

# Endoscopic Submucosal Dissection

## Sociedad Española de Endoscopia Digestiva (SEED) clinical guideline



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### Institutions

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### Introduction

Endoscopic submucosal dissection (ESD) was developed in Japan as a treatment for early gastric cancer (EGC). This technique allows en-bloc resection of the lesions [1] which has demonstrated to be crucial because the local recurrence rate when this is not possible is of 15% [2]. Nowadays, there is a huge experience with ESD in Eastern countries where this technique is considered the gold standard treatment for EGC [3,4]. Indications for ESD have expanded to lesions in other locations (esophagus and colon) and other types of lesions (submucosal tumors). However, the introduction of ESD in Europe and the United States of America has been and still is very slow. The aim of this guideline is to familiarize Spanish endoscopists and gastroenterologists not only with the general indications of the procedure and possible complications but also the dedicated tools.

### Indications

The main objective of ESD is the complete resection of neoplastic lesions to achieve the patient's cure. For this reason, the main indication is superficial lesions with no risk of lymphatic invasion. The risk of metastatic lymph nodes is determined by several factors related to neoplasia, such as cell type and degree of differentiation, size, presence of ulceration, lymphatic and / or vascular invasion and depth of wall invasion. According to the TNM classification [5, 6], early neoplasia of gastrointestinal tract is located in the mucosa

and submucosa layers, but when the submucosa is affected the risk of lymphatic invasion increases up to 22%.

### Esophagus

Barrett's esophagus associated adenocarcinoma represents 50% of all the esophageal tumors [7,8]. By contrast, in Asia and Eastern Africa the epidermoid carcinoma is the histological predominant type [9]. ESD has different indications according to the histological type of the tumor to treat [10–12]:

1. Squamous carcinoma: resection of lesions with a major diameter bigger than 15 mm, in any location and with any size. For lesions of minor size, the rates of resection in block of the EMR are similar to those of the ESD. In lesions of more than 20 mm, cure rate, absence of local recurrence and disease-free survival of ESD reach 99% and are superior to those of the fragmented EMR. On the other hand, the incident of perforation is 2.4% and not significantly different from RME (1,7%) [13, 14]. Due to an incidence of lymph nodes metastasis of 8.5% when the carcinoma is m3 (affectation of the muscularis mucosae without affectation of the submucosal layer), endoscopic treatment should be indicated only for m1 and m2 lesions [14] in which the mortality for total esophagectomy (2%) is equal or superior to the risk of metastasis, without difference in the long-term survival between the endoscopic and surgical treatment [5, 6, 15].

2. Barrett's associated adenocarcinoma: indications of ESD in this group of patients can be divided in 3 groups:
  - a) Absolute: HGD or intramucosal adenocarcinoma up to m2 and lesions bigger than 20 mm but involving less of 2/3 of the circumference of the esophagus.
  - b) Relative: adenocarcinoma m3 or sm1 without evidence of lymph node metastasis, or lesion with HGD or m2 involving less than 2/3 of the circumference.
  - c) Experimental: lesions with sm2 invasion or deeper in high surgical risk patients.

Finally, the risk of new areas of adenocarcinoma in the residual Barrett's esophagus forces to perform an ablative treatment of the rest of the metaplastic mucosa by means of either EMR or radio frequency [16].

### Recommendations:

- ▶ *Endoscopic resection is the best method for staging superficial neoplasms of the esophagus, At the same time it diminishes the rates of esophagectomy and offers a safe and effective treatment to these patients. Level of evidence 2++. Grade of recommendation B.*
- ▶ *In general, endoscopic treatment of esophageal superficial neoplasms is indicated in T1s and T1a tumors with no difference in the long-term survival between the endoscopic and the surgical treatment. Level of evidence 1+. Grade of recommendation A.*
- ▶ *For esophageal squamous carcinoma less than 15 mm the rates of en-bloc resection of EMR are similar to ESD with a null recurrence rate. Level of evidence 2++. Grade of recommendation B.*
- ▶ *Contrarily, for squamous carcinoma bigger than 20 mm, the cure rate for ESD is superior to EMR. Level of evidence 2++. Grade of recommendation B.*
- ▶ *In squamous carcinoma, due to an increased risk of lymph node metastasis in m3 lesions, endoscopic treatment should be indicated only for m1 and m2 lesions. Level of evidence 2+. Grade of recommendation C.*
- ▶ *In Barrett's esophagus with superficial adenocarcinoma, ESD is indicated in lesions greater than 20 mm with HGD, carcinoma in situ or invasive carcinoma up to m2. ESD may be indicated in patients with high surgical risk and invasive adenocarcinoma affecting the first third of submucosal layer (sm1 =*

