be changed during a procedure by using two switches.

Ksnare (Pentax, Japan). This knife consists of a snare with a modified tip designed for circumferential incision-trimming and then snare-resection of the retracted lesion (Hybrid-ESD). This concept is of particular use for lateral spreading adenomas of the colon.

Blunt tip knives

IT Knife 2 (Olympus) was developed by Hosokawa and Yoshida. This knife has a ceramic tip at the distal end of the device, which is insulated, to help prevent damage of the muscle layer. Dissection is performed in vertical or horizontal direction with the help of an electrode situated at the proximal side of the ceramic tip. Dissection using this knife is fast due to the large amount of tissue dissected at once by the long blade and attention should be made for inadvertent perforation [7]. Since visualization of the dissection plan is less optimal than with needle knifes, its use is preferred for gastric lesions and especially when a drooping flap has been created.

IT Knife nano (Olympus). This knife is similar to the IT2 but with a smaller ceramic tip and electrode. These modifications make it attractive for organs with thinner submucosal layer such as the esophagus and colon.

Mucosectom (Pentax) was developed by Kawahara. It comprises a rotatable, (rotating) non-conducting plastic shaft, and a 5-mm cutting wire, located at the side of the plastic shaft. It can be used for incision, dissection and hemostasis.

Swanblade (Pentax). This novel knife has a round, snare-like rotating tip on one side of the sheath. It can be used for marking and dissection.

Hybrid Knife-O type (ERBE), see above.

Safe Knife V (Fujifilm) was developed by Yamamoto. The Safe Knife V has a sandwich-like structure with a central electrode-plate placed between insulated plates. It enables dissection of the submucosal layer with a vertical approach.

Scissor type knives

Clutch Cutter (Fujifilm) was developed by Akahoshi. This is a scissor-like electrosurgical knife with the ability to grasp, pull, coagulate and incise the targeted tissue using electrosurgical current. It has a 0.4 mm-wide and 3.5 mm or 5 mm long serrated cutting edge to facilitate grasping tissue. The outer side of the forceps is insulated to avoid unintentional damage of the muscle layer.

SB Knife (itomo Bakelite, Japan). This knife incorporates a centrally positioned 1.2 mm electrode, surrounded by an electrically insulating coating. Three versions are available: one with a 7 mm blade for the stomach (standard type), a 6 mm blade for the esophagus (short type) and an even smaller version for colorectal applications (Jr Type) [6].

Endo-Maryland Dissector (Ovesco). The tip design is inspired by laparoscopic surgical instruments. Dissection with Maryland can be performed in several ways including dissection by opening the jaws or by grapsing and pulling the submucosal tissue with or without electrocautery. It requires a biopsy channel of at least 3.2 mm [10].

Basic steps of ESD

Demarcation of the borders

The lateral extension of the lesion is evaluated by means of high-definition endoscopy, zoom endoscopy, virtual chromoendoscopy and spray chromoendoscopy. Squamous cell carcinomas and dysplasias are easily demarcated with virtual chromoendoscopy such as Narrow Band Imaging or 0.75%-1% iodine dye spray (Lugol’s iodine). Barrett’s esophagus and flat gastric lesions are studied with acetic acid, methylene blue or indigo carmine (Figure 4). Colorectal lesions are usually stained with indigocarmine and/or crystal violet for analysis of the microvascular pattern under magnification. Improved digital chromoendoscopy capabilities of modern endoscopes often allows the endoscopist to delineate the lesion without the need of dye spraying, as lugol and blue solutions often impair vision when they are mixed with blood.

Marking

Marking is performed with a 5 mm safe margin with intermittent and short application of coagulation. For circumferential

