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REVIEW

Advanced Endoscopic Resection Techniques: Endoscopic Submucosal Dissection and Endoscopic Full-Thickness Resection

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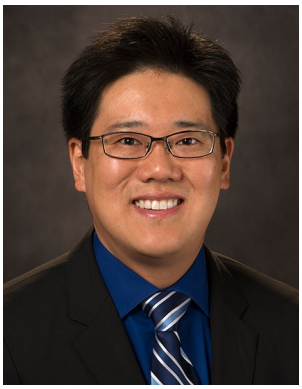
Abstract

Endoscopic resection is first-line therapy in the management of superficial neoplasms throughout the gastrointestinal tract, as well as an increasingly viable therapeutic alternative in the resection of selected small deep lesions throughout the upper and lower gastrointestinal tract. The mainstay of therapy has traditionally been endoscopic snare polypectomy and endoscopic mucosal resection. However, recent innovative advancements in therapeutic endoscopy have provided for the ability to resect large superficial lesions and selected subepithelial lesions in *en bloc* and margin-negative fashion. In this review, we discuss the current state of the art in advanced endoscopic resection techniques including endoscopic submucosal dissection and endoscopic full-thickness resection.

Keywords Endoscopic resection · Endoscopic mucosal resection · Endoscopic submucosal resection · Endoscopic submucosal dissection · Submucosal tunneling endoscopic resection · Endoscopic full-thickness resection



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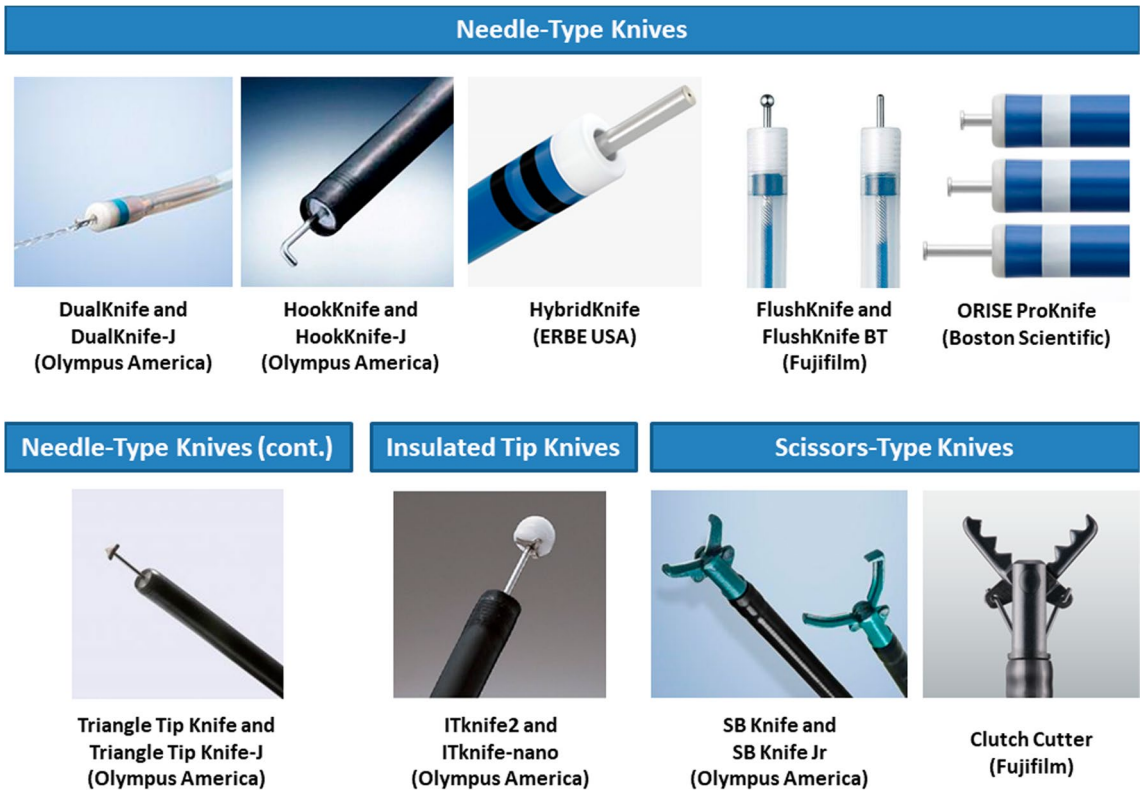

Fig. 1 Specialized knives used for endoscopic submucosal dissection, currently commercially available in the USA

Introduction

Endoscopic resection is a well-established modality for the minimally invasive treatment of various lesions throughout the gastrointestinal tract. The origins of endoscopic resection date back to the advent of snare polypectomy by Shinya et al. in 1969 [1]. Since then, endoscopic resection has evolved to saline-assisted endoscopic mucosal resection (EMR) [2], cap-assisted EMR [3], and band-assisted EMR [4]. Each of these techniques has been further refined and optimized, such that conventional EMR remains the standard endoscopic resection technique worldwide today.

As endoscopic resection has evolved, endoscopists have increasingly adopted a surgical mindset to their technical approach. The fundamental principles of surgical resection demand *en bloc*, margin-negative (R0) resection. With advancements in both technique and technology, this has not only become attainable but desired in present-day endoscopic resection. The advantages of R0 resection are obvious in minimizing the risk of residual or recurrent neoplasia. This is counterbalanced by the risks associated with obtaining *en bloc* resection, namely bleeding and perforation, especially in technically challenging locations throughout the gastrointestinal tract.

Over the last several decades, advanced techniques have been developed which allow for complete resection of larger and deeper lesions. This article reviews the current state of the art in advanced endoscopic resection techniques.

Endoscopic Resection of Superficial Lesions

Conventional endoscopic resection techniques such as EMR and snare polypectomy are limited by lateral size. Given that EMR requires the use of a snare, the absolute *en bloc* resection capability of EMR is limited to 2–3 cm in size [5]. In practical everyday usage, the *en bloc* resection capability of EMR is approximately 1.5–2 cm in size. Larger lesions are removed in piecemeal fashion to avoid perforation [6], but with higher rates of recurrence [7, 8]. Although adjunctive techniques such as ablation of resection margins have substantially reduced the risks of recurrence [9–14], piecemeal resection can result in a non-curative scenario and subsequent need for surgical resection whenever malignancy is detected within a fragmented specimen [15–17].