**Table 1** Summary of current indications of Endoscopic Submucosal Dissection in Early Gastric Cancer.

|                      |  |
|----------------------|--|
| Classic indications  | <ol style="list-style-type: none"> <li>1. Differentiated type early gastric cancer</li> <li>2. Elevated type lesions &lt;20 mm</li> <li>3. Depressed type lesions (no ulcer) &lt;10 mm</li> </ol>  |
| Expanded indications | <ol style="list-style-type: none"> <li>1. Intramucosal cancer of any size with no ulcer and no lymphovascular involvement</li> <li>2. Intramucosal cancer, less than 3 cm in size, no lymphovascular involvement, with or without ulcer</li> <li>3. Intestinal type cancer with submucosal invasion (sm1 &lt;500 µm), with size less than 3 cm and without lymphovascular involvement</li> <li>4. Poorly differentiated type cancer, less than 2 cm in size, no ulcer</li> </ol> |

500 µm). Level of evidence 2+ Grade of recommendation C.

- ▶ In western countries, for Barrett's esophagus associated superficial neoplasms the results of ESD are similar to EMR. Therefore, the choice of the preferred treatment should be based on size of the lesion and the suspicion of invasion of the first third of the submucosal layer. Level of evidence 2++. Grade of recommendation B.
- ▶ The risk of new areas of adenocarcinoma in the residual Barrett's esophagus forces to realize an ablative treatment of the rest of the metaplastic mucosa by means of either EMR or radiofrequency. Level of evidence 2++. Grade of recommendation B.

## Stomach

EGC is defined as cancer limited to the mucosa or submucosa irrespective of lymphnode metastasis [17], having an excellent prognosis after gastrectomy with lymphadenectomy with a 5-year survival rate of more than 90% [18, 19]. The incidence of lymphnode metastasis in early gastric cancer is very low when such cancer is limited to the mucosal layer (3%), however, when cancer invades the submucosal layer it can increase up to 20% [20]. Consequently, local and a less invasive treatment than surgery would be indicated in those gastric cancers limited to the mucosa. The purpose of establishing indication criteria for ESD in gastric neoplasms is to ensure curative resection by complete removal of the tumor. Generally, an endoscopic resection is considered curative (minimal risk of lymphnode metastasis) when submucosal invasion is limited to 500 µm in depth. There are several morphologic features of the lesions (macroscopic classification, mucosal and vascular patterns), which can enable us to predict the risk of invasion in depth. The indications for endoscopic resection of early gastric cancer traditionally established in Japan are (● **Table 1**): well differ-

entiated adenocarcinoma, lesion size <2 cm if it is an elevated lesion or <1 cm if depressed, without ulcer [17]. Nevertheless, such criteria has been extended to lesions of larger size, with ulcer [21, 22] and recently to undifferentiated type adenocarcinoma [23–26]. However, the number of patients that fulfil such criteria and have lymph node metastasis is higher than 12%, explaining the reported poor results. [27]. Regarding prognostic factors, in a study of 487 gastric cancers endoscopically resected, several features were identified as associated with no curative resection: lesion size (>3 cm), with ulcer and histopathology (diffuse type or mixed type of Lauren classification) [28]. The risk of no curative resection is <10% in lesions with no ulcer, <3 cm in diameter and localized in the antrum and gastric body. However, such risk is >40% in lesions with no ulcer, >3 cm and localized in the fornix as well as in lesions with ulcer, size larger than 3 cm located anywhere or size <3 cm located in the fornix. In such cases, surgical treatment is indicated [29].

Contraindications: Advanced age does not seem a contraindication [30, 31]. Data regarding the risk of bleeding in patients who do not discontinue the use of antiplatelet drugs before ESD is controversial [32, 33]. In cases with high risk of thrombotic disease, the necessity to continue treatment with such agents should not be a contraindication for the procedure [32].

### Recommendations:

- ▶ In a well differentiated type EGC, ESD is the first therapeutic option irrespective of size and location of the lesion. Evidence level 1++. Grade of Recommendation A.
- ▶ Size >3 cm, with ulcer and fornix location are associated with a higher rate of no curative resection. Evidence level 2+. Grade of Recommendation C.

▶ Advanced age is no contraindication for ESD. Evidence level 2+. Grade of Recommendation C.