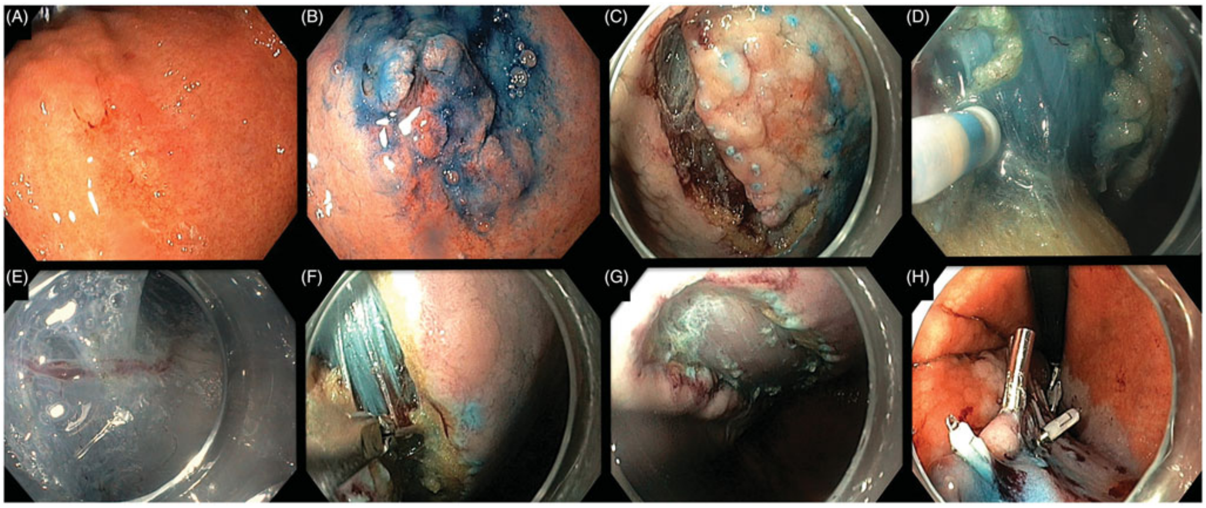

Figure 4. Basic steps of an ESD procedure (A) Flat intramucosal adenocarcinoma of the gastric body. (B) Spray chromoendoscopy with indigo carmine reveals the lateral borders. (C) Marking is followed by incision and trimming of the periphery (D) Submucosal dissection with a 2 mm DualKnife. (E) Small vessels are coagulated with the tip of the knife. (F) Larger vessels are grasped and coagulated with the Coagrasper. (G) Inspection of the artificial ulcer for residual vessels and injuries of the muscle layer. (H) Clipping of the defect in a zipper fashion.

lesions circular dots reveal the anal and oral margins. Instruments used for marking include tip cutting knives (FORCED COAG, effect 2, 20W or SOFT COAG, effect 4, 50–80W or SWIFT COAG effect 2, 40w), the tip of a snare, needle knife used for sphincterotomy or argon plasma coagulation. In order to avoid excessive coagulation of the mucosa, we usually test coagulation settings at a distant normal area of the mucosa. Marking is performed in gastric lesions and esophageal lesions, but it is rarely used in colorectal lesions because of a clearer margin.

Submucosal injection

A solution is injected to the submucosal layer prior to the mucosal incision. Optimal elevation of the submucosal layer is crucial for safe submucosal dissection. The above-mentioned injection agents are used for submucosal injection. Often a 23–25G needle with a transparent stopper is used (e.g., Interject, Boston Scientific, Natick, MA, USA). In order to avoid 'seeding' of potentially malignant cells injection through the lesion is avoided.

Incision of the periphery and trimming

Marking of the periphery is followed by circumferential incision outside the marked area. Sometimes only the proximal and distal side are incised, in order to avoid excessive loss of submucosal solution. Incision of the mucosa is followed by incision of the muscularis mucosa (trimming), which results in retraction of the lesion. This step prepares the access to the submucosal layer underneath the lesion. Incision is performed with a tip cutting knife or a blunt tip knife. However, this later option usually precludes the creation of at least two mucosal entrance holes at the oral and anal side of the lesion. Then, the blunt tip knife is inserted into the distant hole and the endoscope progressively retracted or moved laterally. This method achieves fast incision and is particularly useful when the axis of the knife is vertical to the lesion. However, visibility is less optimal. Usual settings for mucosal incision are ENDOCUT Q/I, Effect 2, cutting duration 3, cutting interval 3 or DRY CUT Effect 2–3, 80W.

