



Evolving Role of Endoscopic Submucosal Dissection in the Management of Barrett's Neoplasia

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Abstract

Purpose of Review We aim to examine evidence on endoscopic submucosal dissection (ESD) for managing Barrett's esophagus related neoplasia by a narrative review.

Recent Findings Available studies and meta-analysis indicate ESD has comparable efficacy rates and adverse events as to endoscopic mucosal resection for managing Barrett's neoplasia. There is a high rate of en bloc, curative resections for T1a cancers, and early promising data for T1b cancers. However, most data is from expert centers and does not report long-term results. Lesion selection needs to be better defined in future large-scale studies.

Summary The role of ESD has been expanding in the management of Barrett's esophagus-related neoplasia. We need robust data of prospective nature with a precisely defined cohort of patients to determine the efficacy of ESD over EMR and to position this well in the BE armamentarium.

Review

Barrett's esophagus (BE) is a precursor to esophageal adenocarcinoma (EAC), often found at an advanced stage with a dismal prognosis. However, patients with BE could benefit from surveillance as any gain in early detection allows endoscopic therapy to prevent the progression to invasive cancer. Currently, endoscopic therapy is considered the standard of care for high-grade dysplasia and intramucosal cancer (T1a). However, those with T1b disease or higher undergo other forms of therapy, including surgery. While surgery in the form of esophagectomy, if only local disease, could be curative but also predisposes to significant morbidity and mortality.

Endoscopic submucosal dissection (ESD), which originated in the East, for managing gastric premalignant and superficial cancers has been employed for managing a variety of gastrointestinal precancerous lesions with reasonable success. Since it allows en bloc resection over endoscopic mucosal resection (EMR), it offers curative resection, detailed histological evaluation (lateral and deeper margins), and organ preservation. Meta-analysis of prior data has shown that ESD has a higher en bloc, R0, and curative resection rates with a slightly higher risk of adverse events compared

to EMR for managing BE-related neoplasia. Patients with visible lesions are at a higher risk of harboring advanced disease, and therefore, it is strongly recommended to pursue endoscopic resection in these cases. If the lesion is larger than 15–20 mm, scarred, and/or bulky, ESD may offer better en bloc resection over EMR for technical reasons. While EMR with currently practiced band ligation method could be effective for T1a disease, in many cases, EMR is not en bloc, and it becomes difficult for the pathologist to determine the margins due to thermal artifact. This makes the management challenging, and a repeat endoscopy with further resection and/or ablation with the risk of future recurrence persists. ESD in these cases with en bloc resection helps with subsequent management with a low risk of recurrence. Those with limited submucosal disease (sm1 EAC) with no nodal involvement could also be considered for ESD in expert hands.

In this review article, we will discuss the rationale for ESD, data on efficacy and adverse events from ESD in managing BE neoplasia, a comparison of EMR and ESD, and current indications and expanding role of ESD in Barrett's esophagus management.

Rationale for ESD

ESD has gained a higher ground in treating Barrett's associated neoplasia for several reasons and most of them are tied to the ability to resect a bigger specimen in one piece, especially in large lesions. When an endoscopist is dealing with any neoplastic or pre-neoplastic lesion, there are two most important points that the endoscopist is pondering: (1) curative resection in the stage of early cancers and (2) risk of recurrence post-resection. Therefore, the ability to resect entire lesion in a single piece with ESD provides theoretical potential to affect both outcomes. Moreover, with deeper resection achieved with ESD, there is an opportunity for the pathologist to review deep margins more closely in addition to lateral margins, which may affect ultimate plans concerning additional interventions in the form of surgical resection or chemotherapy if needed for a particular case. In addition, preventing diagnostic uncertainty may curtail unnecessary additional diagnostic procedures, patient anxiety, and in extreme cases, unnecessary surgical resection.

Efficacy of ESD

The efficacy of resection strategies is assessed by its ability to provide the entire lesion en bloc, whether the margins are free of any neoplasia (R0), and whether this leads to complete resolution of BE-related neoplasia (i.e., curative resection). Similarly, recurrence after resection, either local or metastatic, is important from the standpoint of curative resection and long-term remission. The goal of endoscopic resection is diagnosis, staging, and potential therapy. ESD could help with better lesion assessment microscopically, thus, improving pathological staging.