▶ In cases with high risk of thrombotic disease, treatment with antiplatelet drugs should not be considered a contraindication for ESD. Evidence level 2-. Grade of Recommendation C.

## Colon and rectum

The macroscopic features of colonic lesions are established by their type according to the updated Paris classification [34] that includes the lateral spreading tumours (LSTs) described by Kudo [35]. This classification has a prognostic value as the risk of lymph node invasion in the colon varies depending on the macroscopic type of lesion. In sessile and flat lesions resection is considered curative when invasion into the submucosa is below 1.000 µm due to the low risk of lymph node metastasis [36, 37], while in pedunculated lesions the limit is more flexible leading to the combination of two parameters: invasion into the submucosa of up to 2.000 µm [38, 39] and a maximum diameter of invasion into the submucosa of up to 4.000 µm [38]. Lesions considered amenable to endoscopic treatment in general include (● **Table 2**): 1) lesions of any macroscopic type, 2) adenomas, intramucosal neoplasias or neoplasias with superficial submucosal infiltration, 3) lesions under 2 cm in maximum diameter [40]. Specific indications for ESD include [41] lesions with a high risk of adenocarcinoma or those presenting an additional difficulty for endoscopic resection.

Incidence and risk of submucosal invasion are higher for non-granular LSTs (LST-NG). ESD would be indicated in lesions of this kind that are larger than 2 cm. Granular LSTs with nodules (LST-G mixed) present a higher risk of containing adenocarcinoma under the larger nodule and under pseudodepressed areas. In those cases, the larger nodule should be resected in a single piece or, for larger lesions, the whole lesion should be resected en bloc. Saito et al. consider ESD indicated in LST-G mixed larger than 3 cm [42]. Other indications for ESD include mucosal lesions with submucosal fibrosis secondary to prior resections, biopsies or associated with inflammatory bowel disease [43]. In those cases, the risk of perforation or leaving a residual lesion is higher if ESD is not performed. Adding adrenaline to the submucosal injection solution could decrease the incidence of early bleeding of sessile and pedunculated polyps less than 1 cm

**Table 2** Indications of Endoscopic Submucosal Dissection for colorectal tumors

1. Large sized (> 20 mm in diameter) lesions in which en bloc resection using a snare EMR is difficult, although it is indicative for endoscopic treatment
  - a) LST-NG particularly those of the pseudo-depressed type
  - b) Lesions showing V<sub>1</sub> type pit pattern
  - c) Carcinoma with submucosal infiltration
  - d) Large and depressed type lesions
  - e) Large elevated lesion suspected to be a cancer\*
2. Mucosal lesions with fibrosis caused by prior biopsy or peristalsis
3. Sporadic localized tumors in chronic inflammation eg ulcerative colitis
4. Local residual early carcinoma after endoscopic resection

Abbreviations: LST: Lateral spreading tumor. NG: No granular. Type Vi: Pattern V irregular in the classification of Kudo (malignant lesion but with indication for endoscopic resection)  
\* Includes LST granular mixed (LST-G mix)

[44–46]. Endoscopic resection of large colonic lesions is much cheaper than surgical resection [47] and implies a maintained quality of life for patients that are only attained after 1 to 5 years of convalescence in patients who have undergone surgery [48, 49].

After ESD with en bloc resection of a large colonic lesion a follow-up colonoscopy is required within 3 to 6 months to review the scar and rule out residual lesion and within one year due to the risk of developing new adenomas [50].

#### Recommendations:

- ▶ ESD is indicated in LST-NG over 2 cm. Evidence level 1+. Grade of recommendation B.
- ▶ Other indications for ESD include mucosal lesions with significant fibrosis secondary to prior biopsy or incomplete resection, neoplastic lesions associated to inflammatory bowel disease and residual superficial neoplastic lesions after endoscopic resection. Evidence level 2-. Grade of recommendation D.
- ▶ Adding adrenaline to the submucosal injection solution may help decrease the incidence of bleeding though it does not exclude the use of a technique to precisely coagulate visible vessels arising from the submucosa. Evidence level 1-. Grade of recommendation B.
- ▶ Endoscopic resection of large colonic lesions is several times cheaper than surgical resection and implies better quality of life maintenance. Evidence level 2++. Grade of recommendation B.
- ▶ After ESD with en bloc resection of a large colonic lesion a follow up colonoscopy should be performed in 3 to 6 months to rule out residual lesion and in 12 months to rule out new adenomas. Evidence level 1++. Grade of recommendation A.

