EDITORIAL

# Endoscopic submucosal dissection for Barrett's neoplasia: decade of experience, little progress. Is ESD thE-BEST for complex Barrett's neoplasia?

The most recent American College of Gastroenterology (ACG) and American Society for Gastrointestinal Endoscopy (ASGE) guideline on Barrett's esophagus[1,2] recommends endoscopic eradication therapy as the procedure of choice for patients with high-grade dysplasia (HGD) or intramucosal carcinoma (IMC).

When examination of initial or surveillance biopsy specimens detects HGD suggestive of cancer or unequivocal early adenocarcinoma, the decision about further treatment is influenced by several factors, including tumor cell differentiation, lymphovascular invasion, and involvement of submucosa as detailed by surgical pathologic evaluation. Endoscopic resection (ER) is the preferred therapeutic approach for likely mucosal (Tis-T1a or HGD-IMC) lesions. ER is highly effective if resection is performed properly and critical pathologic information is accurately preserved. Initially adopted from gastric adenocarcinoma criteria, curative endoscopic therapy was extended to a subset of differentiated submucosally invasive (pT1b) adenocarcinoma that has a submucosal invasion depth of less than 500 μm with no lymphovascular invasion.[3] A recent study from Japan validated this cutoff value of less than 500 μm for differentiated esophageal adenocarcinoma appropriate to separate T1b adenocarcinoma with a low risk of metastasis.[4] The investigators compared various depths of invasion in 500-μm increments and incidence of metastasis during a 5-year follow-up. In the group in which cancer invasion in the submucosa was limited to more than 0 to 500 μm without high-risk features, no metastasis was detected in any patient.

Cap-assisted or band-assisted EMR has been the standard modality for ER, but in the past decade, large tertiary centers in Western countries have started to adopt endoscopic submucosal dissection (ESD), which provides the unique benefit of removing the neoplasm en bloc regardless of size and configuration with adequate negative margins. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines state that ESD can be considered in cases wherein the lesion is larger than 15 mm, when there is poor lifting, or Paris type I or IIa+IIc endoscopic features imply possible submucosal invasion.[5] However, the ACG guidelines state that although ESD gives a more complete understanding of the lateral margins of a lesion, EMR is "adequate" for assessing depth of invasion, which dictates clinical management. In the context of these somewhat conflicting recommendations, it is clear that the role of ESD in the treatment of Barrett's neoplasia is not well defined. There is a lack of large comparative studies reporting rates of curative resection, recurrence, or recurrence-free survival of ESD compared with EMR. Randomized controlled trials comparing recurrence rates between EMR and ESD will be difficult to execute because low rates of recurrence in each arm will require a sample size of at least 500 patients to enable conclusions with adequate power to be made.

**We do know that ESD can remove larger lesions than EMR, preserving the histologic architecture. We do know that ESD can remove submucosally invasive cancer with fibrosis better than EMR. So, where should we draw lines between EMR and ESD for their respective appropriate targets or characteristics?**

In a multivariate analysis of long-term outcomes of ER for Barrett's neoplasia, one factor associated with local recurrence was piecemeal resection.[3] The rate of local recurrence with EMR, where piecemeal is the most likely scenario, is not negligible. Widespread EMR has been used in a limited fashion because of a higher rate of stricture. In one multicenter retrospective study, neoplastic recurrence was noted in 6.2% of patients at a median follow-up time of 44 months after confirmed complete remission of dysplasia.[6] In another EMR efficacy study, recurrence of HGD or cancer was reported in 2.7% (2/74) of patients and in 11% (8/74) if low-grade dysplasia was included after complete EMR.[7] Even in the per-protocol analysis of an EUROII study using multimodal therapy to eradicate neoplastic Barrett's esophagus, 2.4% (3/124) of patients did not respond to therapies, and 4% (5/121) had recurrence of neoplasia.[8]


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By contrast, when lesions are removed en bloc, recurrence rates are thought to be lower, and there is more confidence in staging the specimen under pathologic examination. ESD provides the pathologist a resection tissue that has precise orientation and defined margins.[9] For any lesion greater than 2 cm, en bloc resection is unlikely with EMR,[10] and failure of en bloc resection contributes to a higher recurrence rate and can potentially result in advanced histologic characteristics being missed. In addition, we may be referring those patients to surgeons when ER is considered heroic or disadvantageous due to technical limitation of EMR.