Multiple studies have been reported in the literature regarding the efficacy of ESD for Barrett's associated neoplasia. A high en bloc (89 to 100%) [1–25] and R0 resection rates (58% to 100%) [1, 2, 4–27] have been reported after ESD. Curative resection was reported from 44 to 86% [1–6, 9–11, 13–18, 20, 21, 23, 25–27] by prior studies for T1a neoplasia. However, the curative resection rate and R0 resection rate for T1b BE-related adenocarcinoma were somewhat lower (19%) from a single center data [7]. A low local recurrence rate has been reported around 0–16% [1–9, 12–15, 17, 19, 23–25, 27], while metastatic recurrence of 1.7% to 5.5% has been reported [4, 7, 15]. Meta-analysis of eleven studies by Yang et al. reports a pooled en bloc, R0, curative resection rate, and recurrence rate of 93%, 75%, and 65%, 0.2%, respectively [28]. The efficacy of ESD expands to achieve complete remission of all intestinal metaplasia (CRIM) after initial resection of the lesion with advanced pathology. CRIM rates reported by limited studies examining ablation after ESD have shown rates varying between 38 and 78% [1–3, 12, 22, 25, 29]. Finally, ESD could help improve pathological staging since it attempts to provide the entire lesion in one piece. Studies have reported pathological staging improvements post ESD (either upstaging or downstaging) in 10–70% of cases [1, 2, 7, 10, 12, 14, 20, 21, 23, 26, 29]. The mean procedure time for a case has varied from 54 to 169 mins [1–3, 5–8, 10–20, 23–27]. The outcomes of significant studies are summarized in Table 1.

Adverse events from ESD

Whenever larger or deeper tissue resection is undertaken, adverse events related to such interventions become a potential concern in the endoscopist's mind. This also holds relevance in the case of BE-related neoplasia, where an endoscopist must perform the intervention in a relatively narrow cylindrical cavity with mediastinum on the other end. Perforation remains a major concern in such cases. In literature, the perforation rate of ESD has been reported from 0.6% to 10% [1–12, 14–27, 29]. With resection of a larger esophageal lesion (those spanning > 1/2 circumference), there is a high probability of esophageal stricture after ESD. Stricture formation rate ranges from 0 to 60% in the literature [1–11, 14–24, 26, 29]. Chevaux and colleagues reported a

Table 1. Notable studies of ESD for Barrett's related early neoplasia

Author	Neuhaus [12]	Kagemoto [8]	Probst [15]	Chevaux [3]	Hobel [30]	Van Munster [19]	Joseph [7]	Ter-heggen [25]
Study design	Prospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	RCT
Patients	30	23	87	75	22	138	36	20
Mean procedural duration (min)	75	93	140	117	114	143	103.5	54
Mean diameter of the lesion (mm)	20	19	21	20	ND	27	27	16
Rates of resection								
En-bloc	90%	100%	95%	90%	96%	93%	94%	98%
R0	39%	85%	74%	64%	82%	70%	61%	59%
Curative	39%	65%	72%	64%	77%	NS	19%	53%
Adverse events								
Bleeding	4%	4%	1%	3%	9%	2.9%	0%	2.3%
Perforation	0	0	0	4%	5%	0.7%	0%	10%
Stricture	0	15%	9%	60%	14%	14%	2.7%	2%
Complete remission of neoplasia	96%	100%	98%	92%	94%	NS	NS	100%
Complete remission of IM	54%	NS	46%	38%	NS	NS	NS	38%
Ablation of residual IM	Yes	No	Yes	Yes	No	No	No	Yes
Follow-up								
Mean period (months)	17	33	24	20	19	29	9.8	22.6
Recurrence	0	7%	2%	10%	6%	0.01%	8%	5%

CRIM, complete remission of intestinal metaplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; RCT, randomized controlled trial; NS, not studied

high stricture formation rate at 60%, whereas authors report a median circumferential lesion extent of 75% in the study subjects [3]. Post-ESD bleeding is also a concern with deeper resection in submucosa with higher vascularity. Studies report post-ESD bleeding rates from 0 to 9% [1–8, 10–12, 14–23, 25–27, 29]. Yang et al. also reported pooled adverse events rate in their analysis and showed that pooled perforation, stricture, and bleeding rates were 1.5%, 11.6%, and 1.8%, respectively [28].