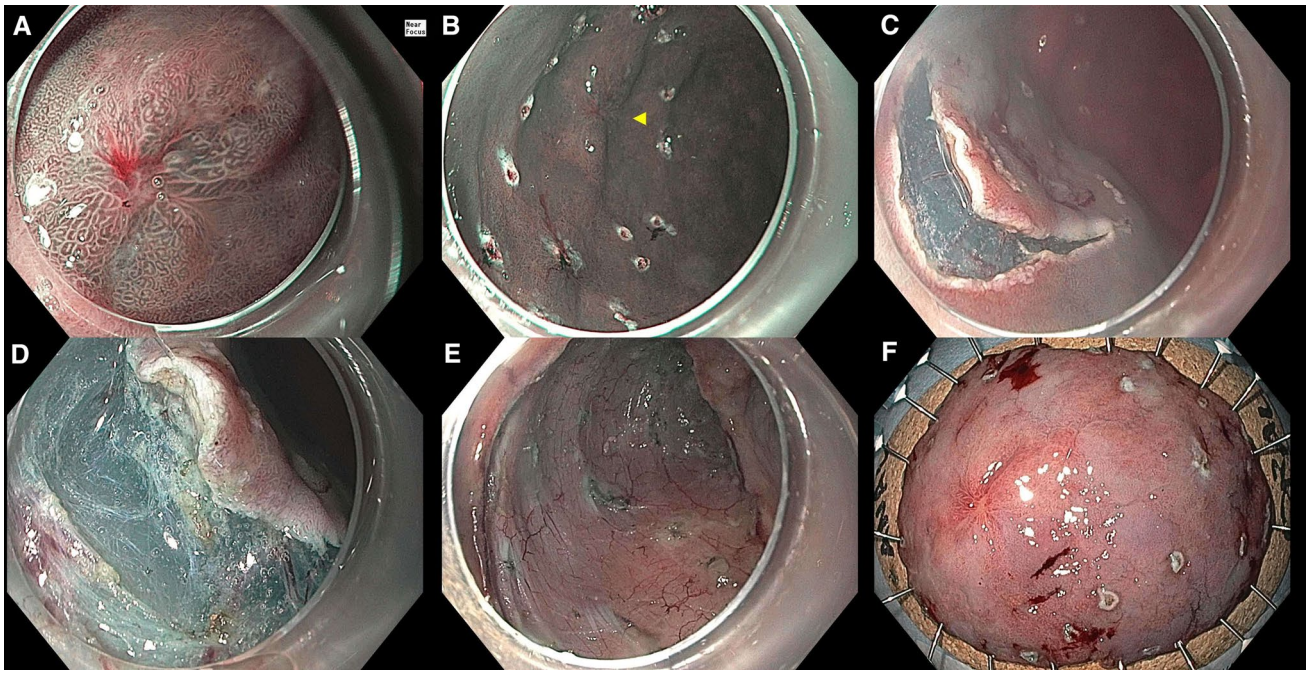

Fig. 2 Gastric endoscopic submucosal dissection. (**a**) A 12-mm gastric adenocarcinoma with ulceration at the gastric antrum, (**b**) marking of lesion borders with extra dots placed to denote oral margin, (**c**) mucosal incision, (**d**) submucosal dissection, (**e**) resection defect, and (**f**) ESD specimen. Final pathology showed moderately differentiated intramucosal adenocarcinoma (pT1a), with no lymphovascular invasion, no perineural invasion, and all margins negative, thus consistent with a curative resection

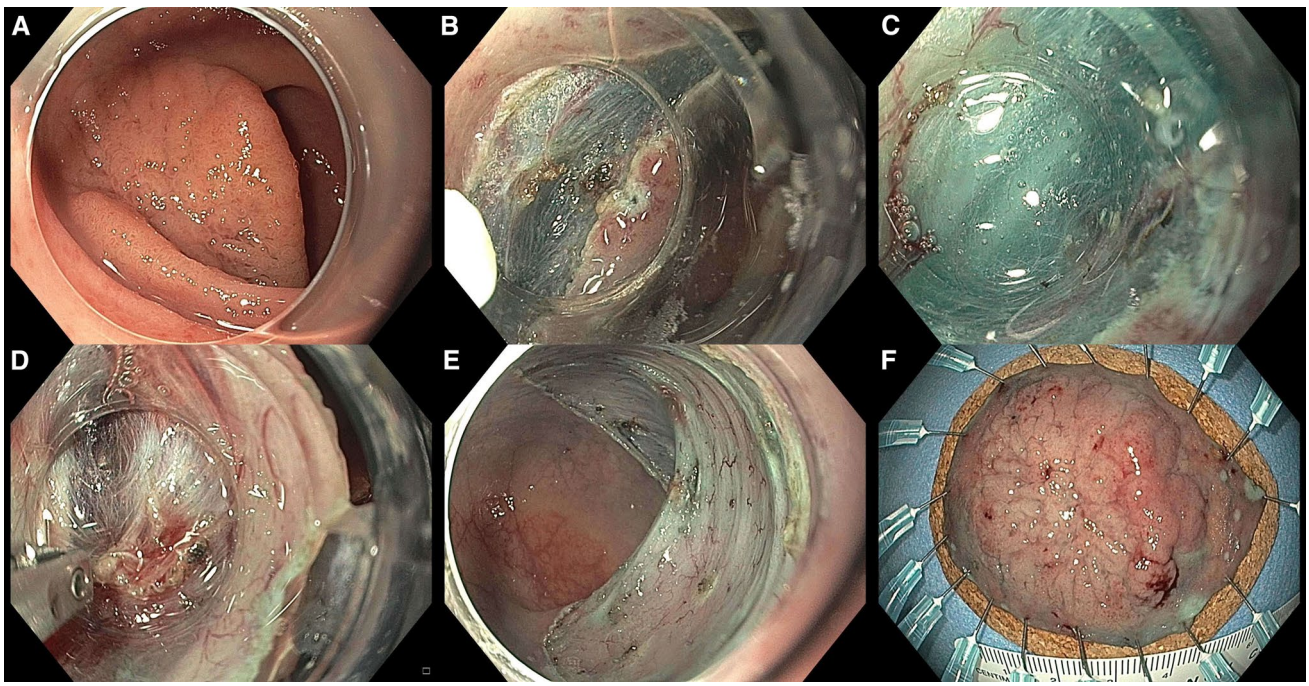

Fig. 3 Colorectal endoscopic submucosal dissection. (**a**) A 55-mm laterally spreading tumor in the proximal rectum, (**b**) mucosal incision, (**c**) submucosal dissection, (**d**) hemostasis of submucosal vessels, (**e**) resection defect, and (**f**) ESD specimen. Final pathology showed tubulovillous adenoma with high-grade dysplasia, with all margins negative, thus consistent with a curative resection

Endoscopic Submucosal Dissection (ESD)

Endoscopic submucosal dissection was developed in Japan in the late 1990s/early 2000s as a technique for resecting large and irregularly shaped lesions with high *en bloc* and margin-negative resection rate. Using a combination of specialized endoscopic knives (Fig. 1), adaptive electrosurgical generators, and high-viscosity injectable lifting solutions, ESD allows for *en bloc* resection of large superficial lesions without limitation on size [18].

ESD is performed using the following well-described technique (Figs. 2, 3) [19–21].

- *Mucosal Incision*. Following submucosal lifting with a high-viscosity solution, a specialized ESD knife is used to make an incision that penetrates the muscularis mucosae and enters the submucosal tissue. The incision is extended laterally until a full circumferential mucosal incision is ultimately made. The circumferential mucosal incision is made away from the lesion borders to ensure the negative lateral margin of the resection.
- *Submucosal Dissection*. The exposed submucosal tissue is initially opened, allowing the scope tip to enter the submucosal space. From within the submucosal space, additional submucosal dissection is made with the ESD knife, in a parallel fashion to the muscle layer so as to avoid muscle penetration and perforation. For lesions involving the mucosa or superficial submucosa, a dissection plane right above the muscularis propria allows the endoscopist to clear a deep margin beneath the lesion. There are many technical nuances to ESD, with much research focused on countertraction and resection strategy [22–25]. A detailed discussion of ESD resection strategy is beyond the scope of this review.

Using this technique, ESD has a well-established track record for efficacy and is considered a first-line endoscopic resection technique for complete endoscopic resection of superficial lesions in the esophagus, stomach, colon, and rectum, with the bulk of the existing literature focused on gastric and colorectal ESD. A large meta-analysis of gastric ESD which included 29,506 tumors across 74 studies showed a pooled estimate of 94% *en bloc* resection rate, 90% R0 resection rate, and 86% curative resection rate, with 2.7% perforation rate [26]. Similarly, a large meta-analysis of colorectal ESD which included 13,833 tumors across 104 studies showed a pooled estimate of 92% *en bloc* resection rate, 83% R0 resection rate, and 86% curative resection rate, with 4.2% perforation rate [27]. The data on esophageal ESD is less extensive however appears to be similarly favorable, demonstrating excellent resection outcomes and lower recurrence rates [28–30]. When compared to EMR, both gastric and colorectal ESD have superior *en bloc* and R0 resection rates and lower recurrence, although with longer procedure times and higher perforation rate. [8, 31, 32].