Submucosal dissection

Two elements are crucial for successful and easier submucosal dissection: the direction of gravity and the detection of the easiest point of access. If appropriate, countertraction measures are taken for better exposure of the dissection plane. Cutting of the submucosal fibers is performed with precision under good visualization and abundant submucosal lifting. Deciding 'where to cut' maybe confusing and is the riskiest part of the procedure. The axis of the tip of the cutting knife should be parallel or oblique to the muscularis area; The pedal is usually pressed intermittently, particularly when visualization is suboptimal; the submucosal fibers should be hooked and retracted before cutting and visible vessels coagulated before dissection; repeated back and forward movements are undertaken as long as the submucosal plane is exposed conveniently, before changing the access point. For circumferential lesions of the esophagus or rectum, the tunneling technique maybe useful [11].

Hemostasis

Small vessels comparable to the thickness of the knife can be directly coagulated before cutting (FORCED COAG, 20–30W). Larger vessels should be coagulated with a small biopsy forceps such as the Coagrasper (Olympus) or the HemoStat-Y (Pentax), either with the tip of the closed forceps (for small vessels) or after grasping and retraction (SOFT COAG, 70-80 watt). Excessive coagulation may traumatize the muscular layer and carbonize adjacent tissue. For this reason larger vessels are isolated before coagulation by dissecting the surrounding tissue and/or by creating a sufficient submucosal cushion. Finally, spray coagulation can be applied for diffuse capillary oozing with the tip of the cutting knife.

Countertraction techniques

The key element for a successful, easier and faster ESD procedure is the convenient exposure of the dissection plane. Gravity should be taken into consideration and the patient's position changed accordingly. In addition, a variety of traction techniques have been published in an effort to improve visualization and access of the submucosa. Each technique has advantages and disadvantages. However, the clip with line method is probably the easiest and most cost effective.

Conventional devices and techniques for traction

Clip with line. This is a simple traction technique using a hemoclip and a silk suture or dental floss [12,13]. A hemoclip is inserted into the endoscope and then the dental floss or suture line is tied at the base of one arm of the clip. Subsequently, the clip is withdrawn inside the cap and the endoscope is advanced to the target lesion. Then the clip is anchored to a mucosal flap for traction. The anchoring site depends on the location of the lesion. In gastric lesions approached in a retro position, the clip is anchored at the anal side of the lesion. For lesions that are dissected in a straight position, the clip is anchored at the oral side. Creation of a mucosal flap is strongly suggested before deployment of the clip, in order to avoid grasping part of the active submucosal plane, which will complicate further dissection. The efficacy of this technique on reducing the overall time of a gastric ESD was studied in 43 matched cases and showed a mean gain of at least 30 minutes per procedure [12].

Clip and snare. A clip is deployed on the mucosal flap which is subsequently grasped with an external polypectomy snare that changes the axis of countertraction by pulling or pushing the snare [4,14,15]

Clip-Flap. This is a simple technique that helps the creation of a mucosal flap (Figure 5). After incision, one or more clips are placed at the edge of the lesion. The effectiveness of this technique was recently demonstrated in a large study with colorectal lesions [16].

Use of external forceps. A grasping forceps is advanced through the secondary channel of a dual channel endoscope, which is used to grasp an auxiliary external bendable forceps. This is later used for traction [17].

Thin endoscope-assisted ESD. In this technique a second thin endoscope (<7 mm) is inserted and the edge of the lesion is slightly elevated using a biopsy forceps or a snare according to the size of the flap [18,19].

Double-channel scope method. Grasping forceps is inserted into the second channel of a double-channel endoscope in order to create traction. Even though the concept is good, the forceps moves synchronously with the scope, thus changing the direction of traction during dissection. Furthermore, double-channel endoscopes have a bigger size, making them inconvenient for tight spaces [20].

Endolifter (Olympus). This device consists of a modified cap, available in two different diameters of 13.85 and 14.95 mm that possesses an accessory channel at 12 o'clock which enables manipulation of an external bending biopsy forceps used for tissue traction [21].

