









# Endoscopic submucosal dissection techniques and technology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review



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**ABSTRACT**

ESGE suggests conventional endoscopic submucosal dissection (ESD; marking and mucosal incision followed by circumferential incision and stepwise submucosal dissection) for most esophageal and gastric lesions. ESGE suggests tunneling ESD for esophageal lesions involving more than two-thirds of the esophageal circumference. ESGE recommends the pocket-creation method for colorectal ESD, at least if traction devices are not used. The use of dedicated ESD knives with size adequate to the location/thickness of the gastrointestinal wall is recommended. It is suggested that isotonic saline or viscous solutions can be used for submucosal injection. ESGE recommends traction methods in

esophageal and colorectal ESD and in selected gastric lesions. After gastric ESD, coagulation of visible vessels is recommended, and post-procedural high dose proton pump inhibitor (PPI) (or vonoprazan). ESGE recommends against routine closure of the ESD defect, except in duodenal ESD. ESGE recommends corticosteroids after resection of >50% of the esophageal circumference. The use of carbon dioxide when performing ESD is recommended. ESGE recommends against the performance of second-look endoscopy after ESD. ESGE recommends endoscopy/colonoscopy in the case of significant bleeding (hemodynamic instability, drop in hemoglobin >2g/dL, severe ongoing bleeding) to perform endoscopic hemostasis with thermal methods or clipping; hemostatic powders represent rescue therapies. ESGE recommends closure of immediate perforations with clips (through-the-scope or cap-mounted, depending on the size and shape of the perforation), as soon as possible but ideally after securing a good plane for further dissection.

**SCOPE AND PURPOSE**

This European Society of Gastrointestinal Endoscopy (ESGE) Technical Review addresses the technical aspects of ESD with a particular focus on the techniques and the technology/devices used during ESD, as well as the prevention and resolution of adverse events.

**1 Introduction**

Endoscopic submucosal dissection (ESD) has emerged as the first-line treatment for superficial neoplasms in the esophagus and the stomach, and the indications for colorectal ESD are also expanding, especially for the rectum [1]. This endoscopic resection technique allows en bloc resection of lesions of virtually any size, being associated with a low rate of adverse events and

low recurrence rates, but it is a demanding technique, with a long learning curve and requiring dedicated equipment.

Although training and implementation has been slower than in the eastern countries where this technique was developed, ESD is now performed in many European centers [2–10]. Recently, the European Society of Gastrointestinal Endoscopy (ESGE) guideline on ESD has been updated regarding indications, preprocedural assessment and management after resection [1]. Technical aspects of ESD were beyond the scope of that guideline, but there is a large body of evidence regarding ESD technique and devices that can help in further improving the outcomes of ESD. Indeed, as ESD is increasingly adopted in Europe, besides appropriate application of the technique it is also important to focus on how to optimize its use in order to decrease procedural time and the occurrence of adverse events.

**ABBREVIATIONS**

<b>CO2</b>	carbon dioxide	<b>IPB</b>	intraprocedural bleeding
<b>EBD</b>	endoscopic balloon dilation	<b>IT</b>	insulated-tip
<b>EID</b>	endoscopic intermuscular dissection	<b>OTS</b>	over-the-scope
<b>EMR</b>	endoscopic mucosal resection	<b>PCM</b>	pocket-creation method
<b>ESD</b>	endoscopic submucosal dissection	<b>PEECS</b>	post-ESD electrocoagulation syndrome
<b>ESGE</b>	European Society of Gastrointestinal Endoscopy	<b>PICO</b>	patients, intervention, comparison, outcome
<b>ESTD</b>	endoscopic submucosal tunnel dissection	<b>PPB</b>	post-procedural bleeding
<b>ESU</b>	electrosurgical unit	<b>RCT</b>	randomized controlled trial
<b>GI</b>	gastrointestinal	<b>SITE</b>	saline immersion therapeutic endoscopy
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation	<b>SLE</b>	second-look endoscopy
		<b>TTS</b>	through-the-scope

## MAIN RECOMMENDATIONS

**MS1** ESGE suggests conventional ESD (marking and mucosal incision followed by circumferential incision and step-wise submucosal dissection) for most esophageal and gastric lesions.

Strong recommendation, low level evidence.

**MS2** ESGE suggests tunneling ESD for esophageal lesions involving more than two-thirds of the esophageal circumference.

Strong recommendation, high level evidence.

**MS3** ESGE recommends the pocket-creation method for colorectal ESD, at least if traction devices are not used.

Strong recommendation, high level evidence.

**MS4** ESGE recommends the use of dedicated ESD knives with size adequate to the location/thickness of the gastrointestinal (GI) wall (noninsulated knives: stomach, 2.0–2.2 mm; esophagus, duodenum, colon, 1.5–1.7 mm; rectum, 1.5–2.0 mm).

Strong recommendation, low level evidence.

**MS5** ESGE suggests that isotonic saline or viscous solutions can be used for submucosal injection during ESD, depending on costs and local availability.

Strong recommendation, low level evidence.

**MS6** ESGE recommends the use of traction methods in esophageal and colorectal ESD.

Strong recommendation, high level evidence.

**MS7** ESGE recommends the use of traction methods for ESD of gastric lesions located in the greater curvature of the upper/middle stomach (particularly if >2 cm) and if difficult access to the submucosa is encountered during ESD.

Strong recommendation, moderate level evidence.

**MS8** ESGE recommends post-procedural high dose PPI (or vonoprazan) after gastric or junctional ESD.

Strong recommendation, low level evidence.

**MS9** ESGE recommends coagulation of visible vessels in the ESD wound after gastric ESD.

Strong recommendation, low level evidence.

**MS10** ESGE recommends against routine closure of the ESD defect, except in duodenal ESD.

Weak recommendation, moderate level evidence.

**MS11** ESGE recommends corticosteroids (local triamcinolone injection, oral steroid therapy, or combination) after resection of >50% of the esophageal circumference, although the optimal strategy remains to be determined.

Strong recommendation, moderate level evidence.

**MS12** ESGE recommends the use of carbon dioxide (CO<sub>2</sub>) in preference to air when performing ESD.

Strong recommendation, moderate level evidence.

**MS13** ESGE recommends against the performance of second-look endoscopy after ESD.

Strong recommendation, moderate level evidence.

**MS14** ESGE recommends that for the majority of intra-procedural bleedings, thermal coagulation with an ESD knife or hemostatic forceps should be preferred over clipping.

Strong recommendation, low level evidence.

**MS15** ESGE recommends performance of endoscopy/colonoscopy in the case of significant bleeding (hemodynamic instability, drop in hemoglobin >2 g/dL, severe ongoing bleeding) in order to perform endoscopic hemostasis with thermal methods or clipping; hemostatic powders represent rescue therapies in the case of failure of the previous methods.

Strong recommendation, moderate level evidence.

**MS16** ESGE recommends closure of immediate perforations with clips (through-the-scope or cap-mounted clips, depending on the size and shape of the perforation), as soon as possible but ideally after securing a good plane for further dissection.

Strong recommendation, low level evidence.

This ESGE Technical Review addresses the technical aspects of ESD with a particular focus on the techniques and the technology/devices used during ESD.

## 2 Methods

ESGE commissioned this Technical Review and appointed a leader (D.L.) who invited the listed authors to participate in this project. The key questions were prepared by the coordinating

team (D.L., P.P.N.). Task force subgroups based on organ (and including the same contributors as for the ESGE ESD guidelines) were formed. Each task force performed literature searches on PubMed/Medline (without language restrictions; last search September 2022) to prepare evidence-based statements on their assigned key questions (framed using the PICO [patients, intervention, comparison, outcome] format). Articles were first selected by title and abstract; their relevance was then confirmed by review of the corresponding manuscripts, and

articles with content considered to be irrelevant were excluded. All selected important articles were individually assessed and graded by the level of evidence and strength of recommendation according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [11]. The statements proposed were discussed between all authors and agreed between all the participants (>90% agreement in all statements).

In October 2022, a draft prepared by the leaders and coordinating team was sent to all group members. The manuscript was also reviewed by a member of the ESGE Governing Board. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised manuscript.

Evidence tables created from the literature review are presented (Supplementary material, available online). When they existed, meta-analyses on the topic were preferred for inclusion in evidence tables, with additional studies not included in the meta-analyses or published after them being also included.

This Technical Review was issued in 2023 and will be considered for review and update in 2028, or sooner if new and relevant evidence becomes available. Any updates to the Technical Review in the interim will be noted on the ESGE website.

### 3 ESD techniques (conventional, tunneling, pocket-creation, traction, underwater, hybrid)

#### RECOMMENDATIONS

**1** ESGE suggests conventional ESD (marking and mucosal incision followed by circumferential incision and stepwise submucosal dissection) for most esophageal and gastric lesions.

Strong recommendation, low level evidence.

**2** ESGE suggests tunneling ESD for esophageal lesions involving more than two-thirds of the esophageal circumference.

Strong recommendation, high level evidence.

**3** ESGE recommends the pocket-creation method for colorectal ESD, at least if traction devices are not used.

Strong recommendation, high level evidence.

**4** ESGE suggests that hybrid ESD should only be considered as a rescue technique and not as a planned therapeutic method.

Strong recommendation, low level evidence.

#### Conventional technique

The conventional ESD steps are: (i) lesion delineation using virtual/dye-based chromoendoscopy and placing of coagulation marks (rarely needed in colorectal ESD because of clearer delineation between normal mucosa and lesion margins); (ii) submucosal injection of colloid/crystalloid solution and dye; (iii) in-

cision of the mucosa with a needle-type knife, to access the submucosa; (iv) circumferential mucosal incision; (v) trimming of the incision edges; (vi) stepwise submucosal dissection below the mucosal specimen; (vii) retrieval of the specimen; (viii) evaluation and treatment of the resection scar.

Complete circumferential incision before dissection, although generally performed in the stomach by insulated-tip (IT)-knife users, is not mandatory as it can be done along with the submucosal dissection phase if a needle-knife type is used. This modification can slow down the absorption of the submucosal solution and reduce the number of submucosal injections, and is frequently used in the esophagus, duodenum, and colon.

It is also noteworthy that gravity has an important role in exposing the submucosa and taking advantage of gravity can speed up and improve the outcomes of ESD. Besides this, technical variants such as tunneling (in the esophagus), the pocket-creation method (PCM) (in the colon), hybrid ESD, and underwater ESD have been developed and evaluated in comparative studies.