Two large multicenter studies have been recently published on the feasibility and success of ESD. One study was from European centers and the other from North American centers. In a European 2-center randomized trial comparing ESD with EMR, en bloc resection rate, R0 resection rate, and clinical complete resection rate were studied in those 2 groups.[11] Any lesion larger than 3 cm was excluded. Twenty patients were included in each of the 2 groups. En bloc resection of the lesion was significantly lower in the EMR group (100% vs 15%, $P < .0001$). R0 resection with ESD was superior as well (59% vs 12%, $P = .01$). The rate of complete resection from neoplasia as judged by the surveillance endoscopy and biopsy was not different between the 2 groups at 3 months and was obtained in all patients irrespective of the technique used. The rate of elective surgery was also not different between the 2 groups based on the pathologic specimen obtained. There were no immediate adverse events in ESD group that required surgical therapy. Although the study findings fill a vital gap in our understanding of the comparison of the 2 techniques, the fact that any lesion larger than 3 cm was excluded limits the applicability of these results in clinical practice, where a resection area larger than 3 cm is frequently encountered when ESD is considered. In our view, the primary advantage of ESD is the ability to resect large lesions. In one meta-analysis, the mean lesion size of resection of 20.4 mm by EMR was significantly smaller than the mean size of resection of 37 mm performed with ESD ($P < .001$).[12]

In another study from North America, 46 patients who underwent ESD for Barrett's neoplasms at 5 referral centers were studied retrospectively.[13] The median follow-up time was 11 months, and the primary endpoint was en bloc resection rate. The mean specimen size was much larger than that in the European randomized comparison study (45 mm vs 14 mm). The authors reported en bloc resection rate, curative resection rate, and R0 resection rate of 96%, 70%, and 76%, respectively. Most incomplete resections (R1) were for lesions in the esophagogastric junction. The esophagus stricture rate was 15%, and all such patients were successfully treated with standard endoscopic dilations. As mentioned above, this study more closely reflects the clinical application of ESD and its superiority when it comes to larger lesions with comparable rate of adverse events to EMR.

Another unique advantage of ESD is the ability to resect lesions with submucosal fibrosis.[14] Several processes, including previous manipulation such as sampling biopsy, attempted resection, or desmoplastic reaction resulting from tumor invasion, can cause submucosal fibrosis. The disease process of Barrett's esophagus itself may also lead to an abundance of submucosal connective tissue, which can contribute to poor lifting with submucosal fluid injection if attempted. In the context of the above-stated advantages of ESD but an undefined role of ESD in the treatment of Barrett's-associated dysplasia, we read with interest the additional data provided by Subramanium et al.[15] This tricenter retrospective study is unique in that it did not exclude lesions that had scarring from previous manipulations. The study included 124 patients, and 24.5% of the lesions were scarred because of previous resection attempts, chemoradiation, or esophagectomy. The mean lesion size was 31 mm, and more than 80% of the lesions were 2 cm or larger. Only in 1 case ESD could not be completed because of significant fibrosis, and indeed esophagectomy confirmed cancer invasion into the muscularis propria. An en bloc resection rate of 90.8% is in the range of that reported by previous publications.[13,16-18] The authors speculated that the inclusion of scarred lesions was likely the reason why 100% en bloc resection could not be achieved. The overall R0 resection rate was 78.9%. The curative resection rate (R0 and absence of poor histologic features) of 65% was also similar to those in previous studies[17,19] but less than in some more recent publications.[13,16,18] Another notable finding was that multivariate analysis showed that the presence of submucosal cancer was an independent prognostic indicator of failure to achieve R0 resection. In most cases with R1 resection, deep margins were involved. The performance of ESD in this study could have improved by the exclusion of tumors that were at high risk for deep submucosal invasion, but in Western countries, where Barrett's dysplasia or cancer frequently occurs in patients with several severe comorbidities, surgery is often considered a high risk, and ER may be the only resection choice available that can also identify a subset of patients with low risk of metastasis and can predict risk for future cancer-related adverse outcomes. Many high-risk patients are willing to accept the "less than perfect" preprocedural prediction of the presence of deeper T1b lesion (staging) separating from T1a to shallow T1b and the potential risk of failure to achieve R0 resection, given that their other option is highly morbid esophagectomy. A median follow-up time of 21 months with endoscopic evaluation was available in 78% of the cases. It is interesting that despite a high en bloc resection rate higher than 90% but with less than ideal R0 resection and curative resection rates of 79% and 65.8%, the recurrence rate was 5.8% (7/121), which is similar to widespread EMR outcome. There were 5