#### Other locations Duodenum

Duodenal lesions susceptible to endoscopic resection include premalignant lesions like adenomas, benign lesions (Brünnner hyperplasia or lipoma), and submucosal lesions with malignant potential like neuroendocrine tumors (NET) or gastrointestinal stromal tumors (GIST) [51]. ESD in duodenum is a complicated procedure due to the existence of a very thin submucosal layer, its high vascularity and also the presence of a thin muscular layer. All these factors increase the risk of bleeding and perforation, being this last reported up to 20% or even more [52]. There is no standardization relating to the size of lesions susceptible to treatment. Benefits of duodenal ESD seem marginal compared to EMR, with the exception of small-medium size encapsulated submucosal tumors (NET, for example), in which endoscopic ultrasound (EUS) has excluded muscular propia layer infiltration or locoregional lymph nodes involvement. The most frequent complication is bleeding [53]. It is important to perform preventive vessel coagulation with coagulation forceps, argon plasma or bipolar catheter. On the other hand, it is mandatory to perform a close surveillance to detect perforation, both acute or delayed. Delayed perforation has been associated with excessive use of electrocoagulation for achieving hemostasis and continuous exposure of the scar to pancreatic juice and bile [54]. Perforation rate is unacceptable high in some studies, reaching 36% of the patients.

#### Recommendations:

- ▶ Due to high complication rates (bleeding, perforation), duodenal ESD must be performed by highly experienced ESD endoscopists. Evidence level 3. Grade of recommendation D.

#### Mesopharynx and hypopharynx

ESD can be adequate for the diagnosis and treatment of early superficial neoplastic lesion in these locations [55,56]. ESD in this location should be performed by highly experienced endoscopists in ESD. To do a precise delimitation of the lesion an iodine instillation can be useful. This exploration must be performed under orotracheal intubation to avoid respiratory complications. Supine patient position could be useful because it enlarges the space for endoscopy manoeuvres due to maximum larynx elevation.

#### Recommendations:

- ▶ Superficial meso- and hypopharynx tumors can be treated by ESD. These explorations must be performed under orotracheal intubation. Supine patient position can facilitate the procedure. Level of evidence 3. Grade of recommendation D.

#### Submucosal tumors

The origin of these lesions in muscular propia layer is not a factor to preclude ESD, but perforation rates in this situation are higher. Average tumor size of resected specimens in various studies is around 20–30 mm maximum and a majority of them are GIST with low grade dysplasia, followed by leiomyomas and NETs. All referred resections were performed in upper digestive tube (esophagus, stomach and cardias), with R0 rates around 95–100% in the longest series. The technique is not standardized, and is described as the use of submucosal tunnel for resection of esophageal and cardiac lesions [57]. There has also been published resections of small rectal carcinoids (<10 mm) without muscular propia involvement [58].

#### Recommendations:

- ▶ Submucosal lesions arising from muscular propia layer could be resected using ESD, especially those with a diameter < 30 mm. Level of evidence 3. Grade of recommendation D.
- ▶ Esophageal or cardiac submucosal lesions can be accessed performing a submucosal tunnel. Level of evidence 3. Grade of recommendation D.

#### Equipment

##### Knives

The conventional ESD technique requires the use of different knives specific for each step of the procedure [59]. The differ-

**Table 3** Characteristics of different knives for endoscopic submucosal dissection.

| Device             | Marking        | Pre-cut | Cutting | Dissection | Hemostasis     | Fibrosis | Beginners      |
|--------------------|----------------|---------|---------|------------|----------------|----------|----------------|
| Needle Knife       | ✓              | ✓       | ✓       | ✓          | X              | ✓        | X              |
| Flex Knife         | ✓              | ✓       | ✓       | ✓          | X <sup>2</sup> | X        | ✓              |
| Hook Knife         | ✓ <sup>1</sup> | ✓       | ✓       | ✓          | X <sup>2</sup> | ✓        | X              |
| IT Knife           | X              | X       | ✓       | ✓          | X <sup>2</sup> | X        | ✓              |
| Triangle-tip Knife | ✓ <sup>1</sup> | ✓       | ✓       | ✓          | X <sup>2</sup> | X        | ✓ <sup>3</sup> |
| Dual Knife         | ✓ <sup>1</sup> | ✓       | ✓       | ✓          | X <sup>2</sup> | X        | ✓              |
| Hybrid Knife       | ✓              | ✓       | ✓       | ✓          | X <sup>2</sup> | ✓        | ✓              |

✓ Suitable.