Despite a well-established track record and excellent clinical outcomes, ESD has not been widely adopted in the USA due to a variety of factors [33]. As such, while formal guidelines exist in Japan and Europe, formal ESD guidelines do not currently exist in the USA.

Esophageal ESD

The indication of ESD in the esophagus needs to be considered separately for squamous cell carcinoma (SCC) and esophageal adenocarcinoma (EAC) due to the difference in the estimated risk for lymph node metastasis (LNM) in association with invasion depth. The existing major guidelines note the following with respect to the role of esophageal ESD (Table 1).

- US National Comprehensive Cancer Network (NCCN) guidelines on esophageal and esophagogastric junction cancer indicates endoscopic resection is appropriate for many T1a lesions and may render potentially curative therapy for T1a and early T1b disease, without further specification with regard to EMR or ESD [34].
- A clinical practice review from the American Gastroenterological Association (AGA) recommends ESD for superficial SCC, with absolute indication for lesions with m1–m2 involvement, and expanded indication for m3 or superficial submucosal (< 200 µm invasion depth) involvement if no evidence for LNM [35]. For Barrett's esophagus, EMR remains the mainstay for most situations. However, ESD can be considered for lesions ≥ 15 mm in size with intramucosal adenocarcinoma or HGD, large or bulky areas of nodularity, suspected superficial submucosal invasion, recurrent dysplasia, and EMR specimens with positive margins for carcinoma.
- Formal guidelines from the European Society of Gastrointestinal Endoscopy (ESGE) recommend ESD for superficial SCCs, while limiting the use of EMR for SCCs < 10 mm in size [36]. For Barrett's esophagus, EMR continues to be preferred, while ESD may be considered selectively for lesions > 15 mm in size, poorly lifting tumors, and lesions at risk for submucosal invasion.
- Formal guidelines from the Japan Gastroenterological Endoscopy Society (JGES) recommend ESD in the management of superficial esophageal SCCs [37]. JGES guidelines also strongly favor ESD over EMR for the resection of superficial EACs due to higher *en bloc* and R0 resection rates, lower recurrence, and roughly equivalent adverse event rates.

Table 1 Esophageal ESD guidelines

Guideline	Year	Recommendation
NCCN (US) [34]	2019	Endoscopic resection is appropriate for many T1a lesions and may render potentially curative therapy for T1a and early T1b disease
JGES (Japan) [37]	2020	Squamous cell carcinoma:
		En bloc resection is required for curability
		The use of traction device using a clip and thread during ESD is weakly recommended
		Prophylaxis of stenosis is recommended after resection involving ≥ ¾ esophageal circumference
		For non-circumferential esophageal squamous cell carcinomas:
		Endoscopic resection is recommended for T1a (EP/LP/MM) and T1b (sm1)
		For circumferential esophageal squamous cell carcinomas:
		Endoscopic resection is recommended for T1a (EP/LP) with major axis length ≤ 5 cm
		Surgery is recommended for T1a (EP/LP) with major axis length > 5 cm
		Surgery is recommended for T1a (MM) or T1b (sm1)
		Adenocarcinoma/Barrett's esophagus:
		ESD is recommended over EMR for superficial esophageal adenocarcinoma
AGA Review (US) [35]	2018	Squamous cell carcinoma:
		HGD and well to moderately differentiated carcinoma
		Paris 0-II lesions
		Absolute indications: m1–m2 involvement with ≤ 2/3 esophageal circumference
		Expanded indications: m3 or sm ≤ 200 μm involvement, any size, clinically N0
		Adenocarcinoma/Barrett's esophagus:
		HGD and well to moderately differentiated T1a lesions ≥ 15 mm (not amenable to *en bloc* resection by EMR)
		Large or bulky areas of nodularity
		Equivocal preprocedure histology
		Recurrent dysplasia
		EMR specimen showing invasive carcinoma with positive margins
ESGE (Europe) [36]	2015	Squamous cell carcinoma:
		En bloc resection is recommended, excluding those with obvious submucosal involvement. ESD is recommended as first option, mainly to provide *en bloc* resection with accurate pathology staging and to avoid missing important histological features
		Adenocarcinoma/Barrett's esophagus:
		ESD has not been shown to be superior to EMR for excision of mucosal cancer
		ESD may be considered in selected cases such as lesions > 15 mm, poorly lifting tumors, and lesions at risk for submucosal invasion

AGA American Gastroenterological Association, *ESGE* European Society of Gastrointestinal Endoscopy, *JGES* Japan Gastroenterological Endoscopy Society, *NCCN* National Comprehensive Cancer Center Network, *T1a (EP/LP)* superficial mucosal involvement (epithelial or lamina propria), i.e., m1–m2, *T1a (MM)* deep mucosal involvement (muscularis mucosae), i.e., m3

Although the safety and feasibility of ESD for EACs have been well-documented including in a meta-analysis [38, 39], studies directly comparing EMR and ESD are limited. In a small randomized controlled study of patients with HGD or EAC and lesion size ≤ 3 cm, ESD provided higher margin-negative and curative resection rates [40]. However, over short-term follow-up at 3 months, there was no difference in complete remission. Long-term outcomes were not evaluated due to the need for large patient numbers.

In Barrett's esophagus and associated adenocarcinoma, endoscopic resection is considered curative if resection margins are negative, with well or moderately differentiated histology, no lymphovascular invasion (LVI), and superficial (defined as ≤ 500 μm) submucosal invasion [35]. Specimens with positive deep margins, or with deep (> 500 μm) submucosal penetration, poorly differentiated histology, or LVI are at higher risk for LNM [41]. Compared to EMR, ESD allows for superior histopathological evaluation and can be considered in cases with increased probability of an unrecognized invasive component, such as bulky lesions, intramucosal adenocarcinoma on biopsy, or equivocal histology [42]. ESD may also be preferred in cases involving non-lifting or recurrent lesions, or in situations where

Table 2 Lymph node metastasis risk in superficial esophageal cancer

Scenario—Squamous Cell Carcinoma [37]	Lymph Node Metastasis Risk (%)
pT1a (EP/LP)	Extremely Low
pT1a (MM) without vascular invasion	5.6
pT1a (MM) with vascular invasion	21.4
pT1b (sm1) without vascular invasion	13.2
pT1b (sm2) without vascular invasion	18.8
pT1b (sm1) with vascular invasion	60.0
Scenario—Adenocarcinoma [43]	Lymph Node Metastasis Risk (%)
pT1a	2.4
pT1b, without lymphovascular invasion	15.6
pT1b, with lymphovascular invasion	43.3

pT1a (EP/LP) superficial mucosal involvement (epithelial or lamina propria), i.e., m1–m2, *pT1a (MM)* deep mucosal involvement (muscularis mucosae), i.e., m3, *pT1b (sm1)* superficial third of submucosal involvement, *pT1b (sm2)* middle third of submucosal involvement

Table 3 Gastric ESD guidelines

Guideline	Year	Recommendation
NCCN (US) [15]	2018	ESD is considered adequate for lesions ≤ 2 cm, well or moderately well differentiated, does not penetrate beyond superficial submucosa, with no LVI, and with clear lateral and deep margins
JGES (Japan) [50]	2020	Absolute indication for EMR/ESD:
		Predominantly differentiated mucosal adenocarcinoma, intestinal type, ≤ 2 cm without ulceration
		Absolute indication for ESD:
		Predominantly differentiated mucosal adenocarcinoma, intestinal type, any size without ulceration
		Predominantly differentiated mucosal adenocarcinoma, intestinal type, ≤ 3 cm with ulceration
		Predominantly undifferentiated mucosal adenocarcinoma, diffuse type, ≤ 2 cm without ulceration
		Relative indications for ESD:
		Outside absolute indications but when surgery is not recommended due to patient condition, or in order to establish an accurate histopathological diagnosis before surgery
ESGE (Europe) [36]	2015	ESD is recommended as the treatment of choice for most superficial gastric neoplastic lesions

AGA American Gastroenterological Association, *ESGE* European Society of Gastrointestinal Endoscopy, *JGES* Japan Gastroenterological Endoscopy Society, *LVI* lymphovascular invasion, *NCCN* National Comprehensive Cancer Center Network

prior EMR specimens showed neoplasia at the deep margin [41]. However, it is important to note that the risk of LNM increases considerably with the depth of cancer invasion and LVI (Table 2) [43–46].