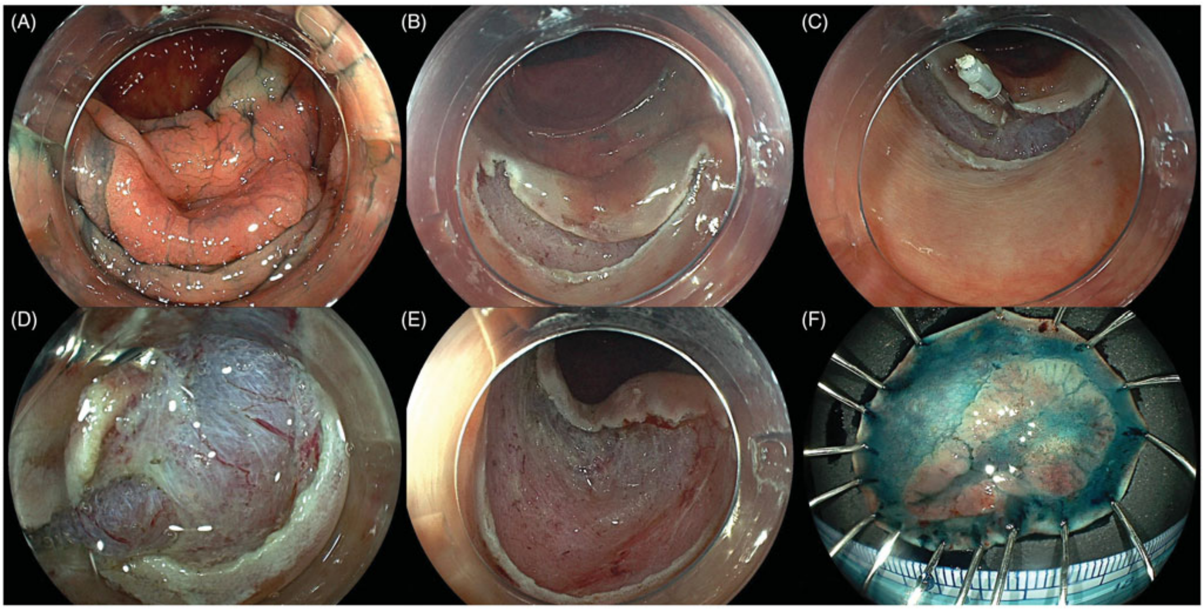

Figure 5. Clip-flap technique. (A) Lateral spreading tumor non-granular type of the transverse colon. Before performing ESD, the lesion is moved upward against gravity. (B) After partial peripheral incision from the anal side, (C) a clip is positioned at the edge of the exfoliated mucosa. The tail end of the clip falls towards the colonic lumen due to gravity. (D) The distal attachment is inserted under the clip, and then the exfoliated mucosa is lifted and the submucosal layer is clearly visualized. At the moment, the clip applies counter-traction to the submucosal layer and facilitates the creation of the mucosal flap. In addition it serves as a grip for the cap. (E, F) Complete resection of the lesion.

Suture pulley method. In this technique, countertraction is applied by suturing the mucosal flap on the opposite gastric wall proximally or distally to the lesion [22]. By pulling the tail of the suture, the tension of the traction can be modified. Although attractive, the main limitation of this method is the need of a double-channel endoscope and its higher cost.

Percutaneous traction. A small snare is introduced into the gastric lumen through a percutaneous gastric port (2-mm diameter), to grasp and pull the lesion away from the muscularis propria, thus facilitating resection [23].

Experimental techniques/devices for traction

Overtube with built in side channel. This device is designed to improve traction for esophageal ESD. An overtube with a side channel is advanced over the scope, thus creating an accessory channel that can be rotated independently of the axis of the endoscope [24].

Magnetic countertraction. A small magnet is fixed with two clips at the mucosal flap. Traction is applied with an external larger marker, which is moved according to the desired direction of traction [25].

Overtube with manipulatory arms. This device consists of an 18 mm in diameter overtube with 2 arms at the tip of the device which are independently manipulated. Such a device enables bimanual tasks to be performed with one instrument used to hold the tissue and a second instrument used for dissection [26].

Closure of artificial ulcers-perforations

Closure of the post-ESD ulcer is a matter of debate and no guidelines exists on best practice. However, in high risk patients with large lesions, under antiaggregation/anticoagulation treatment and/or injuries of the muscle layer, several techniques have been described to reduce the risk of late perforation, bleeding and decrease the hospital stay. Clipping of large defects in a sequential zipper fashion can be cumbersome or even impossible. Alternative options include the use of a double-channel endoscope with an endoloop and clips, a figure of 8-shaped stainless clip in combination with clips, a nylon string loop attached to a clip, over-the scope-clips, the overstitch endoscopic suturing device, tissue shielding with polyglycolic acid sheets and fibrin glue and sucralfate [27].