recurrences at the site of resection in cases where R0 resection was achieved. Why? Would there be an explanation for this? Or does ESD offer no benefit over EMR? Not quite so.

First, the target lesion was larger (>2 cm) or with scar and included about 20% of T1b cancers. For those lesions, one may hesitate to perform or may not offer EMR. It is wrong to assume a similar successful resection rate with EMR for those lesions when ESD succeeds. Second, it should also be noted that further ablation therapy after ESD was not routine in this study. The author's explanation for this rather high local recurrence of 5.8% is 2-fold. The first issue is that local recurrence was defined as HGD or cancer noted within 2 cm of the previous ESD resection site. This may be too generous, and some metachronous recurrences could have misclassified as local recurrences. Barrett's esophagus contains a mosaic of various phenotypic lineages that evolve over time to give rise to more aggressive dysplastic lineages with no specific spatial distribution within the Barrett's segment. Hence, metachronous lesions are not uncommon and can be encountered on subsequent endoscopies. The second issue is marking the area of resection outside the tumor. The authors reported a 2-mm dysplasia-free or cancer-free margin requirement for R0 resection; however, in our practice we attempt to achieve tumor-free margins of 5 mm or more. Leaving any more tumor-free margins may make the total resection area unnecessarily wider, elevating the risk of subsequent stricture, but any smaller margin may increase the risk of local recurrence. When these nuances are taken into account, the only reliable curative option that will make the risk of dysplasia recurrence zero, irrespective of the multifocal nature of Barrett's, will be complete mucosectomy of the esophagus in an en bloc manner. However, this approach leads to a 100% rate of stricture, for which we do not yet have a clinically established prevention method. The stricture rate in this study was 2%, which is very low within patients who had a mean resection circumference of 31%.

This study adds further evidence to the feasibility of ESD in Western countries for large or difficult lesions, but we are still left with unanswered question. For which lesion do we see a clear benefit of ESD over EMR for Barrett's-related dysplasia or cancer? We do know that ESD can remove larger lesions than EMR, preserving the histologic architecture. We do know that ESD can remove submucosally invasive cancer with fibrosis better than EMR. So, where should we draw the lines between EMR and ESD for their respective appropriate targets or characteristics? Does ESD offer salvage therapy for EMR failure or improve a patient's outcome over EMR?

On the basis of the available evidence and additional knowledge offered by this article, larger lesions with or without submucosal fibrosis from either previous manipulations or slight submucosal invasion are those that may be best suited for ESD, with a special note that we need to anticipate technical difficulty during ESD if submucosal invasion is present.

The widespread adoption of ESD as a preferred modality for some Barrett's neoplasia has been hindered by the lack of available expertise with ESD and the lack of ESD training programs in North America. Although this study does not primarily address the threshold of number of procedures needed to establish proficiency in ESD of the esophagus, a clear learning curve was noted for expert endoscopists who have performed ESD in other organs. As we develop training pathways ideal for each organ system and identify more mentors for ESD in the Western countries, more and more ESD procedures will be performed. With the above discussion in mind, we need to carefully monitor ESD outcomes for Barrett's-associated dysplasia or cancer.

## DISCLOSURE

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*Abbreviations: ACG, American College of Gastroenterology; ASGE, American Society for Gastrointestinal Endoscopy; ER, endoscopic resection; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; IMC, intramucosal carcinoma.*

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