X Not recommended.

<sup>1</sup> They can be used for pre-cut with the tip fully retracted.

<sup>2</sup> Useful for coagulation in case of venous bleeding, low flow, or bleeding from small vessels of 1 mm.

<sup>3</sup> Difficult to use in fundus and body.

ent knives for ESD share a common structure: they are plastic catheters with a metallic tip that varies among different models. The vast majority of endoscopic knives is monopolar. Its area of contact with the tissue determines the cutting characteristics of the knife. A knife with a small contact area usually produces a deep cut because it generates a high current density [60].

According to the function they perform, knives can be classified as: knives with cutting–clotting ability and knives with cutting–clotting and injection–wash ability. The latter allow the injection of liquid without exchanging needles, achieving a faster dissection and saving time.

Knives can also be classified as covered (with insulated tip) and not covered. Covered knives have a cutting surface which is partially protected by insulating material, a design aimed at restricting the direction of the cut in order to make dissection maneuvers safer [60]. Not covered knives show their cutting area without restrictions and they usually have a retractable metallic tip of variable length. A clear superiority of a design versus the other has not been proven [61]. In **Table 3** the characteristics of the most used knives are detailed.

#### Recommendations:

- ▶ *The choice of surgical knife depends on personal preferences and the familiarity with the available material. An objective superiority of one design over the rest has not been demonstrated. Level of evidence 2–. Grade of recommendation D.*
- ▶ *There are no differences between the needle-knife and the IT-knife regarding precision or incidence of complications. Level of evidence 2–. Grade of recommendation D.*
- ▶ *The use of a hook-knife is especially indicated when confronting fibrous lesions that prevent an appropriate*

*distension of the submucous layer. Level of evidence 2–. Grade of recommendation D.*

- ▶ *The use of a hybrid knife could facilitate the ESD procedure by shortening procedure time and diminishing complications. Level of evidence 2++ . Grade of recommendation C.*
- ▶ *Utilizing a transparent cap attached to the tip of the endoscope is recommended, as it allows the resection to be performed more safely and with better control. Level of evidence 4. Grade of recommendation D.*

#### Injection Substances

In ESD, submucosal injection creates a cushion beneath the lesion and raises the submucosal layer, separating the mucosa from the muscularis propria [62, 63]. Normal saline (NS) 0.9% maintains the cushion for a short time and usually makes it necessary to perform repeated injections during the dissection phase. Addition of epinephrine and/or colorants such as methylene blue or indigo carmine can facilitate resection by means of reducing the risk of bleeding and improving the identification of the submucosal layer. In order to prevent the short duration of submucosal injection effect, different substances with higher viscosity have been used [62–70]. Hyaluronic acid (HA) is one of the most commonly used substances in Japan but its high cost and in vitro tumor cells stimulatory effect, limit its use in other countries [63–67, 71–74]. Glycerol or glycerin, is an hypertonic substance obtained from mixing 10% glycerol and 5% fructose. This substance is inexpensive and easily available at any center. It has proved higher durability and effectiveness than NS 0.9% [73, 75]. Fibrinogen has also been used in human studies [76]. There are many other solutions such as hypertonic (3%) NaCl, dextrose (20, 30, 50%) and hydroxypropyl methylcellulose

(HPMC) (artificial tears) that have been used in an experimental setting. However, the description of tissue damage in experimental animals indicates that these solutions should be used with caution in humans [77–79]. Also on an experimental level, the use of promising substances with higher viscosity than NS 0.9% has been described. Some of them are autologous blood [69, 80], PS 137-25 (LeGoo–endoTM, Pluromed Inc, Woburn, USA) and 2-mercaptoethanol-sulfonate (mesna). The last one has a chemical effect that softens the submucosa connective tissue [62–67, 69, 73, 76, 78, 79, 81].