#### Tunneling

Lesions involving more than two-thirds of the esophageal circumference may pose problems for conventional ESD (circumferential cutting following by dissection) because of (i) rapid diffusion of the submucosal cushion, and (ii) folding and drooping of the resected mucosa, making the submucosal dissection very challenging. Endoscopic submucosal tunnel dissection (ESTD), which is frequently used in submucosal tumors, may also have some advantages in the resection of large epithelial lesions. In this technique, instead of performing entire circumferential cutting, only two horizontal cuts are initially made at the anal and oral sides, followed by creation of a submucosal tunnel between the oral and anal transverse cuts. Lateral dissection of the tunnel is then performed (close to the muscularis propria and avoiding the more vascularized superficial submucosa), and finally lateral mucosal resection is performed close to the markings.

This technique has shown promising preliminary efficacy for large superficial esophageal squamous cell neoplasms and a literature review including 90 lesions (mean size 38 mm) found an en bloc resection rate of 98%, an R0 resection rate of 86%, and perforation in 1%, with a mean procedural duration of 83 minutes [12]. A retrospective study also showed a faster dissection time and a higher rate of curative resection when compared with conventional ESD [13]. A double-tunnel approach was also described to facilitate resection of circumferential esophageal tumors, involving the creation of two tunnels opposite to each other and subsequent lateral dissection between them [14]. A recent multicenter randomized controlled trial (RCT) also showed that tunnel ESD significantly decreases procedure time for lesions extending to >50% of the circumference, decreases muscular wall injury, and is associated with more frequent complete healing at 1 month [15]. Underwater ESD, alone or in combination with tunneling, may also be used since the buoyancy of the specimen as it floats on the fluid instilled in the esophageal lumen may provide traction to improve submucosal visualization [16].

## Pocket-creation method (PCM)

The PCM is a special colorectal ESD technique in which a small mucosal opening is created to allow entry into the submucosal space with the scope, and then dissection of all the submucosal space under the target lesion is performed before opening the margins. The difference between PCM and ESTD lies in the creation of a blind tunnel with no opening at the far end in the former, while two openings are created in the latter [17]. The advantage of PCM is improved scope stability and angle of access to the resection plane and a more durable fluid cushion. Saline pocket ESD or saline immersion therapeutic endoscopy (SITE) [18] is a variant of the technique in which the pocket is filled with saline, improving visibility (as the refraction effect of the saline magnifies the view 1.5 times), tissue cooling, and lifting [19]. The double-pocket butterfly technique is another variant of the PCM in which two submucosal tunnels are created during the resection; it has been demonstrated in a small series as feasible and safe for rectal circumferential laterally spreading tumors (LSTs) [20].

The PCM method was compared with conventional ESD in a meta-analysis, in which PCM showed significantly higher R0 and en bloc resection rates (93.5% vs. 78.1%, and 99.8% vs. 92.8%, respectively), along with shorter procedure time and faster dissection speed (mean difference -11.5 minutes, and 3.6mm<sup>2</sup>/min, respectively), and a lower overall adverse event rate (4.4% vs. 6.6%) [21]. Two more recent meta-analyses also support the benefits of PCM [22, 23].

Although tunneling and PCM are best suited for esophageal and colorectal ESD (where the tunnel can be accessed with a straight scope), three studies also suggest efficient traction using the submucosal tunneling technique and a water-pocket creation strategy in the stomach [24–26], while PCM was also described in a retrospective cohort of duodenal ESDs to be quicker and safer than conventional ESD for nonampullary duodenal tumors [27]. It should also be noted that the studies evaluating these techniques used conventional ESD as comparator, and traction methods (detailed below) can be an efficient alternative to the PCM.

## Traction-assisted ESD

Traction strategies are increasingly used to facilitate ESD and showed significant benefit in esophageal ESD, colorectal ESD, and selected gastric ESDs. The different traction methods and devices are detailed below (section 7 Traction devices and techniques).

## Underwater ESD

In this ESD variation, gas is removed from the lumen; the lumen is filled with saline or water and the procedure is performed below the liquid. The advantages of underwater ESD are better visualization of the submucosal dissection plane, because of traction (from the buoyancy of the mucosal flap) and magnification of the underwater image, which can be useful in cases of fibrosis or increased submucosal fat tissue. While there are reports of successful underwater ESD in the esophagus [16], stomach [28], duodenum [29, 30] and colon [19, 31], there is only one

comparative study that evaluated conventional ESD versus underwater ESD combined with PCM [24]. PCM plus underwater ESD was associated with shorter procedure time and higher dissection speed, with similar en bloc and adverse events rates. However, it is unclear whether the claimed benefits are due to use of the PCM or to the underwater work. The SITE technique has also been demonstrated in an RCT to be quicker than conventional ESD, with the same efficacy and safety outcomes [32].

In general, saline immersion provides better current conduction than water and should be preferred. Immersion techniques can be used in any part of the digestive tract (with or without PCM) as long as the area holds the saline, but a very clean environment is a prerequisite, especially in the colon where the presence of fecal debris or mucus can hamper the view. Saline immersion is also useful in situations where CO<sub>2</sub>/air insufflation makes the dissection plane move away from the knife, so replacing gas by saline can improve the access to the submucosa. Another advantage is achievement of a clearer view in the presence of submucosal fat, because of the decrease in the splashing of fat, and the improved view through a magnification effect, especially in the colon [31, 33].

Because of the different conductive properties of water and saline, theoretically a bipolar device may be more adequate for immersion ESD, although some studies, including the largest ones, were successful using monopolar devices [24, 29–31]. The electrosurgical setting for the submucosal dissection phase varies between studies and includes the use of forced coagulation [24], endocut [30], and swift coagulation [31] modes.

## Endoscopic intermuscularis dissection (EID)

This is a recently described technique that comprises dissection between the inner (circular fibers) and outer (longitudinal fibers) parts of the muscularis propria. It is proposed for lesions with severe fibrosis and for T1 lesions with deep submucosal invasion, with the aim of a higher probability of a free vertical margin while maintaining the integrity of the rectal wall. While the R0 resection rate was high (81%) and adverse events rate low (12%, all minor) in a case series with 67 patients [34], further studies are needed to confirm the feasibility and safety of EID and to correctly define the lesions that can benefit from this technique.

## Hybrid ESD (knife-assisted resection)

Hybrid ESD (or precut endoscopic mucosal resection [EMR]) comprises a combination of EMR and ESD, involving the use of a snare for finalizing the resection after circumferential cutting and trimming/partial submucosal dissection with a knife. This technique may be useful in certain situations in the various organs to reduce procedural time, and may be necessary as a rescue technique if complete dissection is difficult due to scope instability or lesion location.

A meta-analysis comparing hybrid with conventional ESD for colorectal lesions showed that hybrid ESD is associated with shorter procedural duration and a lower complication rate, although at the cost of a significantly lower en bloc resection rate [35]. The recurrence rate was evaluated in only two studies

and was higher in the hybrid ESD group but without reaching statistical significance (odds ratio [OR] 9.84, 95%CI 0.16–574.16). It should also be noted that most of the time hybrid ESD is a rescue technique that is applied if difficulties are encountered during ESD (mostly during the learning curve) and most data report poorer technical outcomes (en bloc rate 67%) than conventional ESD [36]. Thus, more comparative data are needed to understand whether it can be an alternative for selected lesions, for example, lesions <30 mm, if the lesion base can be dissected down to less than 2 cm before application of the snare.

## 4 ESD knives

### RECOMMENDATION

**5** ESGE recommends the use of dedicated ESD knives with size adequate to the location/thickness of the gastrointestinal (GI) wall (noninsulated knives: stomach, 2.0–2.2 mm; esophagus, duodenum, colon, 1.5–1.7 mm; rectum, 1.5–2.0 mm).  
Strong recommendation, low level evidence.  
There is no evidence to recommend specific ESD knives.

Several dedicated ESD devices are available for performing submucosal dissection, some allowing completion of ESD without device change, being capable of marking, injection, initial mucosal incision, submucosal dissection, and hemostasis,

while some need to be used along with other endoscopic devices.

Knives can be broadly divided into three categories:

**Insulated-tip (IT) type:** These knives are best used when dissecting from the far to the near side of the lesion or laterally. During ESD, IT-type knives generally anchor in the margin of the specimen and the cutting occurs with lateral movements performed with the shaft of the knife (and not with the tip). This allows relatively blind dissection, provided that the endoscopist has a very good orientation of the dissection planes thus maintaining the knife parallel to the muscle layer.

**Needle type:** These knives should be used to dissect from the near to the far side or laterally. The tip of the knife and the dissection plane should always be visible with no blind dissection.

**Scissor type:** These knives have a forceps-like tip that is used to grasp the tissue to be dissected, along with pulling and applying electrosurgical current.

All the available knives are single-use and most are compatible with 2.8-mm endoscopic instrument channels. Several knives are available, with different shapes, sizes, and add-on capabilities such as injection being the characteristics of the most frequently used knives described in ► **Table 1**. Knives with a jet/flush capability are widely used in Europe and have some advantages: no need to change instruments, shorter procedural time, and achievement of a safer submucosal cushion.

However, comparative data for different knives are scarce, and the choice should depend on the organ and lesion location but also on operator preference and training. The present working group feels that, given the scarcity of evidence, endoscopists performing ESD should build up experience with one or

► **Table 1** Knives used most frequently for endoscopic submucosal dissection (ESD).