On the other hand, ESD is considered first-line therapy for esophageal SCCs based on evidence shown in multiple studies in terms of higher *en bloc*, margin-negative, and curative resection rates, with lower recurrence rate compared to EMR [30]. Endoscopic resection for esophageal SCCs is considered curative if the lesion is confined to the m1–m2 layers and the resection margins are negative.

Gastric ESD

ESD was first pioneered in Japan for the management of early gastric cancer and remains the mainstay for the

Table 4 Lymph node metastasis risk in early gastric cancer, without lymphovascular invasion [50, 53, 56]

Scenario	Lymph Node Metastasis Risk (%)
Within JGES absolute indications for ESD	Extremely Low
> 3 cm, differentiated type, pT1a with ulceration	3.0
> 3 cm, differentiated type, pT1b (sm1)	2.6
> 2 cm, undifferentiated type, pT1a without ulceration	2.8
≤ 2 cm, undifferentiated type, pT1a with ulceration	2.9
> 2 cm, undifferentiated type, pT1a with ulceration	5.9
Undifferentiated type, pT1b (sm1)	10.6

pT1a intramucosal adenocarcinoma, *pT1b (sm1)* submucosally invasive adenocarcinoma with ≤ 500 µm depth of invasion

Table 5 Lymph node metastasis risk in early gastric cancer

Score	Lymph Node Metastasis Risk (%)
0	1.6
1	2.6
2	4.9
3	7.4
4	8.3
5	19.9
6	27.3
7	26.7

Based on a scoring system which assigns a score for lesion > 3 cm (1 point), pT1b (sm2) or deeper (1 point), positive deep margin (1 point), positive venous infiltration (1 point), and positive lymphatic infiltration (3 points) [57]

management of superficial gastric cancer worldwide. The existing major guidelines note the following with respect to the role of gastric ESD (Table 3).

- US NCCN guidelines on gastric cancer have noted that ESD is more effective than EMR in potentially curing small early-stage gastric cancers [15]. ESD is considered adequate therapy when the lesion is ≤ 2 cm in diameter, well or moderately differentiated, does not penetrate beyond the superficial submucosa, does not exhibit LVI, and has clear lateral and deep margins.
- Original JGES guidelines stratified ESD indications into "absolute indications" and "expanded indications." [47]. These recommendations were echoed by the ESGE guidelines [36]. However, given favorable results from several multicenter studies [48, 49], the new 2020 JGES guidelines for the management of early gastric cancer have re-categorized these indications as "absolute indications for EMR/ESD," "absolute indications for ESD," and "relative indications." [50]. The absolute indication for EMR/ESD includes predominantly differentiated mucosal adenocarcinoma, intestinal type, ≤ 2 cm in size without ulceration, with the caveat that the risk of incomplete resection is significantly higher with EMR [51, 52]. Absolute indications for ESD (previously "expanded indications") include (1) predominantly differentiated mucosal adenocarcinoma, intestinal type, > 2 cm without ulceration; (2) predominantly differentiated mucosal adenocarcinoma, intestinal type, ≤ 3 cm with ulceration; and (3) predominantly undifferentiated mucosal adenocarcinoma, diffuse type, ≤ 2 cm without ulceration. Situations considered "relative indications" include those where endoscopic management does not meet requirements for absolute indications, but where surgery is not recommended due to the patient's condition, or in order to establish an accurate histopathological diagnosis before surgery, such as lesions with superficial submucosal invasion (pT1b).

ESD is particularly well-suited for the management of early gastric cancer [47, 50]. The development of the JGES gastric cancer guidelines was preceded by multiple large studies which demonstrated low risk of LNM and high survival rate in early gastric cancer. In a large study by Gotoda et al. in 2000 which included 5,265 patients who underwent gastrectomy with lymph node dissection for early gastric cancer, certain groups were identified which were associated with negligible risk of LNM and therefore favorable for endoscopic resection [53]. These findings were subsequently validated in multiple other studies [54–56]. More recently, large prospective multicenter trials were conducted evaluating the performance of ESD for expanded indications in predominantly differentiated pT1a gastric cancer (JCOG0607) and for undifferentiated pT1a gastric cancer (JCOG1009/1010) [48, 49]. Overall 5-year survival in the JCOG0607 and JCOG1009/1010 studies were 97.0% and 99.3%, respectively, and *en bloc* ESD was achieved in 99% in both studies. Based on this positive information, the 2020 JGES guidelines designate these categories as "absolute indications" for ESD [50].

The evaluation of endoscopic curability in ESD for early gastric cancer is based on risk factors for LNM. The 2020 JGES guidelines consider endoscopic resection for early gastric cancer to be curative if the final pathological results met the absolute criteria above, with negative resection margins and no LVI [50]. Additionally, curability can be expected for predominantly differentiated pT1b1 (sm1) adenocarcinoma (< 500 µm invasion depth from muscularis mucosae),

Table 6 Colorectal ESD guidelines

Guideline	Year	Recommendation
USMSTF (US) [63]	2020	*En bloc* resection is recommended:
		All pedunculated polyps
		Non-pedunculated polyps with endoscopic features that predict a high risk for submucosally invasive (pT1) cancer:
		LST-NG with sessile shape or depression
		LST-G with dominant nodule
JGES (Japan) [69]	2020	*En bloc* resection is required:
		Lesions for which en bloc resection with snare EMR is difficult to apply
		LST-NG, particularly LST-NG (PD)
		Lesions showing a V_I-type pit pattern
		Carcinoma with shallow T1 (sm) invasion
		Large depressed-type lesions
		Large protruded-type lesions suspected to be carcinoma, including LST-G nodular mixed type
		Mucosal lesions with submucosal fibrosis, as a result of previous biopsy or prolapse caused by peristalsis
		Sporadic lesions in conditions of chronic inflammation such as ulcerative colitis
		Local residual or recurrent early carcinomas after endoscopic resection
AGA Review (US) [35]	2018	*En bloc* resection for lesions at risk for submucosally invasive cancer:
		Type V Kudo pit pattern
		Depressed component (Paris 0-IIc)
		Complex morphology (Paris 0-Is or 0-IIa + Is)
		Rectosigmoid location
		Non-granular LST ≥ 20 mm in size
		Granular LST ≥ 30 mm in size
		Residual or recurrent colorectal adenomas
ESGE (Europe) [36]	2015	ESD can be considered:
		Lesions with high suspicion of limited submucosal invasion based on depressed morphology and irregular or non-granular surface pattern, particularly if > 20 mm
		Lesions that otherwise cannot be optimally and radically removed by snare-based techniques

AGA American Gastroenterological Association, *ESGE* European Society of Gastrointestinal Endoscopy, *JGES* Japan Gastroenterological Endoscopy Society, *LST* laterally spreading tumor, *LST-G* laterally spreading tumor, granular type, *LST-NG* laterally spreading tumor, non-granular type, *LST-NG (PD)* laterally spreading tumor, non-granular pseudodepressed type, *USMSTF* United States Multi-Society Task Force on Colorectal Cancer

intestinal type, ≤ 3 cm, with negative margins and no LVI. Early gastric cancers that do not fall into these subtypes are considered to have likelihood for remnant tumor, or non-curative resection. The risk of LNM for lesions without LVI has been carefully studied and described (Table 4). A separate analysis of 1,101 cases of gastric ESD followed by surgical resection stratified the risk of LNM through a scoring system (Table 5) which assigned a score of 1 point for each of the following: lesion > 3 cm, positive deep margin, venous infiltration, and pT1b2 (sm2) or deeper, and a score of 3 points for lymphatic infiltration [57].