#### Recommendations:

- ▶ *NS 0.9% is a substance with little durability to maintain the submucosal cushion. The use of other substances with higher viscosity is recommended. Level of evidence 1+. Grade of recommendation A.*
- ▶ *The use of NS 0.9% should be limited to cases where hydrodissection technique is used. Level of evidence 4. Grade of recommendation D.*
- ▶ *Hyaluronic acid is an ideal substance because of its viscosity, but its use is limited by its high cost, low availability in our environment and complains about its safety. Level of evidence 1++ . Grade of recommendation A.*
- ▶ *Glycerol 10% is a reasonable alternative because it is cheap and easily available in our environment. Level of evidence 1+. Grade of recommendation A.*
- ▶ *Fibrinogen has a durability superior to NS 0.9% but its use is limited by its high price. Level of evidence 1+. Grade of recommendation B.*
- ▶ *Dextrose is a reasonable and cheap alternative in Western countries but there are some concerns regarding its safety. Level of evidence 1-. Grade of recommendation B.*

## Electrosurgical generators

Electrosurgical units generate a high frequency current that allows a cutting and/or coagulation effect. This effect is due to the heat generated by the current running through the tissue, and depends on the different characteristics of the current (voltage, time, etc.) and on the tissue resistance.

When using high voltage continual currents (>200V) a greater and continuous heat delivery induces a cutting effect. Coagulation effect (without cell bursting leading to tissue desiccation and coagulation) could be achieved both by low voltage currents or by interrupted high voltage currents.

The cut and coagulation effects could be used at the same time (blend effect), as every cutting effect associates some coagulation and every coagulation effect produces some cutting effect. [86]

New electrosurgery units have specific software that modulate the current and produces a specific tissue effect, for example the “endocut” mode from ERBE (ERBE, Tübingen, Germany). This mode induces tissue transection with continuous low voltage current followed by bursts of cutting current [87]. With this technique the tissue is first coagulated and then cut, with automatic cycles controlled by a microprocessor that take into account changes in the tissue electric resistance, and lead to a precise hemostasia and a safe cut.

### Recommendations

- ▶ Endoscopists have to know the specific characteristics of the electrosurgical generator that they use, and be able to adjust the necessary settings (mode, kind of current, power). Evidence level 4, Grade of recommendation D.
- ▶ The marking of the lesion margins is the first step for ESD, and soft coagulation current is used. Evidence level 4, Grade of recommendation D.
- ▶ A cutting current with coagulation effect is preferred for the initial circumferential incision, ideally with endocut feature or similar. Evidence level 4, Grade of recommendation D.
- ▶ For the dissection of the submucosa a coagulation current is usually advised for conventional knives; for the Hybrid Knife system (ERBE a mixed current with “endocut” mode is preferred. Evidence level 4, Grade of recommendation D.
- ▶ If hemostatic therapy is required, a soft coagulation mode or specific bipolar

accessories are advised. Evidence level 4, Grade of recommendation D.

## Complications and postprocedure care

▼ The two main complications of ESD procedure are hemorrhage and perforation. They are remarkable not only by their frequency but also because they can significantly affect the prognosis and therapeutic success of ESD [88, 89].

### Hemorrhage

This complication may be classified as immediate (during the procedure) or delayed bleeding (within 2 weeks or later) [89]. The reported incidence of bleeding varies across the studies, depending on the location of the lesion. Thereby, the mean incidence is 2% in colorectal lesions, 9.3% in gastric lesions, and 0%–5.2% in the esophagus [90–93]. Immediate bleeding is considered clinically significant when any intervention apart from the endoscopic treatment is needed (i.e. urgent surgery, blood transfusions, vasopressor agents) or a drop in hemoglobin  $\geq 2$  g/dl is detected [90,94]. Delayed bleeding is clinically relevant when there is a decrease of hemoglobin levels  $\geq 2$  g/dl, evidence of overt bleeding and endoscopic intervention is needed [94]. Up to 76% of delayed bleeding episodes take place within the first 24 hours after the procedure [90,95]. In gastric lesions an increased risk of bleeding has been reported when the lesions are located either in the middle or upper third of the stomach. Elderly patients (>80 years), procedure time, size ( $\geq 40$  mm) and endoscopist experience have been also associated with an increased risk of bleeding [95–98].

**Prevention and management of post-ESD bleeding**

1. Endoscopic procedures: prophylactic electrocautery of large submucosal vessels during ESD has shown to decrease the risk of delayed bleeding up to 60% [99]. Performance of *second-look* after ESD is controversial [100]. Electrocautery rather than hemoclip placement is preferred for hemostasis because the latter may make the procedure cumbersome, preventing from continuing with the ESD [101]. Minor oozing can be treated by electrocautery with the same devices used for the ESD (i.e. IT knife, Flex knife...), whereas the hemostatic forceps (Coagrasper) are indicated in case of arterial bleeding.