Knife (manufacturer)	Characteristics	Functions <sup>1</sup>				Application
		Marking	Injection	Mucosal incision	Hemostasis	
<b>Insulated-tip cutting knives</b>						
ITknife (Olympus)	2.2-mm ceramic ball on a 4-mm length cutting knife	X	X	X	√	Gastric ESD
ITknife2 (Olympus)	2.2-mm ceramic ball on a 4-mm length cutting knife, with three electrodes in a triangular shape proximal to the ceramic ball	X	X	X	√	Gastric ESD
ITknife nano (Olympus)	1.7-mm ceramic ball on a 3.5-mm length cutting knife, with a small (0.9-mm) circular electrode proximal to the ceramic ball	X	X	X	√	Esophageal and colorectal ESD
Hybrid-knife O-type (Erbe)	5-mm long knife with an insulated hemispherical dome-shaped tip	√	√	√	√	Anywhere
<b>Noninsulated-tip cutting knives</b>						
HookKnife (Olympus) <sup>2</sup>	4.5-mm maximum length knife (adjustable) with a 1.3-mm tip bent at a right angle (adjustable direction)	√	X	√	X	Anywhere, fibrotic tissue
HookKnife J (Olympus) <sup>2</sup>		√	√	√	X	

► **Table 1** (Continuation)

Knife (manufacturer)	Characteristics	Functions <sup>1</sup>				Application
		Marking	Injection	Mucosal incision	Hemostasis	
TriangleTipKnife (Olympus) <sup>3</sup>	4.5-mm length cutting knife with a noninsulated triangular electrode at the tip (each of 1.6-mm length and extending 0.7 mm from the central part)	√	X	√	√	Peroral endoscopic myotomy (POEM)
TriangleTipKnife J (Olympus) <sup>3</sup>		√	√	√	√	
DualKnife (Olympus)	2.0-mm (gastroscope model) or 1.5-mm length (colonoscope model) knife, with a small, knob-shaped, retractable, noninsulated electrode at the tip	√	X	√	√	Anywhere
DualKnife J (Olympus)		√	√	√	√	
FlexKnife (Olympus)	0.8-mm diameter, with an adjustable loop at the tip that can be altered to varying lengths	√	X	√	√	Anywhere
HybridKnife I-Type (Erbe) <sup>4</sup>	5-mm length knife with straight needle-knife	√	√	√	√	Anywhere
Hybrid-knife T-type (Erbe) <sup>4</sup>	5-mm length knife with a noninsulated 1.6-mm diameter electrode at the tip	√	√	√	√	Anywhere
FlushKnife BTs (ball-type) (Fujifilm)	Cutting knife available in different lengths (1.5, 2.0, 2.5, and 3.0 mm) with a noninsulated ball at the tip	√	√	√	√	Anywhere
FlushKnife Ns (Fujifilm)	Needle-knife type available in lengths of 1.0, 1.5, 2.0, 2.5, and 3.0 mm	√	X	√	√	Anywhere
<b>Scissors/forceps-type knives</b>						
ClutchCutter (Fujifilm) <sup>5</sup>	Rotatable alligator forceps with serrated jaws, insulated outer edge available with lengths of 3.5 and 5.0 mm.	X	X	√	√	Anywhere
SB Knife (Olympus) <sup>5</sup>	Scissors-type knife, rotatable, with insulated blade internally lined with a cutting electrode, Three different sizes of forceps length and opening: SB Knife Jr: 3.5-mm length, 4.5-mm width; SB Knife Short, 6 mm length, 6 mm width; SB Knife Standard, 7-mm length, 8-mm width	X	X	√	√	Fibrotic tissue; Zenker's

X, not possible/not recommended; √, possible

<sup>1</sup> All knives are capable of circumferential cutting and submucosal dissection.

<sup>2</sup> The hook/L shape can be useful to retract the tissue to be cut (pulling it away from the muscularis propria) and allowing cutting in the horizontal and vertical directions (useful in the case of fibrotic tissue).

<sup>3</sup> Frequently used in peroral endoscopic myotomy; less frequently used in ESD because of perforation concerns (relatively large noninsulated distal electrode).

<sup>4</sup> These knives have a central capillary that allows penetration of the pressurized waterjet through the mucosa and lifting of the submucosa without the need for needle puncture.

<sup>5</sup> The jaws are used to grip the submucosa securely and the rotation capability allows a precise approach to the lesion.

a few different knives, the type of knife being at the discretion of the endoscopist. Costs and a rational use of devices should also be considered in the choice of knife.

## Esophagus

In studies reporting on technique and outcomes of ESD for early esophageal squamous cell lesions, various types of ESD knives are described. However only few head-to-head comparisons are available. In a recent multicenter retrospective cohort study, a shorter procedure time was reported if the ESD was

performed using a scissor-type knife versus the conventional ESD knives [37]. However, evidence is too weak to formulate specific recommendations in this respect.

## Stomach

For gastric ESD, there is also a paucity of comparative studies and most centers use insulated-tip knives (ITknife 2, Olympus) or needle-tip knives with injection capability (Dual Knife J, Olympus). However, there are some studies comparing different knives but without showing significant advantages of one

knife over another. The HybridKnife O-type (Erbe) was compared in a randomized study with the iTknife2 (Olympus) and the former was associated with lower procedural time (43 vs. 60 minutes,  $P = 0.001$ ), although there were no differences in efficacy and safety outcomes [38]. In subgroup analysis, procedural time was significantly lower for lesions located in the lower third and in lesions  $\leq 40$  mm but not in other settings. A lower procedural time was also found in an RCT comparing the HybridKnife I- or T-type (Erbe) versus conventional knives without a waterjet function [39]. Another RCT compared the ClutchCutter (a scissors-type knife from Fujifilm) with the IT-knife2 (Olympus) and a lower procedural time was found with the latter (66 vs. 47 minutes,  $P = 0.004$ ) [40].

### Duodenum

Although ESD does not have a place in routine practice in the duodenum, the most experienced centers use short needle-type knives with injection capability [41,42]. Although prospective comparative data are missing, a retrospective study comparing a scissors-type knife and the FlushKnife (Fujifilm) reported better outcomes using the scissors-type knife, with a higher R0 resection rate and a zero intraoperative perforation rate [43]. However, it should be noted that this study comes from a team with experience using a scissors knife for colorectal ESD and most centers use established needle-tip knives.

### Colon

The use of the ITknife nano (Olympus) was shown to shorten ESD time (50 vs. 70 min) when compared with the DualKnife (Olympus) in a retrospective study for  $>40$  mm colorectal lesions [44]. The use of scissor-type knives (ClutchCutter or SB Knife [Olympus]) was also demonstrated to be effective and

safe [45], and was associated with improved rates of self-completion by residents, without improved speed of dissection, in an RCT [46].

## 5 Electrocoagulation

In ESD, devices apply electrocoagulation current to tissues (to perform incisions and to coagulate) that is generated by an electrosurgical unit (ESU). ESUs are high frequency generators that are now capable of sensing changes in tissue impedance and consequently adjusting voltage, thus allowing responsive adaptation to guarantee consistent and safe treatment effects. There are various types of ESUs and they can assist the endoscopist during the different steps of ESD.

Although several ESUs are available on the market, most of the reported experience with endoscopic resection relates to ESUs from Erbe (VIO 200D, VIO 300D, VIO 3) and Olympus (ESG-300), that also have manufacturer's specifications adapted to ESD (► **Table 2**) [47, 48]. ESUs generally have incision/cutting and coagulation outputs that are both used during ESD. In brief, cutting modes generate a steam explosion (spark) by raising the intracellular temperature, while coagulation modes dehydrate and dry tissues by slowly raising the temperature without tissue explosion. However, it should be noted that a spark can also be generated in coagulation modes if more than 200 peak voltage (Vp) is applied; this can occur if the current density is high, and the contact area is narrow. Nevertheless, with some coagulation modes (SoftCoag) the voltage is always  $<200$  Vp and thus only dehydration and drying occurs without spark generation, even with a continuous wave [49].

The latest ERBE generator (ERBE VIO 3) includes the following cut modes: AUTO CUT, smooth incision with minimum to

► **Table 2** Recommended settings of most frequently used electrosurgical units in endoscopic submucosal dissection (ESD). These settings may differ depending on the knife, the location, and individual preferences.

ESD stage	VIO 200D	VIO 300D	VIO 3	ESG-300
Marking (noninsulated instrument)	SOFT COAG, Effect 5, 60–100 W	SOFT COAG, Effect 5, 60–100 W	SOFT COAG, Effect 5 FORCED COAG, Effect 3	ForcedCoag, Effect 2, 20 W SoftCoag, Effect 3, 50 W
Precut/incision (noninsulated knife)	ENDOCUT Q, Effect 2 (Cutting duration 3, Cutting interval 3) DRY CUT, Effect 2–3, 30–80 W	ENDOCUT I, Effect 2–4 (Cutting duration 1–3, Cutting interval 1–3) DRY CUT, Effect 2–3, 30 W	DRY CUT, Effect 3.5 ENDOCUT Q Effect 1–2	PulseCut Fast, Effect 2, 120 W BlendCut, Effect 2, 30 W
Submucosal dissection (knife)	ENDOCUT Q, Effect 2 (Cutting duration 3, Cutting interval 3) DRY CUT, Effect 2, 30–80 W	FORCED COAG, SWIFT COAG, DRY CUT, Effect 2–3, 35–100 W	SWIFT COAG Effect 3–4 DRY CUT Effect 3–4 ENDOCUT Q Effect 1–2	PowerCoag, Effect 2–3, 30 W
Hemostasis (hemostatic forceps)	FORCED COAG, Effect 2, 60 W	SOFT COAG, Effect 5, 60–100 W	SOFT COAG, Effect 5 SPRAY COAG Effect 1–4	PowerCoag, Effect 2, 30 W



moderate hemostasis; HIGHCUT, smooth incision with minimum to moderate hemostasis, used for tissues with poor conductive properties and resections using nonconductive irrigation liquids; DRYCUT, controlled incision with significant hemostasis; and ENDOCUT Q and I, fractioned cutting mode with cutting and coagulation intervals. The coagulation modes available and most used in ESD are: SOFTCOAG, slow, deep coagulation with no tissue carbonization; FORCEDCOAG, effective and fast coagulation with moderate to intense hemostasis; SPRAYCOAG, noncontact, surface coagulation with low penetration; SWIFTCOAG, intensive coagulation enhanced with slight tissue-separating properties; and PRECISESECT, medium coagulation with limited tissue-separating properties, dynamically adapting modulation, and optimized exposure because of less development of smoke and carbonization [47].

The Olympus ESG-300 includes cutting modes such as: PureCut, continuous cutting; PulseCut, controlled cutting with an intermittent duty cycle of different duration; and BlendCut, cutting of varying tissue structures with increased hemostatic capacities. It includes coagulation modes activated by the blue pedal such as: PowerCoag, superficial coagulation with increased dissection capability; ForcedCoag, superficial pinpoint coagulation; SprayCoag, high peak voltage for superficial coagulation without contact between the instrument and the tissue; and SoftCoag, for deeper coagulation [48].

Regarding the different steps of ESD, coagulation marks are usually made using SoftCoag or ForcedCoag, while EndoCut or DryCut are generally used to perform the mucosal incision. Submucosal dissection can be performed using SwiftCoag, EndoCut, ForcedCoag, and PreciseSect modes. For hemostasis, SoftCoag (which does not have tissue-separating properties) is recommended, while ForcedCoag and SprayCoag are also options. A summary of the modes, effect, and power recommendations for Erbe and Olympus ESUs is provided in ► **Table 2** [49–51].

## 6 Solutions for submucosal injection

### RECOMMENDATION

**6** ESGE suggests that isotonic saline or viscous solutions can be used for submucosal injection during ESD, depending on costs and local availability. Strong recommendation, low level evidence.