Duodenal ESD

The duodenum is inherently a challenging location for ESD, due to a highly vascular wall and thin muscularis propria which accounts for a high risk for intraprocedural bleeding and perforation. Even when successful, duodenal ESD is characterized by a high risk of delayed bleeding and perforation, due to exposure of the resection defect to pancreaticobiliary juices [58, 59]. As such, duodenal ESD is limited to a handful of case reports and case series from endoscopists with extensive experience [60–62]. ESGE guidelines do not recommend ESD for duodenal or small bowel lesions due to the high risk of perforation, and advocate for either EMR for superficial lesions, or surgical resection for deeper lesions [36].

Colorectal ESD

EMR and ESD are complementary techniques in the management of superficial colorectal neoplasia, and the optimal approach takes into account lesion size, morphology, location, and availability of local expertise and resources to

Table 7 Lymph node metastasis risk in submucosally invasive colorectal cancer

Scenario	Lymph Node Metastasis Risk (%)
Non-pedunculated Lesions[i, ii]	
< 1000 μm	0
1000–2000 μm	11.9
2000–3000 μm	13.5
> 3000 μm	12.8
Pedunculated Lesions[iii]	
< 3000 μm without lymphatic invasion	0
< 1000 μm with lymphatic invasion	16.7
1000–3000 μm with lymphatic invasion	30.0
> 3000 μm	11.1

Based on a large study which analyzed the risk of lymph node metastasis based on depth of submucosal invasion (defined as depth from muscularis mucosae to deepest portion of submucosa)[75]

[i]Depth of submucosal invasion is defined as depth from muscularis mucosae to deepest portion of invasion

[ii]Where the muscularis mucosae could not be identified, depth of submucosal invasion is defined as the depth from the base of the superficial aspect of the carcinoma to the deepest portion of invasion

[iii]For pedunculated polyps, depth of submucosal invasion is defined as the depth from the neck of the polyp (Haggitt level 2) to the deepest portion of invasion

accomplish a successful resection. The existing major guidelines note the following with respect to the role of ESD in the colon and rectum (Table 6).

- Current 2020 US Multi-Society Task Force on Colorectal Cancer (USMSTF) guidelines on the management of malignant polyps recommend *en bloc* resection for all pedunculated polyps, as well as for non-pedunculated polyps with endoscopic features that predict a high risk of submucosally invasive (pT1) cancer [63]. Specifically, this includes non-granular laterally spreading tumors (LST-NG) with a flat shape or depression, or granular laterally spreading tumors (LST-G) with a dominant nodule [64–67].
- Current 2020 JGES colorectal ESD guidelines recommend ESD for lesions for which *en bloc* resection with snare EMR is difficult, including LST-NG, lesions with type V_I Kudo pit pattern [68], carcinoma with suspected T1 invasion, large depressed-type lesions, and large protruded-type lesions with suspected carcinoma [69]. ESD is also recommended for mucosal lesions with submucosal fibrosis, inflammatory bowel disease-associated dysplasia, and local residual or recurrent neoplasia after endoscopic resection.
- ESGE guidelines state that ESD can be considered for removal of colorectal lesions with high suspicion of superficial submucosal invasion, particularly for LST-NG lesions > 20 mm in size, or those that otherwise cannot be optimally removed by snare-based techniques [36].
- AGA clinical practice review recommended ESD for the following lesion categories: Type V Kudo pit pattern, depressed component (Paris 0-IIc) [70], complex morphology (Paris 0-Is or 0-IIa + Is), rectosigmoid location, LST-NG ≥ 20 mm in size, LST-G ≥ 30 mm in size, or residual or recurrent colorectal adenomas [35].

Endoscopic resection in the colon and rectum is unique given that the colorectal mucosa does not possess lymphatic drainage. Therefore, in situ or intramucosal adenocarcinoma (pTis) is considered equivalent to high-grade dysplasia, as dysplasia confined to the mucosa does not carry a risk for LNM [63, 69]. Unlike in the esophagus and stomach where pT1a refers to intramucosal adenocarcinoma and pT1b refers to submucosally invasive adenocarcinoma, the formal definition of "malignant polyp" and pT1 colorectal cancer refers to submucosally invasive adenocarcinoma [63]. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) stratifies pT1 into pT1a for superficial submucosal invasion (defined as < 1000 μm of submucosal invasion), and pT1b for deep submucosal invasion (> 1000 μm of submucosal invasion) [71].

Given these unique circumstances, there is continued debate regarding which lesions are better suited for ESD rather than piecemeal EMR. Multiple large observational studies of ESD in Asia have reported excellent resection outcomes [72, 73]. Additionally, a Japanese multicenter study of polyps > 2 cm in size demonstrated that 9.9% of endoscopically resected lesions were pT1, of which two-thirds were pT1a (superficial submucosal) and hence potentially curable by ESD [74]. Hence, it is generally agreed by multiple guidelines that lesions with a higher risk of harboring submucosally invasive carcinoma should be resected *en bloc*, as R0 resection by ESD may be curative and prevent the need for additional surgical resection [16, 17, 35, 36, 63, 69].

With regard to curability, JGES guidelines consider pT1 carcinomas to be radically cured when the following conditions are satisfied: (1) negative vertical margin (i.e., histological complete resection), (2) papillary or tubular adenocarcinoma, (3) submucosal invasion depth < 1000 μm (pT1a (sm1)), (4) no LVI, and (5) tumor budding grade 1 (low grade) [69]. The risk of LNM for submucosally invasive adenocarcinoma has been carefully studied and described in a large study by Kitajima et al. of 865 patients who underwent surgical resection for submucosally invasive adenocarcinoma (Table 7) [75]. In pedunculated lesions without LVI, the risk of LNM was 0% for head invasion and 0% for stalk invasion with invasion depth < 3000 μm.