2. Pharmacological treatment: only two randomized controlled trials have assessed the benefit of acid antisecretory drugs compared with no treatment prior to ESD in the prevention of delayed bleeding. None of them found differences between both strategies [96, 102]. In terms of benefit after ESD, antisecretory drugs (PPIs) are usually recommended for 2 months in order to prevent delayed bleeding. In this setting, an 8-week treatment was found to be more effective than a 4-week treatment. However, ulcer healing rates at 4 or 8 weeks of treatment seem to be equivalent [103]. Recently, several randomized controlled trials compared the combination of PPI and mucosal protective agents (the most promising being *rebamipide*) with PPI monotherapy in the healing of iatrogenic ulcer after ESD. The use of PPI along with *rebamipide* might increase ulcer healing rates because of the synergic effect of both drugs [104–107]. *Helicobacter pylori* eradication had no impact on ulcer healing at 2 months follow-up after the procedure [108, 109]. However, one study showed that *Helicobacter pylori* infection was a risk factor for ulcer recurrence after ESD [110]. Furthermore, it is well-known that *Helicobacter pylori* eradication reduces the incidence of metachronous gastric cancer and thereby, it is warranted in this setting [111].

### Perforation

Perforation rate is around 5% [90,91], although in less experienced Western series it increases up to 20% (92–95). Observation of free extraluminal air after an ESD should not be always interpreted as a perforation leading to surgery. Mediastinal emphysema development has been described in a high percentage of patients undergoing esophageal ESD with no symptoms [112].

No recognition of the muscular layer during ESD can precipitate a perforation. Thus, the use of indigo carmine in the injection solution is advisable. It allows to clearly identify the bluish plane, meaning, the correct plane of dissection, thereby, making the procedure easier and safer. Depending on the perforation size and anatomical location, various sealing techniques may be applied such as clipping (simple closure or closure with omentum patch) or the insertion of a covered stent in cases of esophageal perforations [113].

After the endoscopic closure, the main care for patients includes fasting, intravenous fluid therapy and antibiotics with clinical and radiological surveillance. An average duration of two days for fasting in gastric perforations and 4–10 days in colonic perforations has been suggested. For colonic perforations, antibiotic therapy must be administered for 5 to 10 days [114, 115].

### Cicatricial stenosis

This infrequent event is associated with large resections in gastric antrum or esophagus. Although dilation with bougienage or balloon have been extensively used, new therapeutic options have been described in order to prevent the development of stenosis, such as triamcinolone injection [116–118], preventive balloon dilation [119, 120] or oral steroids. In two non-randomized and retrospective studies, oral steroids alone or associated with balloon dilation were superior to endoscopic balloon dilation, reducing the number of dilations [121, 122]. Other new treatments include biodegradable or metal stent insertion, topical application of mitomycin C or apposition of cell layers to prevent stricture formation [123–126]. Management of antral stenosis has been based on endoscopic balloon dilation, with a significant risk of perforation [127, 128]. Finally, mucosal incision and local triamcinolone injection have been assayed [129].

### Other complications

Other less frequent complications described in ESD are aspiration pneumonia, transient bacteremia [112], phlegmonous gastritis [130], gastric ischemia, gastric hematoma [131], transmural pneumatosis, deep vein thrombosis, mediastinal emphysema and tension pneumomediastinum or pneumoperitoneum [132–135]. Peritoneal carcinomatosis is a rare complication and only one case has been published after gastric perforation. A retrospective series of 90 patients who underwent ESD with gastric perforation did not show this fearsome complication in the long-term.

#### Recommendations:

- ▶ Prophylactic treatment of large submucosal vessels during ESD decreases the risk of delayed bleeding and therefore it should be routinely performed. Evidence level 2++. Grade of Recommendation B.
- ▶ Second-look after ESD contributes little to the prevention of delayed bleeding and therefore it should not be systema-

tically recommended. Evidence level 1-. Grade of Recommendation C.