EMR vs. ESD

EMR and ESD continue to be important tools in the arsenal of endoscopists in managing any dysplastic and early-stage neoplastic lesions of the GI tract. However, guidance from major GI societies seems to differ in the initial strategy for management. A recent clinical practice update from American Gastroenterological Association (AGA) prefers ESD over EMR for large nodular lesions or lesions with a suspicion of submucosal invasion [31]. On the other hand, the European Society for Gastrointestinal Endoscopy (ESGE) recommends piecemeal resection with EMR over ESD as the preferred approach in managing BE-associated neoplasia in most cases [32]. There is also a reluctance to perform or send patients for ESD procedures for various reasons, including lack of ESD expertise, knowledge, facility cost and reimbursement, and longer procedure times. Safety issues with the procedure remain a primary barrier to adoption, followed by an unstructured training environment to gain expertise for this intervention. The lack of high-quality studies exploring the superiority of EMR vs. ESD for BE-related early neoplasia compounds this clinical dilemma. To this date, only a small, randomized trial conducted in Germany of ESD experts [25] examining 20 patients in each arm showed the superiority of ESD for a higher R0 resection rate. However, they could not establish superiority over EMR for other clinically relevant outcomes, such as complete remission of neoplasia and neoplasia recurrence. Also, the authors noted higher adverse event rates and longer procedure duration with ESD compared to EMR. However, the authors also acknowledge that the trial was very small in sample size, and a large patient and procedure volume might be needed to find a difference if it exists. However, no further evidence since then has come out in the form of RCTs. Fortunately, there are plans to undertake a trial of 331 patients in Amsterdam soon (NCT05276791), which could provide a few remaining important questions or provide supportive evidence in favor or against. The rest of the comparative evidence comes from retrospective and prospective studies [22–24, 29]. All of them report positive outcomes such as higher en bloc, R0, and curative resection rate with comparable adverse events [22–24, 29]. Pathological certainty of diagnosis also seems to be higher with ESD compared to EMR [24], and reports of higher CRIM rate at two years favor ESD compared to EMR [22]. However, as those studies are carried at centers of expertise, this evidence needs to be understood in the same context, as those endoscopists might be better at case selection for ESD

and EMR. A summary of the pro and cons of ESD and EMR is presented in Table 2. Key steps involved in band ligation EMR and ESD are shown in Fig. 1.

Current indications

In patients with BE-associated neoplasia/dysplasia, ESD would be the preferred resection technique for lesions ≥ 25 –30 mm, poorly lifting, and with endoscopic features concerning submucosal invasion—situations in which EMR would yield suboptimal results. Frequent or piecemeal EMR also increases the risk for recurrence and fibrosis at the site, making future intervention difficult. ESD can also be used to decrease pathological uncertainty, achieve R0 resection, and avoid surgery (especially sm1 disease with no lymphovascular invasion and good-moderate differentiation) in any suspicious visible lesion in BE segment.

Expanding indications

Emerging evidence demonstrates the expanding role of ESD in managing Barrett's neoplasia with early submucosal cancer (T1b, sm1), previously resected lesions with concern for residual disease, multifocal intramucosal cancer or dysplasia, and as an organ-conservation strategy in select cases. ESD can be a reasonable option also for cases with no evidence of nodal metastatic disease and absence of deep submucosal invasion to determine the extent of invasion with the goal of possible endoscopic resection, especially if a patient is a poor surgical candidate. Munster et al. [19] recently reported data from 9 high volume centers on 130 ESD cases showing a 97% en bloc resection rate where 52% of the lesions were T1b achieving a modest combined R0/en bloc rate of 49% for submucosal cancers (T1b) (vs. 87% for mucosal neoplasia, i.e., T1a). Residual neoplasia was found in 11 patients (2 had sm 1; 9 had sm 2 or 3) at 6–8 weeks follow-up. The remaining 108 patients did not have residual neoplasia at first surveillance and underwent follow-up (R1: 9 months, R0 17 months) with 0 local recurrence and seven metachronous lesions. The authors concluded that half of the patients with submucosal cancer had a deep positive margin, but only one-third were noted to have persistent neoplasia at follow-up endoscopy. Therefore, a follow-up endoscopy may provide a method of prognostication in 8–12 weeks after ESD to determine the need for surgery. While this is data from high-volume centers and ESD experts, it highlights ESD's evolving positioning for managing T1b cancer. While prospective comparisons of ESD and esophagectomy are required, ESD could have a selective role in managing submucosal EAC. Patients unfit for surgery who put a higher emphasis on quality of life and accept a higher recurrence risk might prefer ESD over surgery. Therefore, there is a need for better prospective, robust, high-quality data on ESD for submucosal cancer to

Table 2. Pros and cons of EMR and ESD for Barrett's related early neoplasia

EMR	ESD
<p>Advantages</p> <ul style="list-style-type: none"> • Preferred approach for managing BE-associated neoplasia with a visible lesion in majority of cases • Lower risk of adverse events compared to ESD • Shorter procedure time compared to ESD • Can be performed by endoscopists with basic endoscopic skills <p>Disadvantages</p> <ul style="list-style-type: none"> • Higher risk of incomplete resection compared to ESD • Lower pathological certainty of diagnosis compared to ESD • Lower en bloc, R0, curative resection rate compared to ESD • Limited use in managing large nodular lesions, or lesions with suspicion for submucosal invasion 	<p>Advantages</p> <ul style="list-style-type: none"> • Preferred for large nodular lesions (> 2–3 cm), or lesions with suspicion for superficial submucosal invasion • Higher pathological certainty of diagnosis compared to EMR • Higher en bloc, R0, curative resection rate compared to EMR • Higher CRIM rate at 2 years compared to EMR <p>Disadvantages</p> <ul style="list-style-type: none"> • Higher risk of adverse events compared to EMR • Longer procedure time compared to EMR • Requires specialized training and expertise • Reluctance to perform or send patients for ESD due to safety concerns, lack of knowledge and expertise, and facility cost and reimbursement