Submucosal injection is a fundamental part of ESD, allowing the expansion of the submucosal layer and separation of the lesion from the muscularis propria, to provide safer dissection and decreased perforation risk. The first injection should take place immediately outside the lesion margins/markings since this is where initial mucosal incision will be done. If a circumferential mucosal incision is to be made, the injection should be done in the periphery of the specimen since the circumference will be incised first; the center of the lesion does not need to be injected in this phase. When using an insulated-tip knife, the entire circumference can be injected, whereas if a needle-type

knife with injection capability is used, stepwise injection should be done as needed. After initial mucosal and/or circumferential incision, injection should be done as needed in the submucosal tissue that is to be dissected, the principal rule being that the tissue to be cut should be injected before dissection. The injection should be directly into the submucosa: injection through the lesion is discouraged. The injection should always be parallel to the muscle layer, avoiding injection perpendicular to the wall of the organ.

The inclusion of dyes in the submucosal solution allows a clearer identification of submucosal tissue, and the addition of vasoconstrictors may decrease intraprocedural bleeding. The ideal injection solution should be long-lasting, inexpensive, available, and should not damage tissues. Normal isotonic saline was the first and most frequently used injection solution, but alternative solutions are available with properties that may contribute to decreasing procedure duration and reducing adverse events; these are detailed in ► **Table 3**.

Given its availability, low cost, and absence of toxicity and tissue damage, normal saline remains a valid option for submucosal injection, especially in smaller lesions [52]. Although there is consistent evidence that hypertonic and viscous solutions increase the duration of the submucosal cushion, and decrease the number of injections needed and procedure duration, their benefits regarding clinical outcomes are more controversial. Indeed, there was no evidence of benefit from using alternative agents for most important outcomes, such as en bloc resection, curative resection, and adverse events, in a systematic review published in 2016 [53]. Since the publication of that systematic review, further data have been scarce. An RCT compared sodium carboxymethylcellulose with sodium hyaluronate, finding no differences in procedure time, clinical efficacy, or adverse events [54].

Most knives now have an injection function to allow for very quick, multiple injections when required. This reduces the need for injection needle and instrument exchange, making ESD more time-efficient. However, injection of solutions with high viscosity (e.g. hyaluronic acid, proprietary solutions) may be difficult through the knives; and such solutions could require needle injection, entailing additional instrument exchange and time. Some of this time could be saved by a reduced need for injection but more comparative data are needed to support this theory.

### Add-ons to submucosal injection solutions (adrenaline, dyes)

Regarding additional substances that can be added to normal isotonic saline, even though there is little evidence for or against the practice, most endoscopists use some kind of blue dye to improve visualization by creating contrast with mucosal and muscle layers, and also diluted adrenaline. The latter showed decreased procedural time in a propensity-matched study, probably because of less intraprocedural bleeding and improved visualization [55].

Concerning blue dye, we suggest using only a few drops diluted in normal isotonic saline, since higher concentrations may darken the submucosal space and make vessel visualization

► **Table 3** Solutions for submucosal injection.

	Characteristics	Advantages	Disadvantages
Normal saline	0.9% sodium chloride	Widely available, low cost No toxic effect or tissue damage	Rapid absorption Shorter duration of lifting
Colloids (Hydroxyethyl starch; succinylated gelatin)	Colloidal solutions that exert oncotic pressure similar to human albumin	Widely available, low cost No toxic effect or tissue damage Longer submucosal elevation (vs. normal saline)	Off-label use (not in drug datasheet of colloid solutions)
Dextrose water	Hypertonic solution	Available, low cost Longer submucosal elevation (vs. normal saline)	Potential histopathological damage to resected tissue and impaired ulcer healing
Glycerol	Hypertonic solution (10% glycerin, 5% fructose in normal saline)	Longer-lasting submucosal elevation No tissue damage	Costs (vs. normal saline)
Hyaluronic acid (HA)	Glycosaminoglycan with high viscosity and water retention properties (0.4% sodium-HA solution)	Longer-lasting submucosal elevation	High cost, less available Concerns about stimulation of residual tumor cells in piecemeal resections
Hydroxypropyl methylcellulose	Cellulose derivative with viscoelastic properties	Longer-lasting submucosal elevation Minimal tissue reaction Less expensive than hyaluronic acid	Concerns about antigen-antibody reaction (synthetic product)
Fibrinogen solutions	Solutions with high viscosity	Longer-lasting submucosal elevation Microvascular hemostatic properties	Costs (reasonable)
Eleview	Synthetic solutions supplied containing water, normal saline, poloxamer 188, polyoxyl-15-hydroxystearate and medium-chain triglycerides	Long-lasting submucosal elevation (up to 45 minutes)	High cost
ORISE gel			High cost Foreign-body granulomatous reaction; mimics mucin on hematoxylin and eosin (H&E) staining

more difficult. With regard to adrenaline, most practitioners use diluted adrenaline, 1:20 000, 1:50 000, or 1:100 000. Others do not use adrenaline, arguing that it may increase the risk of tachyarrhythmia during the procedure; although this hypothesis makes sense, it has not been clearly proven. A 1:50 000 adrenaline dilution may be a good option for most patients since it is unlikely to provoke significant tachyarrhythmia and may have the required effect of decreasing intraprocedural bleeding. On the other hand, in patients with significant cardiovascular risk, it may be a safer option not to use adrenaline prophylactically.

However, our search found no study comparing outcomes with different adrenaline dilutions, or with or without adrenaline, and/or with or without blue dyes, and for this reason no recommendation can be made.

## 7 Traction devices and techniques

### RECOMMENDATIONS

**7** ESGE recommends the use of traction methods in esophageal ESD.

Strong recommendation, high level evidence.

**8** ESGE recommends the use of traction methods for ESD of gastric lesions located in the greater curvature of the upper/middle stomach (particularly if > 2 cm) and if difficult access to the submucosa is encountered during ESD.

Strong recommendation, moderate level evidence.

**9** ESGE recommends the use of traction methods in colorectal ESD.

Strong recommendation, high level evidence.

### Technical aspects

After achievement of mucosal incision and trimming of the submucosa, different traction techniques have been developed to lift the mucosal flap and provide better exposure of the submucosal space, facilitating visualization with accurate identifi-

cation of the dissection plane and vessels [56]. The use of gravity, position changes, and distal attachments (caps) may suffice to complete ESD. However in certain locations these may not be enough and for this reason new traction devices and strategies (external or internal traction) have been developed with the goal of decreasing procedure time and adverse events.

The topic of traction in ESD can be approached by classifying the techniques into those that do or do not require an extra device. Traction as provided by a distal cap attachment should always be considered in ESD, given its advantages in exposing the submucosa. An overview of the advantages and disadvantages of different traction techniques is presented in ► **Table 4**.

### Distal attachment cap

Soft distal attachment caps help to prevent the endoscopic field of view being obstructed by the mucosa, and provide a clear and stable view during ESD. Several models are available, adapted to each endoscope diameter, with side-holes and/or gutters for better fluid drainage, and of different shapes, for example cylindrical, or tapered to facilitate tunneling in the submucosal layer.

### Traction techniques without device assistance

**(a) Gravity-assisted ESD** The submucosal plane can be naturally exposed by the effect of gravity on the mass of the specimen as it is progressively freed from the underlying planes. This im-

proves visualization; increases tissue tension, which decreases the contact area between the tissue and electro-surgical knife thus enabling a more effective cut; and allows the immediate drainage of blood in the case of bleeding.

Changes in patient position have been shown to help in exploiting gravity, especially in the colon. In this technique, the optimal position is estimated by the location of the fluid in the lumen: it should be on the opposite side to the lesion. In general, the dissection should start from the higher (opposite to gravity direction) side to allow the specimen to be pulled by gravity, with consequently better submucosal exposure. Thus, after initial dissection, the specimen may fall to the lumen center exposing the submucosal space. Although at the beginning of dissection the traction due to gravity may be low, as dissection progresses the weight of the specimen also increases and so do the traction forces.

Nevertheless, a study showed that positional changes in colonic ESD were not helpful in 22% of cases, compared with 3% in rectal ESD [57]. It must also be borne in mind that patient mobilization in order to exploit traction due to gravity is time-consuming, and may lead to a reduction in scope maneuverability, especially in the colon.

**(b) Tunnel, tunnel-and-bridge, and pocket creation ESD** In the tunnel technique, after proximal and distal mucosal incision, a submucosal tunnel is created joining the two edges. Then two lateral mucosal incisions are made (the margin that

► **Table 4** Advantages and disadvantages of external and internal traction techniques.

Traction method	Advantages	Disadvantages	Cost
<b>External traction</b>			
Clip-and-line	Easy to use Widely available	Only one traction direction	€
Clip-and-snare	Traction and push Widely available	Cumbersome in the ESD field of view Unexpected interaction with the scope	€
External forceps	Push and pull movements Widely available	Insertion may be difficult and traumatic Unexpected interaction with the scope	€
Endotrac	Easy to use Ability to change traction direction	Linked to the scope movement Requires working at a distance from the dissection plane	€€€
Double scope	Dynamic and real-time triangulation	Friction between scopes Problems with light artifacts from both light sources Requires two endoscopy platforms and operators	€€
Tracmotion, Endolifter	Ability to change traction direction	Linked to the scope movement Requires working at a distance from the dissection plane	€€€
<b>Internal traction</b>			
Double-clip traction	Widely available Adjustable during procedure Traction adjustment by insufflation variation	Not commercially available Latex allergy Risk of specimen injury	€
ProdiGI traction wire	Easy to use and place Repositionable clips	Cumbersome in the ESD field of view Limitation for large lesions	€€
Magnet-assisted traction	Adjustable during procedure Allows adjustment of traction by insufflation	Risk of specimen injury	€€

is on the gravity [lower] side is incised first), completing the procedure. Traction is provided by the stretching of the specimen between the lateral edges [58].

In the rectum and the cardia, the use of retroflexion allows a variant of the tunnel technique, the “tunnel-and-bridge” method. After tunneling from the proximal to the distal edge of the lesion, and completing the lateral mucosal incisions without submucosal dissection, the scope is passed through the tunnel. Retroflexion is then applied leading to continuing traction on the specimen by the scope itself, allowing completion of the procedure by cutting the remaining lateral submucosal fibers [59].

The pocket-creation method (PCM), discussed above, provides traction from two sources: from the specimen edges’ being left in place during the first phase of the procedure and from traction by the endoscope itself during the partial tunneling in the pocket.

**(c) Tissue traction** In the esophagus, leaving a short tissue piece attached at the oral side may be sufficient to maintain traction during underwater or tunneling dissection.