Two simple and cost-effective ways of closure of wide mucosal defect are (a) the technique of lateral incision and clips illustrated in Figure 6 [28,29] and that of double-layer suturing [30]. This later is carried out in two steps. First an initial set of 3–4 hemoclips are applied at the center of

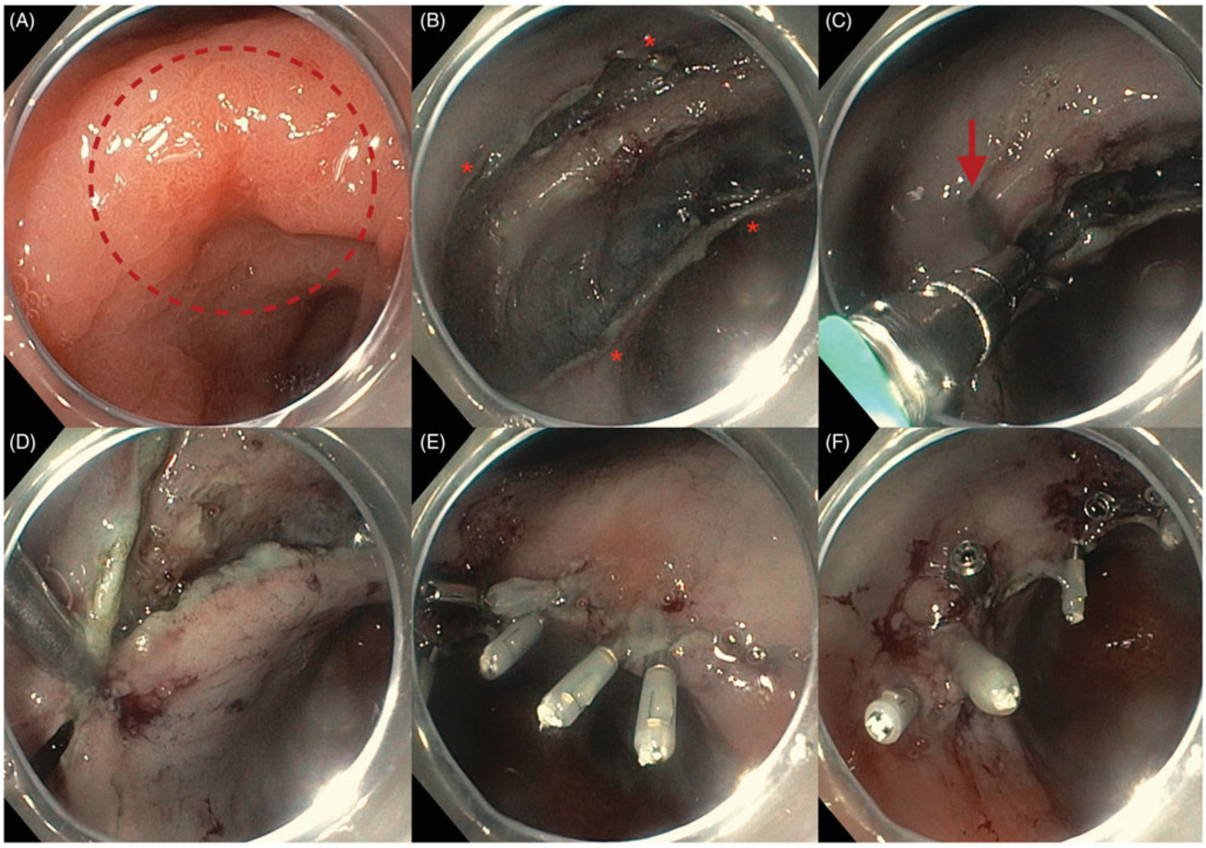

Figure 6. Closure of an artificial ulcer with lateral incisions and clips (A) Early gastric cancer of the angulus (Paris IIb + IIc, Tis) (B) Post-ESD mucosal defect. Small incisions (holes) are made using a DualKnife around the lateral borders (asterisks). C The extremity of the first clip is 'anchored' into the hole (arrow) and the mucosal border is dragged towards the opposite mucosal border (D) The other arm of the clip is inserted into the opposite hole and then it is deployed (E, F) After placement of two clips using the aforementioned method, the remaining gap is clipped in a conventional zipper fashion. Used with permission from reference [29].