CRIM, complete remission of intestinal metaplasia; *EMR*, endoscopic mucosal resection; *ESD*, endoscopic submucosal dissection

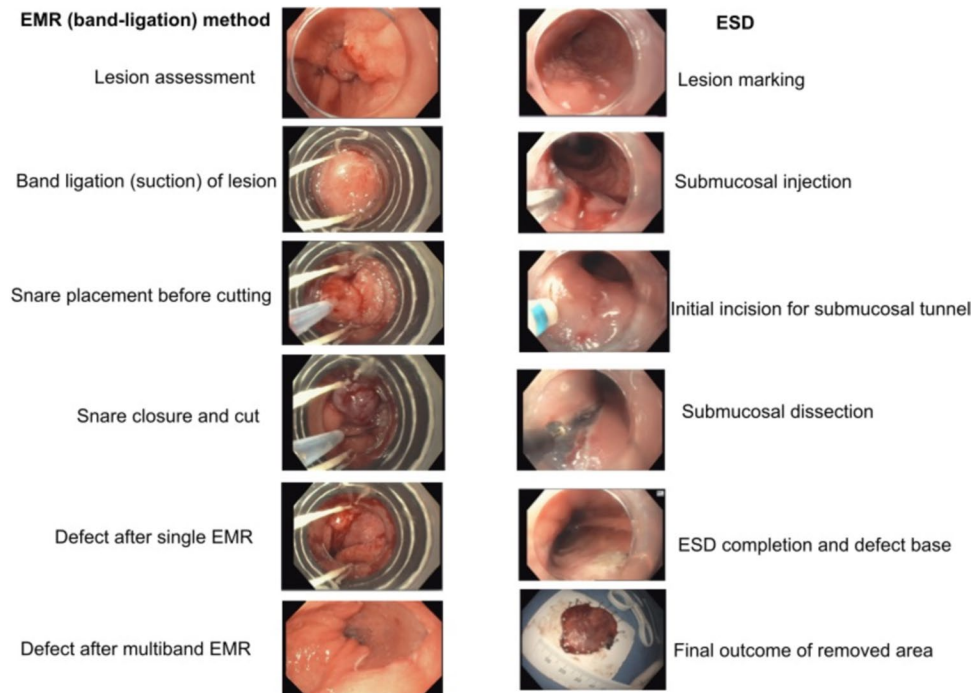


Fig. 1 Pictorial representation of steps involved in endoscopic mucosal resection and endoscopic submucosal dissection. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

define the positioning of ESD further. A summary of expanding indications is presented in Table 3.

Future perspectives

As the role of ESD continues to evolve in Barrett's neoplasia with its increasing uptake over EMR, the future is promising. There is a need for prospective trials comparing cap-assisted EMR and ESD for lesions < 3 cm size. The role of ESD compared to esophagectomy also needs to be explored further for T1b cancers. Another focus should be on developing new endoscopic devices

Table 3. Indications for ESD in Barrett's related early neoplasia

Current indication	Expanding indications
<ul style="list-style-type: none"> • BE-associated neoplasia/dysplasia, lesion size ≥ 25–30 mm, poorly lifting or concerning for submucosal invasion 	<ul style="list-style-type: none"> • Early submucosal cancer (T1b, sm1) • Previously resected lesions with concern for residual disease • Multifocal intramucosal cancer or dysplasia • Organ-conservation strategy in select cases • ESD can be an option for patients who are unfit for surgery, prioritize quality of life, and accept higher recurrence risk.

and techniques that may further expand the indications of ESD and enable en bloc resection of larger or more complex lesions. Additionally, potential exploration of biomarkers or molecular signatures is required to predict the risk of lymph node metastasis or recurrence after ESD and thus help guide patient selection and follow-up strategies. Another important aspect is the standardization of ESD training and accreditation, which is crucial to ensure the quality and safety of the procedure across different centers and regions. Finally, integrating ESD into a multidisciplinary approach involving pathologists, radiologists, and surgeons may facilitate personalized and coordinated management of Barrett's neoplasia, tailored to each patient's clinical and pathological characteristics.

Compliance with Ethical Standards

Conflict of Interest

Dhruvil Radadiya and Madhav Desai declare no competing interests.

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