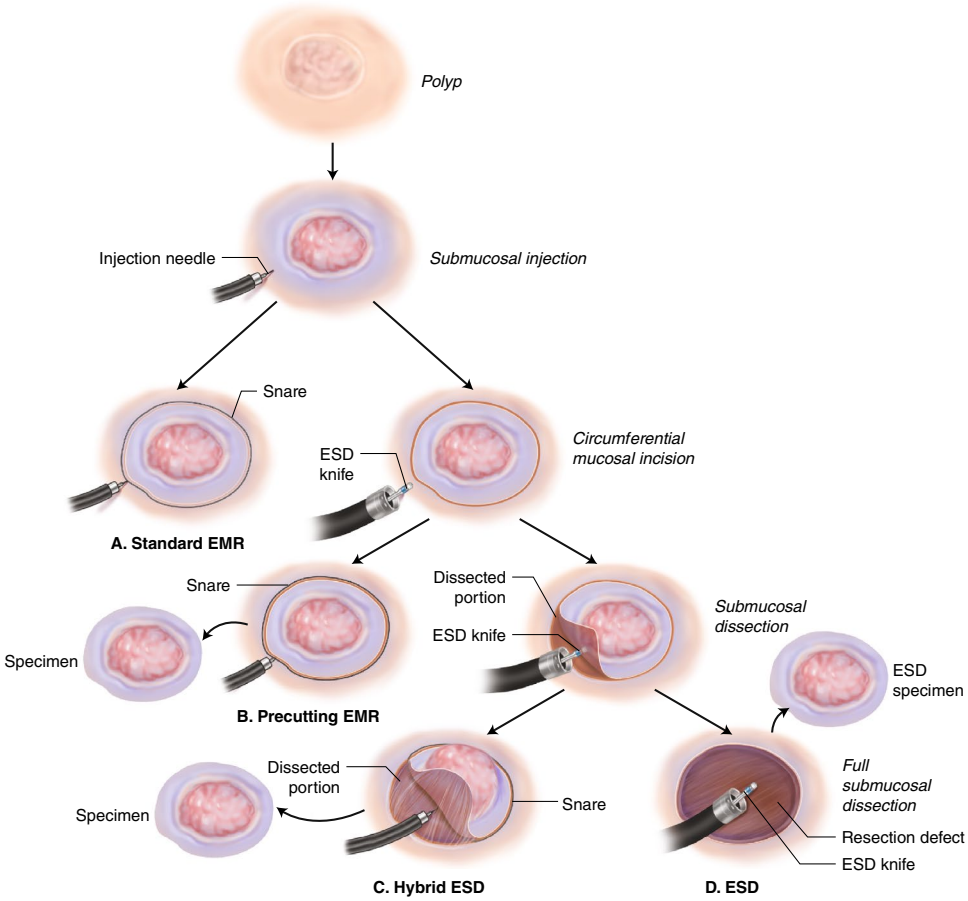

Fig. 4 Schematic demonstrating (**a**) standard EMR, (**b**) precutting EMR, (**c**) hybrid ESD, and (**d**) ESD

In non-pedunculated lesions, the risk of LNM was 0% for invasion depth < 1000 µm. A separate large meta-analysis determined a significant risk for LNM if there was submucosal invasion depth > 1000 µm, LVI, poor differentiation, or tumor budding [76].

Owing to regional differences in expertise and the type of lesions referred for ESD, and concerns of healthcare costs, studies of colorectal ESD in the USA are limited and have led many to suggest a limited role for ESD in Western countries [77, 78]. Nevertheless, a recent US-based study of outcomes in colorectal ESD demonstrated excellent overall outcomes, with mean lesion diameter 4.9 cm. [79] *En bloc*, margin-negative, and curative resection rates were achieved in 97.4%, 97.4%, and 93.5% of all colorectal ESD cases. Microperforation and delayed bleeding rates were seen in 1.3% and 3.9%. On a multivariable analysis, the presence of tattoo predicted failure to achieve curative resection; and the presence of tattoo, lesion size > 5 cm, and prior EMR attempts predicted a prolonged procedure time.

A large Australian cost-effectiveness modeling study demonstrated that ESD is cost-effective when applied selectively for colorectal lesions with submucosally invasive cancer [80]. When compared to laparoscopic surgery, ESD has been demonstrated to have favorable resection outcomes with potentially superior safety profile [81, 82]. A recent meta-analysis comparing ESD with minimally invasive transanal surgery for the treatment of rectal tumors demonstrated similar rates of resection, adverse events, and recurrence; however, ESD was shown to have significantly shorter procedure times and duration of hospitalization [83].

Hybrid EMR/ESD Techniques

Owing to the complexity of conventional ESD, several hybrid resection approaches have been described primarily for medium-sized lesions, including precutting EMR and hybrid ESD (Fig. 4) [84–87]. Precutting EMR is used to describe endoscopic resection whereby a circumferential incision is made around the lesion, followed by conventional EMR with placement of an endoscopic snare around the circular cut margin. Hybrid ESD is used to describe endoscopic resection whereby a limited submucosal dissection is performed after a circumferential incision, followed by conventional EMR. The benefit of either approach rests in the ability to provide clear lateral margins to minimize the risk of residual or recurrent neoplasia, potentially with a shorter procedure time.

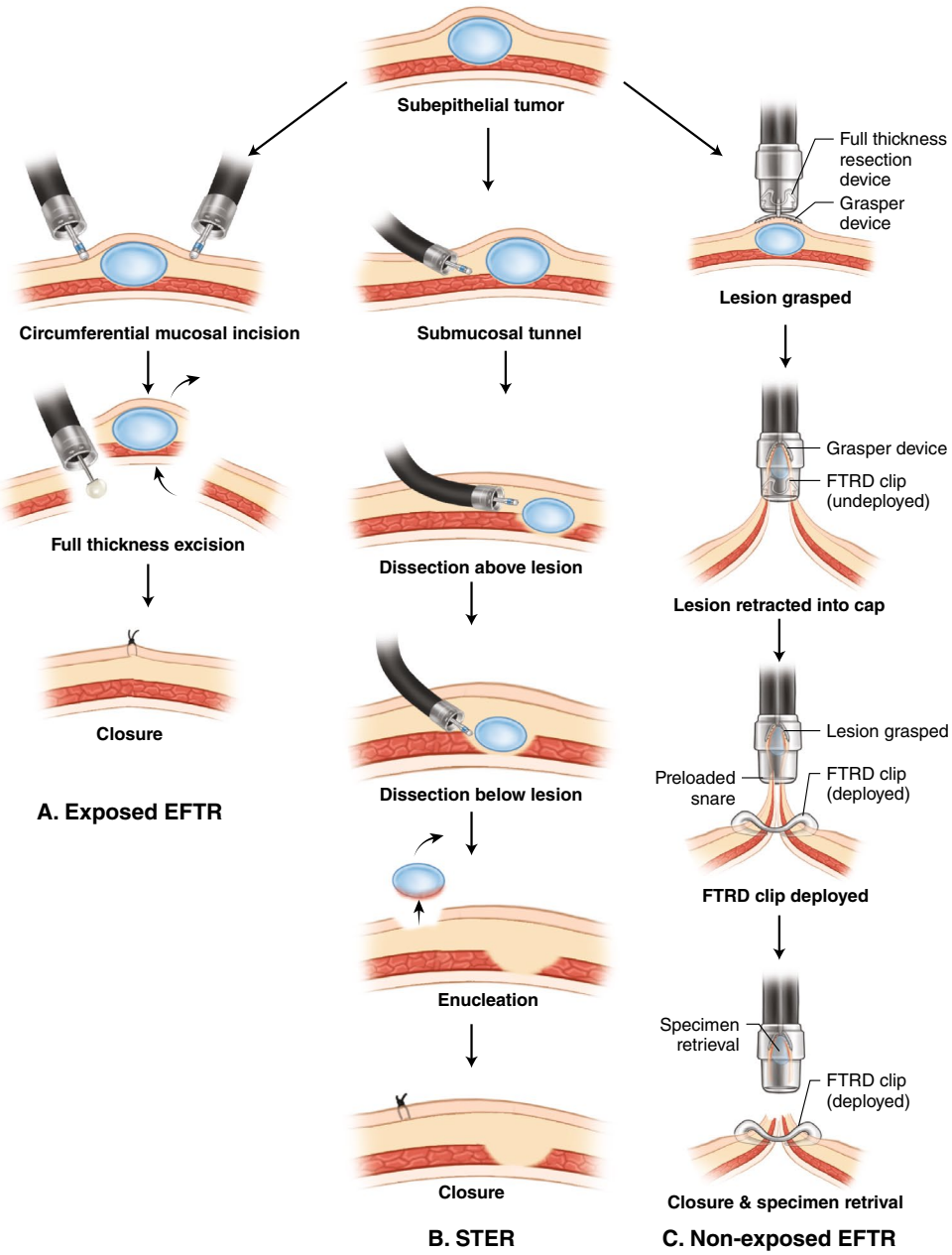

Fig. 5 Schematic demonstrating (**a**) exposed EFTR, (**b**) STER, and (**c**) non-exposed EFTR

A recent meta-analysis compared hybrid ESD with conventional ESD for colorectal lesions [88]. The study included 751 patients across 16 studies, with a mean lesion size of 28 mm. Hybrid ESD was demonstrated to be shorter in duration and associated with fewer adverse events, with similar rates of recurrence and surgery as compared to conventional ESD. However, hybrid ESD was associated with reduced *en bloc* resection rates, which may be a reflection of its use as a "rescue" strategy when conventional ESD is technically unsuccessful. [89].