#### Device-assisted traction: External techniques

**(a) Clip-and-line** Also called clip-and-thread, this is a simple technique in which, outside the patient, a clip is introduced through the working channel. A silk line or dental floss is tied to one of the arms of the clip. The clip is then drawn back into the working channel. The scope is then inserted into the patient, with the line running outside the scope. The clip is subsequently deployed to the edge of the specimen, grasping the mucosal flap but taking care to not grasp the muscle layer. The lesion can then be pulled in the oral or anal direction by external traction on the line. This technique, although simple and cheap, involves removal and reintroducing of the scope, and control of traction may be difficult and only allows pulling in one direction.

**(b) Clip-and-snare** This is similar to the clip-and-line method but uses a snare (instead of line/floss) that is pre-mounted at the tip of the endoscope, and again runs alongside the scope, to provide external traction, which allows pull or push movements. There is also an adaptation of the clip and snare method with a dedicated line with a clinch-knotted loop at its tip that is hooked around one arm of an hemostatic clip (EndoTrac) [60]. The wire can be loosened and adapted, alternating traction and facilitating changing the direction of traction.

**(c) External forceps** Outside of the patient, a grasping forceps inserted through the working channel is used to grab a second external grasping forceps near the tip. The scope is then reinserted with the two grasping forceps, one in the working channel and the external forceps running alongside the scope. The external forceps is anchored to the edge of the lesion and the other grasping forceps is then released and retrieved through the working channel. Although this can provide push and pull movements, the introduction of the device may be difficult and traumatic.

**(d) Double-endoscope** In this technique a second small-caliber endoscope is used to apply traction to the mucosal flap with a grasping forceps [61, 62].

**(e) Use of a double-channel endoscope** A double-channel scope combined with the use of forceps, including rotatable

devices such as the TracMotion (Fujifilm), can also be used to provide modifiable traction during ESD [63].

**(f) Additional external channel or device** The use of an external channel or device, designed to be attached distally to the scope has also been described (AWC, Ovesco; Endolifter, Olympus) [64, 65]. These can allow passage of devices (e. g. forceps) to apply traction, acting as an extra hand, and can facilitate ESD.

#### Device-assisted traction: Internal traction techniques

**(a) Double-clip traction** This ESD method uses a short flexible traction device. This may be a spring (also called the S-O clip method) or a rubber band [66] or multiloop on a ring thread. After partial or complete circumferential incision and trimming of the edge, a clip attached to a spring or rubber band is advanced through the operating channel and attached to the edge of the mucosal flap. A second clip is used to hook the rubber band/spring and is then fixed to the contralateral digestive wall. The rubber band double-clip method can be adapted to the anatomy by choosing a band length according to the size of the lumen/lesion.

The technique has been recently improved by providing multiple traction points, using four rubber bands linked to a central rubber band, to get traction on the different edges of the lesion; this multipolar “spider” traction was applied in the stomach [67] and in the colon [68].

**(b) Internal traction wire** This device (e. g. the ProDiGi Traction wire, Medtronic) consists of a metallic clip pre-assembled with a curved flexible wire loop made of nitinol alloy with shape memory, that is attached to the margin of the specimen [69]. A second clip is used to grasp the loop and attach it to the ipsilateral digestive wall behind the lesion, thus providing traction via the arch of the metal loop. The second clip can be easily detached from the GI wall with a biopsy forceps, and further clips can be applied in other locations if modification of traction is needed.

**(c) Magnetic-assisted traction** Two techniques, namely magnetic anchor and magnetic bead-assisted, have also been demonstrated to facilitate colorectal ESD. A standard clip is used to attach the mucosal flap of the target lesion to a thread that is in turn connected to a magnet. Lifting is effected by a second magnet outside the body of the patient or by a second magnetic bead connected to a clip fixed on the contralateral wall.

**(d) Adaptive traction with adjustable force** This is possible using the homemade A-TRACT device. The multipolar (“spider”) system described above is enhanced by the addition of a loop that may be tightened. As the force exerted by the central rubber band decreases as dissection progresses, the loop is tightened thus maintaining the traction force [70–73].

#### Evidence

A recent meta-analysis including only RCTs (12 studies) showed that traction is associated with shorter procedural duration, lower adverse events, and lower perforation rate, although a benefit on R0 resection was not verified. On subgroup analysis, the magnitude of effect/benefit was higher in esophageal and colorectal ESD [74]. Specifically, in esophageal ESD traction was associated with significantly shorter procedural time

(mean difference –15 min) and significantly lower overall complications and perforation, and in colorectal ESD traction was associated with significantly shorter procedural time (mean difference –33 min) and lower overall complications. However, in the stomach there was a trend to shorter procedural time and lower overall complications and perforation but this did not reach statistical significance. A summary of the available traction studies is presented in **Table 1 s** (available online in Supplementary material).

In the esophagus, prospective studies report the usefulness of the clip-and-line technique [75–77] to facilitate ESD and reduce dissection time. The clip-and-line technique in association with tunneling also showed a high success rate in the hands of less experienced endoscopists in a western setting [75, 78]. This technique combines the traction ability of two different techniques and potentially makes ESD safer and quicker, but it requires further validation and comparison with conventional technique. In the stomach, most studies used the clip-and-line/dental floss traction technique. An RCT showed a significant reduction in procedural time but only for lesions located in the greater curvature of the upper or middle stomach [79]. In the duodenum, traction has also been reported in a case series of 29 patients, with a shorter procedural duration and reduced risk of perforation [80].

In the colon, additional studies besides those included in the previous meta-analysis showed that the double-clip and rubber band method is useful for difficult lesions (fibrotic recurrent adenoma or periappendiceal) and is associated with reduced procedure time and completion of resection [7, 81, 82]. A recent European multicenter single-arm study also showed that this method allows achievement of outcomes comparable to those from Japanese experts (en bloc 96%, R0 88%) with a resection speed twice as high as previously reported (mean dissection speed 39.4 mm<sup>2</sup>/min) [83]. A recent animal study also showed a potential superiority of the double-clip and rubber band method compared to the PCM in animal models [84].

Two studies also showed the feasibility of magnetic traction with improved speed of dissection in one of these studies [85, 86].

The double-clip traction strategy also facilitates performance of ESD by trainees and shortens their learning curve, also improving early results in terms of dissection speed and effectiveness of ESD [84]. Therefore, this technique could be introduced in the training phase although the precise timing of introduction still needs more evidence.

In summary, use of traction consistently decreases procedure time and adverse events in esophageal and colorectal ESD, with some studies also finding higher en bloc and R0 rates. In the stomach, the benefit of routine traction is less clear but it can have a role in lesions located in the upper and middle third, especially in the greater curvature. Since most traction techniques are associated with low costs and low adverse events, they should be routinely considered in esophageal and colorectal ESD and can be considered if technical difficulties are encountered during gastric ESD.

## 8 Hemostasis

### RECOMMENDATIONS

**10** ESGE suggests administration of preprocedural proton pump inhibitors (PPIs) before esophageal and gastric ESD. Weak recommendation, low level evidence.

**11** ESGE recommends post-procedural high dose PPI (or vonoprazan) after gastric or junctional ESD although the optimal dosage and administration route have not been established. Strong recommendation, low level evidence.

**12** ESGE recommends coagulation of visible vessels in the ESD wound after gastric ESD. Strong recommendation, low level evidence.

**13** ESGE recommends against routine prophylactic coagulation of visible vessels in esophageal/duodenal/colorectal ESD. Weak recommendation, low level evidence.

**14** ESGE recommends that after gastric ESD, in patients with high risk of post-procedural bleeding (receiving anti-thrombotics and/or lesion resection size 40 mm), additional prophylactic methods can be considered, such as clipping of major vessels or shielding with polyglycolic acid sheets and fibrin glue. Weak recommendation, low level evidence.

**15** ESGE recommends against routine closure of the ESD defect, except in duodenal ESD. Weak recommendation, moderate level evidence.

### Intraprocedural bleeding

Intraprocedural bleeding (IPB) is frequently encountered during ESD and most of the time it is considered an inherent event rather than a complication. IPB should thus be considered a complication if it impairs en bloc resection, or if it is associated with a drop in hemoglobin >2 g/dL, or hemorrhagic shock, or procedure interruption with need of radiological or surgical intervention to control bleeding. Preprocedural administration of proton pump inhibitors (PPIs) increases gastric pH at the time of ESD; theoretically this improves coagulation, although a study did not find a benefit on IPB [87]. Although the evidence is scarce and a clear clinical benefit has not been demonstrated, the administration of a single dose of PPI before the resection of gastric or gastroesophageal junctional lesions is a common practice, being a cheap and safe measure that can potentially decrease IPB, with consequent decrease of procedural time.

Prophylactic thermal coagulation of visible vessels in the dissection plane before cutting can reduce bleeding events. To minimize bleeding risk, compliance with guidelines for anti-thrombotic therapy management is advised. Although an extensive revision of antithrombotic therapy management is outside of the scope of this technical review, it is important to state that ESD should not be performed in patients receiving thienopyridine therapy since this is associated with a higher post-procedural bleeding (PPB) risk (~25%) [88]. However

compelling evidence suggests that low dose aspirin does not significantly increase IPB/PPB risk while its discontinuation is associated with a significantly higher risk of thrombotic events (**Table 2s**) [89].

Minor oozing from small vessels during ESD can be treated by soft/swift coagulation with the tip of the ESD knife, and significant bleeding from larger vessels with a hemostatic forceps, without interfering with continuation of the procedure [90]. The prophylactic coagulation of larger vessels before cutting with the tip of the knife, using forced coagulation at low voltage (effect 1, 10W), was also reported to be effective and safe [91]. Of note, when working under saline, the use of bipolar hemostatic forceps might be more effective. The bleeding point should be precisely coagulated to avoid excessive thermal injury that may lead to delayed perforation or post-ESD electrocoagulation syndrome (PEECS).

The use of caps and waterjet facilitate identification of and access to the bleeding vessel, reducing the need for blind coagulation. Red dichromatic imaging, a modality that improves the identification of bleeding points, was reported to improve the visibility and the detection of the bleeding point and to reduce endoscopist stress, although it did not decrease hemostasis time nor ESD time [92, 93].

In cases of significant bleeding that cannot be controlled with the previous methods, hemoclipping can be applied as a rescue treatment, but its use is discouraged as this may interfere with further dissection. If hemoclips are needed, proceeding with submucosal dissection around the bleeding vessel to create space before deploying the clip should be considered. A self-assembling peptide has recently been reported in an RCT to be an effective alternative to thermal ablation in controlling nonspurting IPB [94].

### Risk factors for and prevention of delayed bleeding

The risk of PPB is different according to the location, being higher in gastric and duodenal ESD (5%–10% and 5%–17%, respectively) and lower after esophageal (1.8%) and colorectal (2.7%–4.3%) ESD [95–100].