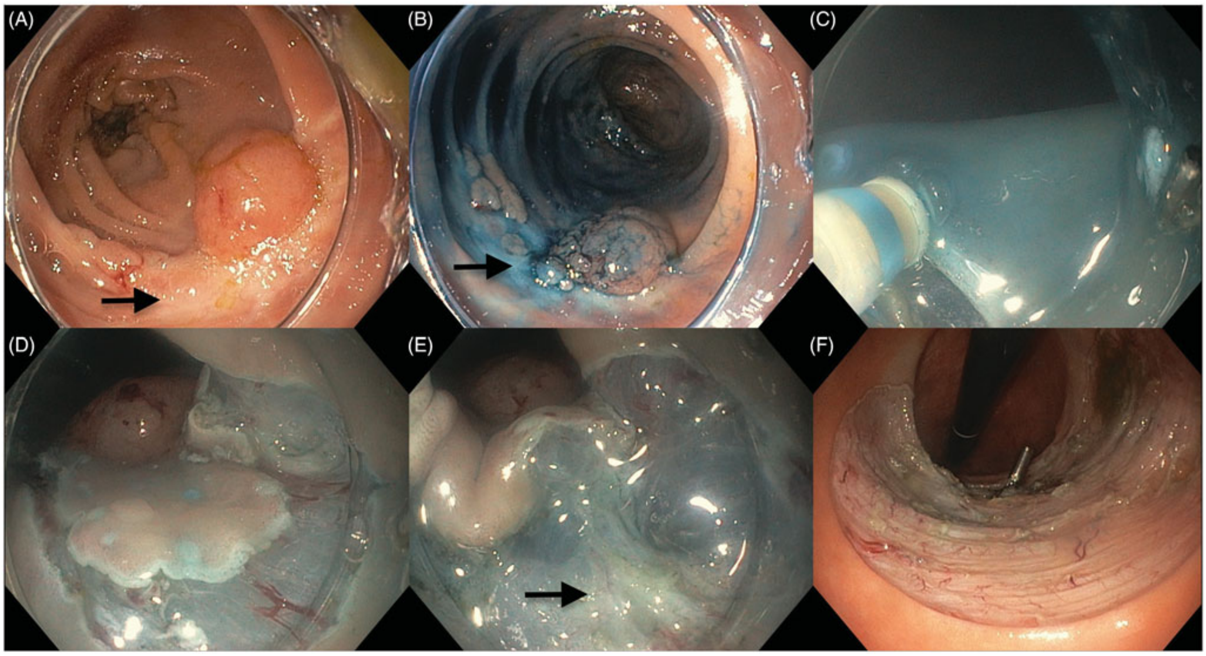

Figure 7. (A, B) Residual nodular mixed type granular lateral spreading adenoma with signs of grade F2 severe fibrosis (arrows), secondary to several previous piece meal snare resections (C, D) Initial incision with a DualKnife was performed at the normal mucosal away form the fibrotic area. (E, F) Dissection was copious due to the adherence of the submucosal layer to the muscular layer. At the end of the procedure, a clip was deployed to close a tiny wall defect.

the ulcer. Now that the ulcer has been shrunk and the edges of the mucosal defect are closer to each other, a second set of clips is deployed in the spaces between the previous clips. In practice, closure of a 4-cm defect needs ~10 conventional clips.

Most recently, a promising suturing method was introduced for the closure of large artificial ulcers, with the help of a single channel endoscope, a slip knot string and standard clips [31]. A slip knot loop is anchored onto the mucosal defect's proximal margin with a clip. Additional clip anchored the slip knot loop and is placed at the opposite side of the margin. The slip knot loop is tightened by pulling the string. Additional clips are placed to achieve complete closure.

Moreover, a modified clip and snare technique has been described for the closure of large defects. A pre-looped snare over the endoscope is tightened over a deployed clip at the margin of the defect and provides appropriate countertraction for further closure in a zip fashion [32].