Endoscopic Resection of Deeper Lesions

EMR and ESD are limited to superficial resection and do not provide for the resection of lesions involving the deeper layers of the gastrointestinal tract. Therefore, resection techniques such as endoscopic full-thickness resection (EFTR) have been developed (Fig. 5). A recent technology status evaluation report by the American Society of Gastrointestinal Endoscopy (ASGE) broadly categorizes EFTR techniques into exposed and non-exposed categories [90]. These techniques are limited by lateral size, but have provided the ability to resect deeper lesions within the gastrointestinal tract.

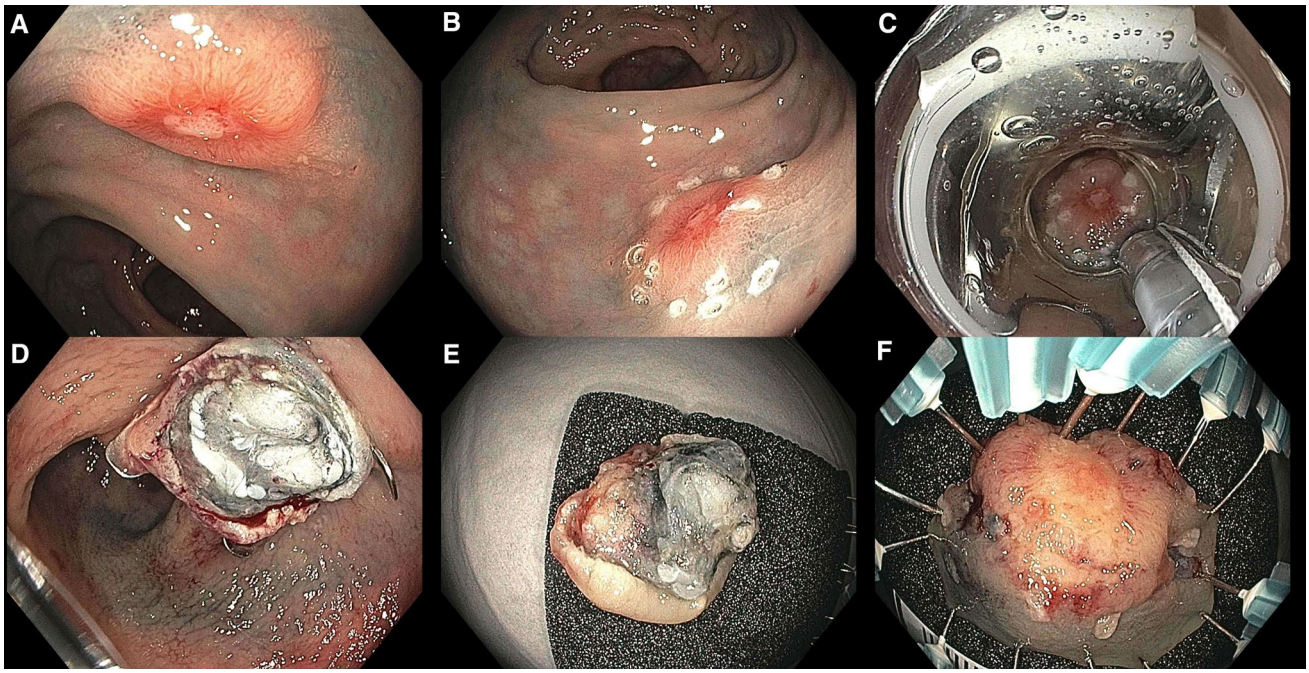

Fig. 6 Non-exposed endoscopic full-thickness resection. (**a**) A 13-mm neuroendocrine tumor in the mid-rectum, (**b**) marking of lesion borders, (**c**) EFTR with the full-thickness resection device, (**d**) resection defect with FTRD clip, (**e**) serosal side, and (**f**) mucosal side of the EFTR specimen. Final pathology showed well-differentiated neuroendocrine tumor invading into the submucosa, with lymphovascular invasion and perineural invasion, with all margins negative

Exposed Non-tunneled Full-Thickness Resection

The non-tunneled exposed technique has been described for subepithelial lesions (SELs), particularly with involvement of the muscularis propria [91]. The approach is similar to ESD, except that dissection is continued through the muscularis propria circumferentially around the lesion in order to achieve *en bloc* resection. Obviously, with an exposed non-tunneled EFTR, the closure must also be performed in a full-thickness fashion. Full-thickness closure can be achieved using a variety of methods, including a loop-and-clip technique, over-the-scope clip (OTSC; Ovesco Endoscopy, Tübingen, Germany), or with endoscopic suturing (OverStitch; Apollo Endosurgery, Austin TX).

Large series evaluating this technique are limited owing to the exposed nature of the resection and risk for persistent perforation. In a retrospective series of exposed EFTR for 23 gastrointestinal stromal tumors (GISTs) < 2 cm in size, lesions were successfully resected and closure achieved using an OTSC with twin-grasper forceps [92]. Localized peritonitis occurred in 9% of cases. A separate study demonstrated a reduction in procedure time and need for abdominal decompression when a retraction method was utilized [93].

Exposed Tunneled Full-Thickness Resection

In this approach, more commonly known as submucosal tunneling endoscopic resection (STER) [94–96], a mucosal incision is typically made approximately 5 cm away from the target lesion. A submucosal tunnel is then created from the mucosal incision site to the target lesion. When the target lesion is reached, additional dissection is carried out through the submucosa above the lesion, and circumferentially through the muscularis propria in order to fully enucleate the lesion. The specimen is then retrieved via the tunnel. Using this approach, a full-thickness closure is not necessary. The mucosal incision is closed with standard clips or endoscopic suturing, and the muscular defect is not repaired. Given the small size of the tunnel, STER is only feasible for lesions ≤ 4 cm in diameter, and performed for lesions in areas where submucosal tunneling is technically feasible (i.e., distal esophagus, gastric cardia, and gastric antrum).

The safety and efficacy of STER were recently evaluated in a meta-analysis which included 1,085 lesions across 28 studies [97]. The pooled *en bloc* and complete resection rates were 97.5% and 94.6%. The most common complications included air leakage (14.8% for subcutaneous emphysema and pneumomediastinum, 6.1% for pneumothorax, and 6.8% for pneumoperitoneum), and 5.6% perforation rate.

The largest existing study evaluating endoscopic resection of lesions originating from the muscularis propria included

726 patients, of which 530 patients underwent exposed non-tunneled EFTR and the remainder underwent STER [98]. The study reported a 12.9% overall adverse event rate (12.1% for exposed EFTR vs 15.3% for STER), which included 12.1% perioperative perforation and 0.7% localized peritonitis. Of the patients who had adverse events, 11.7% required surgical management. On multivariate analysis, larger tumor size, extraluminal growth, and extensive connection of tumor to the muscularis propria were associated with perioperative perforation. A separate study comparing STER with exposed non-tunneled EFTR demonstrated similar efficacy although with longer procedure time necessary for defect closure with the exposed non-tunneled approach [99].