#### Esophagus

PPB is rare after esophageal ESD, occurring in 1%–2% of cases [95]. Unlike for the stomach, there is no literature concerning the effectiveness of coagulating visible vessels or wound closure to prevent PPB. Nevertheless, coagulation of vessels is performed in some centers, with a minimal risk of adverse events, which can contribute to the low PPB rates after esophageal ESD.

#### Stomach

In gastric ESD, several risk factors for PPB were identified in a meta-analysis, namely: antithrombotic therapy (OR 1.63); male sex (OR 1.25); cardiopathy (OR 1.54); cirrhosis (OR 1.76); chronic kidney disease (OR 3.38); tumor size >20 mm (OR 2.70); resection size >30 mm (OR 2.85); location in the lesser curvature (OR 1.74); flat/depressed morphology (OR 1.43); carcinoma histology (OR 1.46); ulceration (OR 1.64); and procedure duration >60 minutes (OR 2.05) [101]. These risk factors can be taken into account when deciding inpatient surveil-

lance duration and the eventual use of additional preventive measures to reduce bleeding risk. Individualized risk prediction tools for PPB with moderately good accuracy have been developed, including the BEST-J score that includes 10 variables and classifies patients into four categories with different bleeding risks [102–104].

PPI administration after gastric ESD has been shown to decrease PPB when compared with histamine-2 receptor antagonists (H2RAs) [101]. Also continuous PPI infusion for 48–72 h after ESD is frequently used, although the benefit of this aggressive acid-suppressive approach has been questioned by RCT findings of similar PPB rates in patients given intravenous bolus PPI [87, 105], oral PPI [106], and even placebo [107] (**Table 3s**). Vonoprazan, a potassium-competitive acid-blocker (P-CAB), approved in Japan, has also been evaluated in this setting, but several meta-analyses did not show superiority of this therapy in reducing PPB when compared with PPI, although P-CABs have shown some advantages in ulcer healing speed [108–112]. Regarding preprocedural PPI administration, there is no evidence of benefit in preventing PPB although there are potential advantages in reducing IPB [113].

PPB prevention can also be accomplished with endoscopic interventions. During ESD, intraprocedural bleeding should be managed with knife coagulation or hemostatic forceps (**Table 1**, **Table 2**), and coagulation of visible vessels at the end of the procedure has been shown to significantly reduce PPB in a retrospective study [114] (also see **Table 4s**) and has been routinely implemented in practice thereafter. Additional measures (e.g. mucosal closure; shielding of resection scar) have also been evaluated but the evidence does not support their routine utilization (**Table 5s**). However, in patients at higher risk of PPB (receiving antithrombotic therapy, and/or resection specimen  $\geq 40$  mm), shielding of the ESD scar with polyglycolic acid sheets and fibrin glue was found to significantly reduce PPB risk in two retrospective studies and an RCT [115–117] and can be considered in these cases, although further evidence of benefit is necessary. Experience in endoscopic suturing is limited and needs further study to evaluate the role of mucosal defect closure on PPB, although initial results showed a reduced risk of PPB in patients receiving antithrombotic therapy [118].

#### Duodenum

Although ESD in the duodenum is seldom recommended in practice, when it is performed the PPB risk is high (18%) and so the implementation of preventive measures to decrease bleeding risk is advised. Coagulation of visible vessels after ESD has never been compared to a strategy without coagulation, but a study showed a benefit of vessel coagulation in preventing immediate bleeding after EMR, although it did not decrease PPB [119]. Coverage of mucosal defects and systematic closure of the defect with conventional clips, over-the-scope (OTS) clips, or mucosal sutures also seem to reduce PPB (**Tables 4s, 5s**) [43, 120, 121]. Although comparative data are scarce, given the high risk of PPB, preventive measures should be implemented. For large distal duodenal resections, some

also advise external biliopancreatic drainage if the defect cannot be successfully closed.

### Colon

According to some meta-analyses on this topic, PPB is less frequent in colorectal ESD as compared to EMR (ESD 2.8%–4.3% vs. EMR 4.3%–9.6%) [100, 122], although other meta-analyses found similar bleeding rates [123–125]. A possible explanation for this difference among studies is that dissection through the lower third of the submucosal plane in ESD mandates complete prophylactic coagulation of all large penetrating feeding vessels, while in EMR snare electrocautery in the more superficial submucosal plane poses the risk of thermal injury and exposure of larger vessels in the deeper submucosa that can subsequently rupture and lead to delayed bleeding [98, 126].

In colorectal ESD, the most consistent risk factor for PPB is rectal location with an OR between 4.2 and 10.1 (vs. the colon); this contrasts with polypectomy/EMR data, where proximal location is associated with higher PPB risk. This underlines the possibly different mechanisms and risk for delayed bleeding in EMR vs. ESD. Abundant vasculature and higher intraluminal pressures and stretching might contribute to the higher bleeding rates following rectal ESD. Other possible risk factors for PPB include lesion size, use of antithrombotics, hypertension, malignant invasion, and  $\geq 3$  arterial bleedings during the procedure [127–133].

In colonic EMR, a recent meta-analysis showed that prophylactic clipping of the EMR defect in large and proximal lesions can significantly reduce the risk for delayed bleeding (Tables 4s and 5s) [134]. However, a convincing protective effect of endoscopic closure of the ESD defect with regard to bleeding and other complications has not been yet established. A recent meta-analysis comprising 8 studies suggested that prophylactic endoscopic closure may decrease the occurrence of delayed bleeding after colorectal ESD (pooled OR 0.19, 95% CI 0.08–0.49), but no significant decrease in incidence of PEECS and delayed perforation was found. However, these results must be interpreted with caution as mainly retrospective cohort studies were included [135]. A recent RCT including 220 patients showed that prophylactic clip closure after colorectal ESD did not decrease complication or surgery rates, including delayed bleeding and PEECS [136]. A recent study with propensity matching also showed that closure did not significantly decrease major bleeding (2% vs. 5%,  $P=1.0$ ) although it was associated with a significantly lower risk of overall adverse events (mostly minor) [137].

## 9 Prevention and treatment of post-ESD strictures

### RECOMMENDATIONS

**16** ESGE recommends corticosteroids (local triamcinolone injection, oral steroid therapy, or combination) after resection of >50% of the esophageal circumference, although the optimal strategy remains to be determined. Strong recommendation, moderate level evidence.

**17** ESGE recommends against steroid therapy after gastric and colorectal ESD.

Weak recommendation, low level evidence.

### Esophagus

In esophageal ESD, bleeding, perforation and mortality are very rare (<2%). However, stenosis is a frequent adverse event whose occurrence is strictly related to the circumferential extent of ESD. Endoscopic resections comprising >50% of the esophageal luminal circumference are prone to stricture formation, and after full circumferential resection strictures occur in almost all patients [138–140]. A meta-analysis found that upper third location (OR 1.5), IIa/IIc morphology (OR 2.8), tumor deeper than m1 (OR 7.5), tumor deeper than m2 (OR 12.7), circumferential extent >3/4 (OR 38), and longitudinal length (mean difference 13.7 mm) are risk factors for stricture development [141].

Measures to decrease stricture rate include corticosteroids (either oral and/or locally injected), pre-emptive balloon dilation, temporary stent placement, injection of botulinum toxin, shielding of the scar with polyglycolic acid sheets and synthetic peptide gels (Table 6s).

Prophylactic balloon dilation after ESD involving >75% of the circumference has been shown to be safe and to reduce the incidence of stricture. However, it requires multiple dilation sessions and is inferior to corticosteroids.

Several retrospective reports, one matched case–control study and two RCTs showed a beneficial effect of injection of corticosteroids (triamcinolone) in the remaining submucosa immediately after ESD [142–144]. The stenosis rate following local injection of triamcinolone for noncircumferential lesions was 10%–45%, which tended to be lower than the stenosis rate of 61%–82% without such injection. Furthermore, the mean number of balloon dilation sessions required after stenosis tended to be fewer following local injection (injection 0–1.7 sessions vs. noninjection 2–6). However, triamcinolone did not prevent stenosis after circumferential resections (stenosis rates of 100%) [144, 145]. Other authors have used a combination of local and oral steroids but without showing a significant benefit [145, 146]. A stepwise approach (triamcinolone injection with add-on oral steroids in the case of >90% resection was also proposed, and showed low stricture rates [147].

Oral steroids are also widely used and have advantages, such as no need of special techniques/equipment and no variability in procedures (as occurs in injection therapy). The use of oral

steroids for stricture prevention after esophageal ESD was first reported by Yamaguchi et al. [148]. Prednisolone was administered orally at a dose of 30 mg per day starting on the 3rd day after ESD, titrated in weekly decrements of 5 mg, and discontinued after 8 weeks. Among patients with a mucosal defect of more than 75%, including total circumferential ESD, the incidence of stricture was significantly lower than in patients with prophylactic endoscopic balloon dilation (EBD) (5% vs. 32%, respectively). The efficacy of oral prednisone was further demonstrated in several retrospective cohort studies, and shorter as well as longer steroid courses have been described [149–152]. The efficacy of oral steroids, in tapering doses over an 8-week period has also recently been reported following ESD for Barrett's neoplasia [153].

A recent network meta-analysis supports the effectiveness of corticosteroids in patients with widespread esophageal ESD in the reduction of stricture rates and number of dilations needed [154]. Some retrospective studies compared oral steroids with injection treatment and found no significant difference [155, 156]. However, since direct head-to-head comparisons between oral and locally injected corticosteroids are missing, no specific recommendation can be made on the optimal route and regimen. Topical budesonide application has also been reported in a prospective cohort of patients with a more than 50% mucosal defect, but no significant difference in stricture rate could be shown (16% budesonide vs. 28% controls) [157].

Complications of oral steroid administration have been reported and are possibly related to the dosage and duration of steroid intake and patient immune status [152]. When using local administration, injection into the muscularis propria should be avoided since it might cause delayed perforation and abscesses [158].

Other strategies for stricture prevention have also been investigated, but none can be recommended at this stage. Prophylactic stent placement has been studied, with interesting results reported but also induction of stent-related complications such as perforations and stent migration. Regenerative medicine and the application of matrix or polyglycolic acid sheets, alone or in combination with steroids, showed some benefit in a retrospective study [159]. An RCT demonstrated the benefit of placing a polyglycolic acid-sheet coated stent after ESD involving >75% of the circumference when compared with stent alone [160]. In an RCT, injection of botulin toxin in the esophageal wall was shown to reduce the rate of stricture formation but a comparison between botulin toxin versus triamcinolone injection showed no significant difference [161, 162].