Indications for ESD in Japan and Europe

Early squamous cell carcinoma of the esophagus

ESGE recommends ESD for superficial esophageal squamous cell cancers without signs of submucosal involvement, if en bloc resection is probable [1]. According to the Japan Esophageal Society, the absolute indication for endoscopic resection is defined as flat lesions (Paris 0 – II) and circumferential extent of ≤2/3 and is considered curative in case of m1–m2 invasion, therefore with a depth infiltration not exceeding the lamina propria layer [30]. Endoscopic resection alone is acceptable in surgical high risk cases when infiltration involves m3–sm1 esophageal squamous cell cancer even exceeding an extent ≥¾ of the circumference but without lymphatic or vessel infiltration [1,33].

Barrett's esophagus

The role of ESD in the management of Barrett's esophagus is debated due to the satisfactory results obtained by standard endoscopic mucosal resection techniques for the resection of visible lesions <1 cm in combination with other ablative methods for the destruction of residual flat Barrett mucosa. ESGE guidelines currently favor ESD only for selected cases, such as lesions larger than 15 mm, poorly lifting tumors, and lesions at risk for submucosal invasion [1].

Early gastric cancer

ESGE [1] and Japan Gastroenterological Endoscopy Society (JGES) [34] recommend ESD for gastric lesions that accomplish the following criteria:

Absolute indication:

Macroscopically intramucosal (cT1a) differentiated carcinoma measuring less than 2 cm in diameter. The macroscopic type does not matter, but there must be no finding of ulceration (scar); i.e., UL(–).

Expanded indications:

1. UL(–) cT1a differentiated carcinomas greater than 2 cm in diameter

2. UL(+) cT1a differentiated carcinomas less than 3 cm in diameter

3. UL(–) cT1a undifferentiated carcinomas less than 2 cm in diameter.

4. Differentiated-type adenocarcinoma with superficial submucosal invasion (sm1, ≤500 μm), and size ≤3 cm.

When vascular infiltration is absent together with the above-mentioned criteria, the risk of lymph node metastasis is extremely low, and it may be reasonable to expand the indications. If a lesion falls within the indication criteria at the initial ESD or endoscopic mucosal resection, subsequent locally recurrent intramucosal cancers may be dealt with under expanded indications.

Colorectal lesions

ESGE suggests ESD for the removal of colonic and rectal lesions with high suspicion of limited submucosal invasion that is based on two main criteria of depressed morphology and irregular or nongranular surface pattern, particularly if the lesions are larger than 20 mm [1]; ESD can be considered for colorectal lesions that otherwise cannot be optimally and radically removed by snare-based techniques, such as in cases of extensive fibrosis or lesions larger than 3 cm (Figure 7). JGES recommends ESD for the following indications [35]:

1. Lesions for which en bloc resection with snare mucosal resection is difficult to apply such as:
   - Lateral spreading tumors –non granular type
   - Lesions showing a V_I –type pit pattern
   - Carcinoma with shallow T1 submucosal invasion
   - Large depressed-type tumors
   - Large protruded-type lesions suspected to be carcinoma
2. Mucosal tumors with submucosal fibrosis
3. Sporadic localized tumors in conditions of chronic inflammation, such as ulcerative colitis
4. Local residual or recurrent early carcinomas after endoscopic resection

Current indications for endoscopic mucosal resection (EMR) according to ESGE [1]

- EMR may be considered for superficial esophageal squamous cell cancers without obvious submucosal involvement that are smaller than 10 mm. However, even for these cases ESD remains the first option.
- EMR is the treatment of choice for the excision of mucosal cancer in Barrett's esophagus. ESD should be preferred for lesions larger than 15 mm, with poor lifting and lesions at risk for submucosal invasion.
- EMR is restricted for gastric lesions smaller than 10–15 mm with very low probability of advanced histology.
- The majority of colonic and rectal superficials lesions can be effectively removed with standard polypectomy and/or EMR. ESD can be considered for lesions with high suspicion of limited submucosal invasion or for those that cannot be optimally removed by snare-based techniques

ESD-derived techniques

LECS

Hiki described first in 2008 an innovative procedure called LECS that combined the strongest points of interventional endoscopy and laparoscopic surgery for the removal of gastric wall lesions. Following that, a series of other innovative techniques such as inverted LECS, laparoscopic-endoscopic full-thickness resection, clean non-exposure technique and non-exposed wall-inversion surgery have emerged. When performed by expert teams, they show a lot of promise and achieve solid oncologic results. The reader is referred to a recent detailed review describing the aforementioned techniques [36].