- ▶ Acid antiselector agents administered before the procedure do not reduce the risk of delayed bleeding and are therefore not recommended. Evidence level 1-. Grade of Recommendation C.
- ▶ Proton pump inhibitors are superior to histamine-2 receptor antagonists in prophylaxis of the delayed bleeding after ESD. Eight week administration of standard dose of proton pump inhibitors is recommended. Evidence level 1+. Grade of Recommendation A.
- ▶ Treatment with proton pump inhibitors is better than histamine-2 receptor antagonists in order to achieve ulcer healing. Level of evidence 1-. Grade of Recommendation B.
- ▶ Clipping may prevent further contamination and reduce the risk of peritonitis, allowing conservative management of this complication. Evidence level 3. Grade of recommendation D.
- ▶ Two days of average duration of fasting in gastric perforations and 4–10 days in colonic perforations have been suggested. For colonic perforations, antibiotic therapy must be administered for 5–10 days. Evidence level 3. Grade of recommendation D.
- ▶ Triamcinolone injection (one or more sequential doses), applied for prevention of cicatricial stenosis, can achieve a reduction in the incidence of stricture and the need for additional treatment with balloon dilation. Evidence level 3. Grade of recommendation D.
- ▶ Preventive balloon dilation was effective and without adverse effects in two non-randomized clinical trials. With this therapy, the objective is to prevent stenosis developed from the initial stages of wound healing by periodic dilations until the complete healing of the mucosa. Evidence level 3. Grade of recommendation D.
- ▶ Early treatment with oral prednisolone, starting at 2–3 days post-ESD and continued for 8 weeks, alone or associated with balloon dilation, is superior to endoscopic balloon dilation. Evidence level 3. Grade of recommendation D.
- ▶ Management of antral stenosis has been based on endoscopic balloon dilation, with a significant risk of perforation. Evidence level 3. Grade of recommendation D.

### Training in ESD

ESD is a complex and demanding technique. The skills required for ESD performance are commonly achieved after a long learning curve under expert's tutoring [136–137]. There are recommendations regarding training in ESD, both in Asiatic and Western countries [138–150]. Animal training under expert's supervision is essential, since it allows the trainee to overcome some of the limitations in learning ESD in real patients [150–151]. Some experts have proposed that the best way to set up a training program is to initiate procedures in the ex vivo porcine gastric model. After some practice, the trainee can move on to the in vivo animal model, where the endoscopist may experience a sense of reality of complications such as bleeding and perforation [151–153]. After having completed several gastric cases, the trainee may move to different locations: esophagus, rectum [148]. There are some encouraging reports which have shown that a high level of competence, with 100% en-bloc resection rate, could be achieved by non-supervised Western endoscopists after completing 30 ESD cases in the ex vivo gastric animal model [154]. We should keep in mind that stepwise difficulty level, based on location and features of target lesions, seems to be mandatory. Not adhering to these principles may be associated with severe complications, which ultimately could be harmful for the patient and for the expansion of ESD [155].

#### Recommendations:

- ▶ Japanese experts recommend that for ESD training, the apprentice must have: 1) extensive knowledge in clinical care; 2) excellent skills for general endoscopic procedures: i. e. a) good experience in mucosal lesions assessment; b) nice ability for target biopsies; c) smooth cecal intubation technique; d) broad experience in hemostatic techniques, polypectomy and EMR. Level of evidence 4. Recommendation grade D.
- ▶ Endoscopists should be competent in gastric ESD before moving to colorectal ESD. Level of evidence 4. Recommendation grade D.
- ▶ Japanese experts have proposed a 4-step training strategy: 1) **Initial stage:** basic knowledge for detection and assessment of early gastric cancer, and awareness of ESD indications. 2) **Second stage:** Attend several ESD procedures performed by

experts. 3) **Third stage:** Participate as assistant for an experienced endoscopist in ESD interventions; meanwhile, the trainee should initiate a training program in the animal model, ideally completing the first 30 cases within a year.

3) **Fourth stage:** Complete 30 gastric ESD under expert's supervision, preferably small, distal, and fibrosis and ulcer free lesions. Afterwards, 40 cases should be performed in proximal gastric locations. Finally, 40 colorectal ESD should be completed, preferably in the rectum during the initial training period. Level of evidence 2+. Recommendation grade C.

▶ Japanese experts recommend a caseload of 30 colorectal ESDs for a level of competence in this location. Level of evidence 3. Recommendation grade D.

▶ In Europe, the recommended stepwise road map for ESD training would be as follows: 1) **Essential knowledge of theory** regarding diagnosis and treatment of early neoplasia in digestive tract.

2) **Observation** of ESD procedures performed by Asian experts.

3) **Engagement in an animal training program** under expert's supervision for basic skills acquisition. 4) **Initiate selected human ESD cases supervised** by experienced endoscopist. 5) **Continued animal training** for skill improvement. Level of evidence 3. Recommendation grade D.

▶ In Europe competence on ESD requires performing at least 10–20 every year. Level of evidence 4. Recommendation grade D.

▶ In Europe, a less exhaustive ESD training program than the one recommended by Japanese experts appears to be good enough to acquire basic competence on this technique. Level of evidence 2. Recommendation grade D.

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