Non-exposed Full-Thickness Resection

The non-exposed EFTR technique is conceptually analogous to surgical wedge resection and involves the use of a dedicated full-thickness resection and closure device (Full-Thickness Resection Device; FTRD; Ovesco Endoscopy) (Fig. 6) [100–103]. During the procedure, the target lesion is retracted into a specialized cap, and a modified over-the-scope clip is deployed over the retracted lesion to produce a serosa-to-serosa approximation. This step creates an intestinal wall duplication which isolates the target lesion, allowing for full-thickness resection above the serosal closure using a snare. Given that closure pre-emptively occurs before resection, free perforation is avoided during this procedure. However, owing to the size of the over-the-scope clip and dedicated cap, from a practical standpoint resection sizes are typically limited to 2-3 cm in diameter.

The safety and efficacy of this technique have been studied in multicenter settings primarily in Germany and Italy [100, 103]. In the largest prospective multicenter study, 181 colonic lesions including difficult adenomas, early adenocarcinomas, and SELs underwent resection with the FTRD [100]. Technical success was achieved in 89.5%, with 76.9% R0 resection rate. The R0 resection rate was lower in lesions > 2 cm in size compared to lesions ≤ 2 cm in size (58.1% vs 81.2%), which reflects device-related limitations. Adverse events occurred in 18 patients, including 6 perforations (3.3%), 4 cases of delayed bleeding (2.2%), as well as appendicitis and small bowel fistula. Emergency surgery was necessary in 4 cases (2.2%). A recent meta-analysis including 733 lesions across 18 studies indicated a pooled *en bloc* resection rate of 95% and R0 resection rate of 82%, with estimates for perforation and bleeding of < 0.1% and 2%, respectively [104]. These data suggest that a non-exposed EFTR technique is safe and effective for lesions not amenable to conventional endoscopic resection.

Recently, a dedicated upper FTRD device (gastroduodenal FTRD or gFTRD, Ovesco Endoscopy) was introduced. In a prospective multicenter pilot study of 29 gastric lesions, technical success was achieved in 89.7%, with 76% R0 resection rate [101]. Adverse events included minor periprocedural bleeding (31%) which was endoscopically managed, with no perforation. Of note, owing to the size of the device, a 20-mm balloon and guidewire assistance are used to facilitate insertion into the esophagus.

Training in Advanced Resection Techniques

The steep learning curve associated with ESD and other advanced resection techniques has limited its adoption to a small number of highly specialized centers especially in the USA. In Japan, ESD is traditionally taught using a master-apprentice model, in which proficiency is gradually gained through stepwise introduction to the procedure.

Owing to differences in disease prevalence in the USA with a higher proportion of colorectal cases and low prevalence of early gastric cancer, the traditional master-apprentice model has not been practical for US-based endoscopists. Furthermore, a major gap exists in baseline didactic training. Fundamental concepts in endoscopic resection such as lesion classification (Paris and laterally spreading tumor classifications) [66, 67, 70], imaging-enhanced endoscopy classifications (NBI International Colorectal Endoscopy (NICE) and Japan NBI Expert Team (JNET)) [105–108], electrosurgical generator settings [109], principles of resection outcomes such as *en bloc* and R0 resection, and American Joint Committee on Cancer (AJCC) TNM cancer staging are not routinely taught nor emphasized in US-based fellowship programs [110]. For those nevertheless seeking to learn ESD, there are currently three broad approaches to training.

The most common approach in the USA is a stepwise approach, described by Draganov et al. [111, 112]. This begins with background mastery and expertise in EMR, followed by self-study of ESD via hands-on training on animal models and participation in various ESD training courses. This is followed by a visit to a high-volume endoscopy center in Japan for observation and clinical exposure to ESD. After returning to the USA, the model advises to start human ESD in lesions with lowest technical difficulty, while continuing to improve from a technical standpoint.

Alternatively, Stavropoulos et al. described an untutored prevalence-based approach [113]. This begins with background mastery and expertise in advanced endoscopy, followed by developing expertise with peroral endoscopic myotomy (POEM), observation of ESD at live courses, self-practice in animal models, and subsequently starting human ESD cases. Using this approach, ESD proficiency was attained after approximately 250–300 cases.

Recently, a third approach has been described by our group [114]. This was a tutored prevalence-based approach, a formal ESD fellowship designed within the 1-year ASGE

advanced endoscopy fellowship. The trainee had no prior ESD experience, and training started immediately with colorectal cases, differing from a traditional Japanese model and modified to fit the realities of ESD practice in the USA which involve a bias toward more challenging and colorectal cases. The trainee started by assisting and observing the expert endoscopist, then partially performing easier aspects of ESD cases, with gradual increase in involvement and difficulty until entire cases could be completed. Proper patient selection, endoscopic diagnosis, electrosurgical generator settings, and resection strategy and techniques were concurrently taught and evaluated. With this approach, ESD was safely and effectively taught in a 1-year fellowship and allowed the trainee to successfully transition to independent academic practice [115]. A long-term follow-up study of the trainee's subsequent learning curve is underway.

There are no current studies analyzing the efficacy of training for EFTR. However, for non-exposed EFTR, the device manufacturer (Ovesco) requires attending a mandatory training course prior to being cleared to purchase and use the device. The 1-day course features didactic lectures explaining the technique and its nuances as well as preventing major adverse events and includes hands-on training on an *ex-vivo* animal model.

Conclusions

Endoscopic resection has existed for over 50 years since the advent of snare polypectomy. Multiple generations of pioneers in gastrointestinal endoscopy have developed and established endoscopic resection as standard of care in the management of superficial neoplasms throughout the gastrointestinal tract, as well as an increasingly viable therapeutic alternative in the resection of selected small deeper lesions.

Advanced endoscopic resection techniques today draw upon advancements in endoscopic imaging, dedicated resection devices, and complex electrosurgical generator units. ESD represents a major advancement in the management of superficial lesions in the gastrointestinal tract, whereas EFTR is a limited but increasingly viable endoscopic alternative in the management of deeper lesions. While it is unknown what advancements the future may hold, much of which will be influenced by development of new technologies and techniques, and financial realities in healthcare, we are excited for what the next 50 years will bring in endoscopic resection.

Key Points

1. Endoscopic resection is first-line therapy in the management of superficial neoplasms throughout the gastrointestinal tract, as well as an increasingly viable therapeutic alternative in the resection of selected small deep lesions throughout the upper and lower gastrointestinal tract
2. Endoscopic resection for superficial lesions in the esophagus: ESD is considered first-line therapy for the management of superficial squamous cell carcinomas. EMR is the mainstay for treatment of visible dysplastic lesions and early adenocarcinomas in Barrett's esophagus; however, ESD is beneficial for larger lesions measuring > 15 mm.
3. Endoscopic resection for superficial lesions in the stomach: ESD is considered first-line therapy for the management of early gastric cancer, with extensive evidence to support its safety and efficacy and with superior resection outcomes over EMR.
4. Endoscopic resection for superficial lesions in the duodenum: Due to high risk of delayed adverse events, EMR is preferred for the management of superficial duodenal lesions, with a limited role for ESD.
5. Endoscopic resection for superficial lesions in the colon and rectum: ESD and EMR are complementary techniques in the management of superficial colorectal neoplasia, with ESD favored for large polyps with risk for submucosally invasive carcinoma.
6. EFTR using either an exposed tunneled technique (STER) or non-exposed technique with a dedicated resection device provides an effective alternative in the resection of SELs throughout the gastrointestinal tract. A secure closure method is essential for success in EFTR.

Declarations

Conflict of interest Phillip S. Ge has no conflicts of interest or financial ties to disclose. Hiroyuki Aihara reports fees as a consultant from Boston Scientific, Olympus, Fujifilm Medical Systems, Auris Health, Lumendi, Medtronic, ConMed, and 3D Matrix.

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