POEM

POEM is the application of esophageal myotomy by utilizing a submucosal tunneling method. Since the first case of POEM was performed for treating achalasia in Japan in 2008 by Inoue, this procedure is being expanding in western countries. Furthermore, the indications for POEM progress to include long-standing, sigmoid shaped esophagus in achalasia, even previously failed endoscopic treatment or surgical myotomy, and other spastic esophageal motility disorders [37]. A recent meta-analysis demonstrated comparable results in terms of safety and short term efficacy between POEM and surgical Heller's myotomy [38]. However, long-term results are lacking. Several ongoing randomized trials comparing POEM to pneumatic dilatation and surgery will further elucidate the role of POEM in achalasia.

STER

Inspired by POEM procedures, Xu et al. [39] used working space for endoscopic resections called STER. This technique is applied for tumors up to 3.5 cm in size, since larger tumors cannot be easily extracted from the submucosal tunnel. An entrance hole is created 5 cm proximally to the lesion, and a submucosal tunnel is extended beyond the lesion. For lesions involving the muscularis propria, full thickness resection maybe necessary. After removal of the lesion, the entrance is closed with conventional clips.

Emerging applications inspired from POEM and ESD

Submucosal tunneling combined with myotomy has been reported in the management of a variety of 'functional' disorders such as gastroparesis [40] and most recently Hirschprung disease of the rectum [41]. Furthermore, submucosal tunneling methods have been utilized for the recanalization of complete post-radiation esophageal obstruction [42], for the inversion of esophageal diverticulum and peritoneal sampling [43]. Other innovative applications include the management of esophageal fistula [44] and reflux disease [45].

Training opportunities in Europe

The learning curve of ESD is long and includes multiple steps. In addition, it should be restricted only for endoscopists with appropriate skills such as patience, accurate orientation in the operation field, precision and familiarization with the oncologic principles of staging and postoperative management. The training is initiated with *ex-vivo* and then *in-vivo* animal procedures in combination with the observation of many ESD procedures. After familiarization with the available endoscopic tools, electrosurgical settings and management of bleeding and perforation, the trainee is invited to perform basic steps of the procedure in human cases under close surveillance. Marking, peripheral incision and trimming are the first steps followed by dissection and understanding the orientation of the dissection plane. Only after acquaintance of these ESD steps, the endoscopist should handle individual cases under surveillance until obtaining full autonomy. Usually, organs with thicker walls such as the stomach and lower rectum are selected for the first cases.

Lately, several hands-on animal courses endorsed by the ESGE have been organized in several countries including Greece, Austria, Spain, Holland and Germany that are addressed to beginners and more experienced ESD practitioners. These workshops are of the utmost importance in order to better perceive how to use different endoknives and how to handle complications such as bleeding and perforation. Hopefully, national endoscopic societies will promote official ESD training programs in the corresponding high volume centers of each country.

What to expect in the future?

Great efforts are made to improve actual equipment. Besides Olympus, who developed the first ESD knives in 1998, several new designs flooded the market in the past years and many others are under evaluation in an effort to create the 'swiss army knife' of ESD, which will be accessible, easy to use, safe and suitable for various applications. In addition, we expect slimmer therapeutic endoscopes with the image quality of diagnostic zoom endoscopes, and advanced flexibility properties permitting the endoscopist to access difficult points such as the angulus and the gastric cardia. Other hot topics in the ESD-related research field include new substances for long-standing submucosal lifting, novel hemostatic and 'ulcer-healing' powders, easy to use suturing devices, novel counter-traction techniques, augmented reality and robotic flexible technology [46].

Conclusions

ESD incorporates a fascinating world of procedures and devices that constantly evolve. Besides sufficient training, familiarization with available equipment and techniques is a prerequisite for successful, safe and cost effective intervention. Hopefully, additional training opportunities through animal and live workshops and also establishment of reimbursement of the dedicated-material by national health systems will make ESD more accessible in the West.

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