## Stomach

Stricture is a rare complication after gastric ESD, occurring overall in 1%–7% [163, 164]. Subcircumferential resection (>75%), location in cardia, antrum, or prepyloric areas, pyloric deformity and longitudinal length >5 cm were identified as risk factors for stricture after gastric ESD [163–165]. In a retrospective study, the stenosis rate reached 31% in cases of resection of more than 75% of circumference, but corticosteroid therapy (local injection and/or systemic) was not associated with a low-

er stricture rate ( $P=0.26$ ) nor with a lower number of EBD sessions, although time to stricture development was higher in the steroid group [166]. Prophylactic EBD was also proposed for patients at high risk of stricture and was associated with a lower perforation rate when compared with conventional EBD in a small study [165].

Thus, there is no evidence to recommend steroid therapy or prophylactic EBD after gastric ESD, although it is advisable to monitor for obstructive symptoms in patients with risk factors for stricture, in order to start early EBD if stricture occurs.

## Duodenum

Duodenal strictures after ESD occurred in 0.8% [167] to 4% of 50 cases and were effectively treated with balloon dilations [168]. No data on steroid prevention can be found in the literature.

## Colon

Only few studies report on the incidence, management and risk factors for stricture formation after colorectal ESD. In contrast to esophageal ESD, strictures after colorectal ESD are rare (0–4%, even for wide-field resections [169–171]) except for cases with resection of  $\geq 90\%$  of the circumference; this can be explained by the natural dilating properties of solid stool and bowel movements that gradually expand the narrowed lumen [169, 172, 173]. According to the extent of the resection, reported stricture rates are 18% for resection of more than 75% of circumference, 11%–44% for more than 90% of circumference and 50%–71% for total circumferential resection [169, 173, 174].

In resections extending to more than 75% of the circumference, involvement of the anal canal was also identified as an independent risk factor for stricture formation, for symptomatic obstruction, and for the need of more dilation sessions [174]. In this study, the use of preventive corticosteroids (local triamcinolone injections, betamethasone suppositories, or oral prednisolone tapered over 2 months at the discretion of the endoscopist) was not associated with a lower stricture rate.

In conclusion, resection of >75% of the circumference and particularly of >90% of the circumference are risk factors for post-ESD stricture, but no supportive evidence exists for a preventive role for steroid suppositories or injection after colorectal ESD. In the case of stricture formation, virtually all patients can be treated successfully by EBD.



## 10 Additional methods to prevent adverse events

### RECOMMENDATIONS

**18** ESGE recommends the use of carbon dioxide (CO<sub>2</sub>) in preference to air when performing ESD.  
Strong recommendation, moderate level evidence.

**19** ESGE recommends against the performance of second-look endoscopy after ESD.  
Strong recommendation, moderate level evidence.

**20** ESGE recommends against routine antimicrobial prophylaxis after ESD.  
Weak recommendation, low level evidence.

### CO<sub>2</sub> insufflation

#### Upper gastrointestinal tract

Carbon dioxide (CO<sub>2</sub>) has been shown to be safe with respect to transcutaneous partial pressure of CO<sub>2</sub> and oxygen saturation for esophageal and gastric ESD [175], and in an RCT the use of CO<sub>2</sub> significantly reduced mediastinal emphysema after esophageal ESD, but no significant differences were found in pain scores between the two groups (**Table 7s**) [176]. The use of CO<sub>2</sub> insufflation also had beneficial effects in gastric ESD (less post-procedural pain [177], less analgesic consumption [178], and lower incidence of Mallory–Weiss lacerations [179]). However, significant differences in the incidence of AEs were not found in a meta-analysis that included 4 RCTs [177], despite a trend to trend to lower PPB and perforation risk in the CO<sub>2</sub> arms (PPB 7.1% vs. 13.2%, OR 0.51, 95%CI 0.22–1.19; perforation 1.6% vs. 4.0%, OR 0.39, 95%CI 0.10–1.57).

#### Colon

Although the use of CO<sub>2</sub> insufflation has been demonstrated to be safe for use during colorectal ESD in patients under sedation, even in the setting of obstructive pulmonary diseases, few comparative studies have demonstrated its clinical impact (**Table 7s**) [180, 181]. In an RCT, CO<sub>2</sub> insufflation significantly reduced residual gas in the gastrointestinal tract following colorectal ESD as compared to air insufflation ( $P < 0.001$ ); this outcome was thought to be associated with less discomfort, although the incidence of ESD-related complications did not differ between groups [182]. An earlier systematic review and meta-analysis has shown that insufflation with CO<sub>2</sub> in colonoscopy reduced abdominal discomfort during and after the procedure without any adverse reactions [183]. In another large prospective observational study, CO<sub>2</sub> use was associated with a 62% decrease in post-procedural admissions after endoscopic resection of large colonic lesions (from 8.9% to 3.4%,  $P = 0.01$ ), mainly due to a significantly reduced number of admissions for pain (from 5.7% to 1.0%,  $P = 0.006$ ) [184]. Given the risk of perforation with ESD and the hemodynamic and respiratory consequences in the event of tension pneumoperitoneum, the use of CO<sub>2</sub> is recommended for colorectal ESD [185].

### Second-look endoscopy (SLE)

**Esophagus** There are no reported data on SLE after esophageal ESD and it has not been found to be beneficial in any other settings. Therefore, ESGE recommends against routine SLE after esophageal ESD.

**Stomach** SLE with prophylactic coagulation of vessels was not able to decrease PPB rates after gastric ESD in two meta-analyses [101, 186]; there was indeed a trend to higher bleeding rates in patients who underwent SLE and prophylactic hemostasis during SLE. Therefore ESGE recommends against performance of routine SLE after gastric ESD (**Table 8s**) [101, 186].

**Duodenum** Although ESD is not recommended outside expert centers and recommended only for highly selected indications, SLE is performed after duodenal ESD in some centers [187, 188], but no comparative data exist to support this.

**Colon** Likewise, SLE after colorectal ESD is generally not performed as no supportive evidence exists. Only one recent Korean study has evaluated the value of SLE with prophylactic hemostasis or coagulation of visible vessels following colorectal ESD [189]. The authors concluded that the incidence of high risk ulcer stigma during SLE was low (5.3%), and that SLE was not effective in preventing delayed bleeding – the three PPB cases (0.8%) occurred in the SLE group, one in a patient with high risk stigma on SLE and two in patients with low risk ulcer stigma.

### Prophylactic antibiotherapy

**Upper GI tract** According to a prospective study, the incidence of bacteremia after esophageal ESD is very low (1%, 95%CI 0–5%); no patient had infectious symptoms and none required antibiotics after ESD [190]. Likewise, the incidence of bacteremia after gastric ESD is low and transient, even in patients with intraoperative perforation being only 2.5% [191, 192]. Furthermore, in a propensity-matched retrospective study including patients with fever after ESD but without perforation, the use of antibiotics did not decrease fever duration but hospitalization time was longer [193]. Thus, prophylactic antibiotherapy is not recommended after esophageal or gastric ESD.

**Colon** In the colon, the evidence for prophylactic antibiotherapy is more controversial. An RCT including 100 patients found that prophylactic ampicillin and/or sulbactam decreased PEECS rate (2% vs. 16%,  $P = 0.031$ ) [194]. On the other hand, a more recent multicenter RCT including 380 patients showed that perioperative antibiotics did not significantly decrease the incidence of PEECS, at 4.7% in the antibiotic group versus 7.5% in the nonantibiotic group ( $P = 0.209$ ) [195]. Another large retrospective case–control study from Japan showed that the post-ESD infection rate was low (1.2%) and that antimicrobial prophylaxis did not prevent postoperative infection (OR 0.73, 95%CI 0.08–6.61) [196]. In this regard, another study identified cecal location (OR 14.5), presence of submucosal fibrosis (OR 2.8), and female sex (OR 2.6) as independent risk factors for PEECS [197].

In conclusion, given the low incidence of PEECS, and its good prognosis with prompt treatment if it occurs, the prophylactic use of antibiotics in all patients is not recommended and should

be reserved for high risk cases. However, in practice, many centers use antimicrobial prophylaxis in the case of a distal rectum location extending to the dentate line, to avoid ESD-related bacteremia. This is on account of the hemorrhoidal veins' drainage directly into the systemic circulation, bypassing the filter of the liver, unlike the case for other colorectal locations [198]. Nevertheless clear data to justify the practice are still missing.

### Closure/shielding of the wound to prevent delayed perforation/PEECS

**Esophagus and stomach** Post-ESD delayed perforation and PEECS rates are low and thus routine closure of the wound has not been demonstrated to prevent these adverse events.

**Duodenum** There is a lack of direct head-to-head comparisons of closure versus nonclosure in order to decrease delayed perforation, although there is some evidence from retrospective studies that closure with conventional clips [41] or OTS clips [43, 199, 200], and laparoscopic closure [43, 201–204] on the serosal side may decrease delayed bleeding and perforation rates. Complete defect closure after duodenal ESD was also associated with a better outcome in a large retrospective Japanese cohort [205]. Furthermore, string clip closure might help, joining the edges of the mucosal defect, and was associated with shorter length of stay after duodenal ESD [206].

**Colon** A recent multicenter RCT showed no significant benefit of endoscopic clip closure on the incidence of PEECS and delayed perforation (16% in the clipping group vs. 24% in the non-clipping group, with all cases of PEECS being managed conservatively by fasting and intravenous antibiotics [207].

We conclude that there is no firm evidence of benefit in mucosal closure after colorectal ESD, and conventional clip closure can be technically difficult or impossible in larger defects. Various new methods of clipping or suturing have also been developed to achieve complete closure, with technical success rates varying between 88% and 100% [208–211]. However, these methods potentially increase costs and procedural time, and efficacy data are thought to be premature. Nevertheless, it should be noted that immediate clip closure for a minor intraprocedural perforation or muscularis injury remains critical in the prevention of delayed perforation [212].

## 11 How to handle adverse events

### RECOMMENDATIONS

**21** ESGE recommends that for the majority of intraprocedural bleedings, thermal coagulation with an ESD knife or hemostatic forceps should be preferred over clipping.

Strong recommendation, low level evidence.

**22** ESGE recommends performance of endoscopy/colonoscopy in the case of significant bleeding (hemodynamic instability, drop in hemoglobin >2 g/dL, severe ongoing bleeding) in order to perform endoscopic hemostasis with thermal methods or clipping; hemostatic powders represent rescue therapies in the case of failure of the previous methods.

Strong recommendation, moderate level evidence.

**23** ESGE recommends closure of immediate perforations with clips (through-the-scope or cap-mounted clips, depending on the size and shape of the perforation), as soon as possible but ideally after securing a good plane for further dissection.

Strong recommendation, low level evidence.

**24** ESGE suggests joint management with a surgical team in the case of delayed perforation.

Strong recommendation, low level evidence.

**25** ESGE recommends that in the case of suspected post-ESD electrocoagulation syndrome (PEECS), after excluding overt perforation by abdominal CT, conservative management is adequate (including fasting and broad-spectrum antibiotics).

Strong recommendation, low level evidence.

**26** ESGE recommends endoscopic dilation if stricture develops after ESD.

Strong recommendation, high level evidence.

The most common AEs associated with ESD are PPB (1%–2% in the esophagus, 5%–10% in the stomach, 5%–17% in the duodenum and 2.7% in the colorectum) and perforation (<3% of cases). Stricture is also a frequent AE after resection of >50% of the esophageal circumference and after circumferential pyloric or colorectal resection. PEECS can also rarely occur after ESD. These AEs are most often managed conservatively with endoscopic and medical treatment, and surgery due to adverse events is rare (<1% of all ESDs).

### Post-procedural bleeding

In upper GI PPB, repeat endoscopy is usually proposed and allows treatment of the great majority of delayed bleedings [52]. In some rare cases, surgery or radiologic embolization can be used in the event of failure of endoscopic hemostasis.

The available methods to treat PPB are thermal ablation of the culprit vessel and endoscopic clipping; hemostatic powders can also be used as rescue therapy.

On the other hand, PPB after colorectal ESD usually follows a mild and often self-limiting course and rarely leads to hemorrhagic shock or need for blood transfusion. One study analyzing 10 delayed bleeding cases following 124 colorectal ESDs reported no cases of hypovolemic shock or requirement for blood transfusion. In 4 patients (40%) bleeding subsided spontaneously within a few hours without the need for endoscopic intervention [130]. In another study comprising 439 ESDs and 27 delayed bleeding cases, none required endoscopic hemostatic intervention or blood transfusion when a watch-and-wait strategy was followed [133]. Another study showed that colonoscopy and hemostasis were needed in only 12% and 6%, respectively, of patients with hematochezia [213]. These findings support conservative management and close observation in patients presenting with delayed bleeding without hemodynamic consequences or ongoing hematochezia [98, 213].

Emergency endoscopy using standard hemostatic methods (hemoclips or hemostatic forceps) is the first-line treatment in massive PPB, although the optimal technique has not been determined. Caution is necessary during the application of coagulation, minimizing the risk for thermal muscle injury in the thin colonic wall. Novel hemostatic topical agents are currently being explored and may prove beneficial as a nondiathermic adjunct modality to manage bleeding [94]. However, given the paucity of data, no recommendations on their use can be made.

## Perforation

Perforation should be classified as immediate (if perforation is detected during or at the end of ESD) or delayed (if diagnosed based on clinical/radiological signs after ESD). In general terms, in immediate perforations endoscopic closure should be attempted, and decompression and diversion of gastrointestinal content through a nasogastric or nasoduodenal tube should be considered [181]. Tension pneumoperitoneum or pneumothorax should also be decompressed, as an emergency if there is hemodynamic instability or respiratory failure. For this, a venous catheter with a 16-G needle attached to a syringe with saline is inserted in aspiration in the left upper quadrant. When gas enters the syringe, the needle is removed, the catheter is left in place and when the embolus is removed the gas comes out from the cavity through the syringe [185].

Organ-specific considerations are detailed below.

## Esophagus

Acute (periprocedural) perforations are reported in 1.5%–5.0% after esophageal ESD, resection of  $\geq 75\%$  of the circumference being the only independent risk factor [214, 215].

There is no systematic evidence on the optimal management of esophageal perforation, the literature being limited to case reports, but most cases can be endoscopically managed without the need for surgery [95, 212–218]. Most periprocedural perforations are closed with clips, whereas larger perforations might be treated with temporary stent placement, OTS clipping, or endoscopic vacuum therapy.

Delayed perforations are rare but can be serious. Treatment with self-expanding metal stent (SEMS) placement has been described, as well as vacuum therapy, but esophagectomy may be

needed [219, 220]. These patients should be jointly managed with the surgical team and options include conservative management, clipping, stenting, vacuum therapy, and surgery. There is not much data on any of these options and they should be chosen depending on local expertise and the patient's condition.

## Stomach

In gastric ESDs, immediate perforation occurs in  $< 3\%$  of cases, and delayed perforation is even rarer ( $< 1\%$ ). Risk factors identified in a meta-analysis include: liver disease (OR 1.98); location in the upper third of the stomach (OR 3.62); flat/depressed morphology (OR 1.59); resection size  $> 20\text{ mm}$  (OR 1.42); submucosal invasion (OR 3.05); piecemeal resection (OR 3.88); and procedure duration  $> 2$  hours (OR 4.12) [221]. Although there are no proven measures that can reduce perforation risk, CO<sub>2</sub> insufflation [177] and traction methods [74] showed a trend to lower perforation risk in meta-analyses (CO<sub>2</sub> 1.6% vs. 4.0%, OR 0.39 [0.10–1.57]; traction 0.5% vs. 2.0%, OR 0.30 [0.09–1.05]).

When immediate perforation occurs during ESD, the size of the perforation is usually small and it can be closed using TTS clips; alternative methods may be used in the case of larger defects, such as OTS clips or TTS clips plus endoloop. It should be borne in mind that perforation closure can interfere with further resection, and so the timing of clip application should be individualized. If the perforation is successfully closed, 24–48 h fasting, intravenous antibiotics, and close observation is adequate and mostly successful, and a CT scan with oral contrast is recommended to confirm absence of extravasation prior to resumption of oral feeding; however, if the patient's condition worsens or if there are symptoms or signs of peritonitis, surgical referral is mandatory [185, 222].

Delayed perforation is very rare. If the patient is stable and without symptoms/signs of peritonitis, fasting, intravenous antibiotics and close observation can be an option, but if the patient presents with peritonitis/sepsis, immediate surgical referral is mandatory.

## Duodenum

For duodenal ESD, PPB and perforation rates are higher compared with colonic ESD with an incidence  $> 10\%$  in different studies including in superexpert centers, and reaching 15%–25% in some of those studies [42, 43, 223–226]. The major risk factor for delayed perforation is location distal to the ampulla of Vater [227]. In retrospective studies [187, 228] complete closure of the ulcer was protective against delayed bleeding and perforation, and therefore closure should always be attempted after duodenal ESD. ESGE reminds that duodenal ESD is still an experimental technique reserved to expert centers in research protocols.

In the case of intraprocedural perforation, endoscopic closure should be attempted because it can prevent delayed surgery in 33%–89% of cases [41, 199]. It has been proposed that complete mucosal defect closure is associated with a better outcome in the case of perforation than no closure of the mucosal defect or closure of the muscularis injury. If the lesion

is distal from the duodenal bulb, the post-resection ulcer may be exposed to pancreatic juice and bile acids, causing delayed bleeding and perforation.

Delayed perforation occurred in 1.5%–6.3% of cases in Japanese studies [188, 205] leading to surgery in a few cases. In the case of posterior perforation in the retroperitoneum, conservative management with antibiotics might be an option in certain cases. Biliopancreatic fluid diversion by nasobiliary/pancreatic catheters is proposed in the case of descending duodenum perforation [205]. Nevertheless, surgery or percutaneous drainage of collections seems to be the first-choice option for delayed perforations in most studies [199].

## Colon

Perforation is the most significant complication in colorectal ESD. Although rates are decreasing through accumulating experience and technical improvement, perforation still occurs in 4%–9% [96, 125, 229]. The vast majority are direct perforations and only a minority (0.2%) are delayed perforations [229]. A recent meta-analysis including 97 studies reported a pooled rate of emergency surgery for adverse events of 1.1% (0.8% in Asian countries, 3.1% for non-Asian countries) [96]. This meta-analysis found that low volume centers ( $\leq 24$  ESDs/year) had a significantly higher rate of emergency surgery (1.9% vs. 0.7%). Risk factors for perforation include tumor size, severe submucosal fibrosis, fold convergence, poor maneuverability, operator experience, right-sided location, and underlying semilunar fold [127, 230, 231]. Based on these risk factors, recent scoring systems have been validated in Asia to predict the likelihood of perforation; these may help to identify lesions that should be referred to high volume centers [232, 233].

Immediate complete clip closure for intraprocedural perforations following colorectal ESD was successful in up to 96% in two studies, with surgical rescue indicated for only one patient [230, 234]. Different clips (TTS and OTS) and techniques are available and should be selected on a case-by-case basis according to operator experience and availability. Experience in endoscopic suturing is limited and needs further study. For a delayed perforation or unsuccessful endoscopic closure in an intraperitoneal location, endoscopic management is generally considered inappropriate and emergency surgery is mostly indicated [212, 230].

A local charter for perforation management could be proposed at each center to organize the treatment of perforations, involving radiologists, anesthesiologists, and surgeons, as advised by ESGE guidelines on perforation management [185, 235].

## Post-ESD electrocoagulation syndrome (PEECS)

PEECS is very rare in esophageal and gastric ESD, being higher in the colon (5%–14%) [197, 236, 237]. Independent risk factors for PEECS include female sex, submucosal fibrosis, procedural time >90 minutes, and cecal location [197, 236]. In clinical practice, abdominal CT evaluation is often indicated to rule out a frank perforation that requires prompt surgical repair. PEECS is usually managed conservatively including close clinical

observation, fasting, and broad-spectrum antibiotic administration.

## Esophageal strictures

There is now a consensus that a mucosal defect extending to more than three-quarters of the lumen circumference is a predictive factor for stricture formation after esophageal ESD, with an observed 100% stricture rate after circumferential resection of a length more than 5 cm [149]. Patients should therefore be informed of this high risk, and the probable need for multiple dilation sessions [149].

Dilation therapy can be started as early as 2 weeks after ESD, using conventional balloons and/or bougies, being cautious to avoid overdistension, as perforations have been described. For patients not treated with prophylactic steroids, addition of oral steroids in early sessions should be considered. In the case of refractory strictures, a combination of dilation and local injection of corticosteroids should be the second step, before considering stenting. There are no new reports on the management of these patients, except a recent retrospective study reporting on 83 patients who presented with post-ESD symptomatic esophageal strictures. Clinical success with dilation, plus triamcinolone injection in 50% of the patients, was achieved in 84% while refractory strictures were seen in 16% [156]. Squamous cell carcinoma (SCC), upper esophageal location, recurrent strictures, and intraprocedural complications were statistically associated with refractory strictures.

## Disclaimer

The legal disclaimer for ESGE Guidelines [238] applies to this Technical Review.

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