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Review Article

Endoscopic submucosal dissection in the West

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ABSTRACT

Endoscopic resection has emerged as the first line therapy for pre-malignant conditions throughout the gastrointestinal (GI) tract. Resection techniques have evolved from forceps avulsion and snare polypectomy to endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). While ESD was originally developed in Japan for resection of early gastric neoplasia, its use in the East has expanded rapidly to all types of superficial neoplasia throughout the GI tract. Despite the widespread use of ESD in the East, Western adoption of the ESD technique has been lukewarm. The hesitancy to adopt ESD is multifactorial, likely secondary to concern about the increased risk of complications, procedure duration and reimbursement, as well as the long learning curve of ESD. Despite this initial hesitancy, preliminary reports of the use of ESD for the resection of superficial neoplastic lesions in the West have been encouraging. The aim of this review is to highlight the current use of ESD for superficial neoplastic lesions throughout the GI tract in the West.

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Keywords: Barrett esophagus; Colonic neoplasms; Colonic polyps; Endoscopic mucosal resection; Stomach neoplasms

Introduction

Gastrointestinal (GI) malignancies continue to be a major cause of morbidity and mortality across the Western World.¹ In addition, a concerted effort to treat patients at risk for developing these conditions by identifying and removing any precursor neoplastic lesions has been advocated by numerous experts and adopted by many societal guidelines.^{2–4} As the ability to accurately characterize and classify the risk of distant disease within these lesions has progressed,⁵ the use of endoscopic resection has emerged as the first line therapy for these lesions throughout the GI tract.^{2–4,6–8} Resection techniques have evolved from forceps avulsion and snare polypectomy to endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The choice of either EMR versus ESD for resection of these lesions has remained a controversial issue. While EMR has proven to be a safe and efficient method for resection of superficial neoplastic lesions, non-pedunculated colonic lesions larger than approximately 2 cm and esophageal lesions larger than 1 cm typically require piecemeal resection, which may hinder the accuracy of histologic staging and may be associated with incomplete removal of neoplastic tissue. In EMR, there is poor control of the lateral margins as the

snare may slip off the intended target and capture a smaller area of the lesion. The deep resection margin during EMR is often within the superficial submucosa, which is sufficient for adenoma resection but may not be deep enough to yield an adequate margin when treating early cancers.⁹ Multiple prior studies have demonstrated high rates of recurrent neoplasia at the resection border/sites.^{10,11} ESD helps mitigate many of these challenges. ESD, originally developed in Japan for resection of early gastric neoplasia,¹¹ is now used extensively in the East to treat superficial neoplasia throughout the GI tract. Despite the widespread use of ESD in the East, Western adoption of the ESD technique has been lukewarm. The hesitancy to adopt ESD is multifactorial, likely secondary to the increased risk of complications, steep learning curve and concerns regarding procedure duration and reimbursement.¹²

Despite this initial hesitancy, early reports of ESD in the West have been encouraging and a growing number of publications highlight the safety and efficacy of ESD in the hands of western operators.^{13–19} However, the potential different natural history of colonic lesions,²⁰ lower rates of early gastric neoplastic lesions and higher rates of Barrett's associated neoplasia^{2,3} in the West versus the East all suggest that the arena in which a Western endoscopist performs ESD may be very different than a practitioner from the

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East. The aim of this review is to highlight the current use of ESD for superficial neoplastic lesions throughout the GI tract in the West and provide next steps and future directions for the practice of ESD in the West.

Esophageal Endoscopic Submucosal Dissection

ESD in the esophagus in the West represents an interesting contrast to the Eastern experience.

The vast majority of ESDs in the West are performed for early Barrett's neoplasia compared to ESD for superficial squamous cell carcinoma in the East (Fig. 1). However, despite the difference in pathology, ESD resection of esophageal lesions in the West has demonstrated similar results to the East. In a metaanalysis controlled for country of origin (Asia vs Europe/USA), R0 and curative resection rates of ESD in Barrett's neoplasia were found to be similar, as were the rates of perforation and stricture.²¹

While either EMR or ESD are considered appropriate therapy for Barrett's neoplasia, direct comparisons between ESD and EMR for the treatment of Barrett's related neoplasia are limited. In the only direct randomized comparison of ESD and EMR for Barrett's neoplasia, Terheggen et al²² noted similar successful resection rates between ESD versus EMR with no difference in complete remission from neoplasia at 3 months (ESD 15/16 vs EMR 16/17, $P = 1.0$). Recurrence of cancer was only observed in one case (ESD) after an approximately 24-month follow up period.¹³ The overall numbers were relatively small (20 EMR and 20 ESD) and a detailed analysis of pathology samples was not reported. When compared to EMR, the specimen produced by ESD results in greater diagnostic certainty with more definitive vertical and lateral margins, and this significantly impacts the ability to reach a definitive diagnosis.⁹ Current Western societal guidelines only

recommend consideration of ESD for esophageal lesions larger than 15 mm, or lesions at risk for submucosal invasion (i.e., poorly lifting tumors).²³

Endoscopic submucosal dissection in the stomach

The western experience with ESD in the stomach mimics the excellent safety and efficacy of the procedure in the East with high rates of *en bloc* resection and R0 resections, with similar rates of bleeding (early and late) and perforation.¹⁵⁻¹⁷

Based on this safety and efficacy data, several Western Experts²⁴ and the NCCN²⁵ guidelines for gastric cancer recommend consideration of ESD as first line treatment for any early gastric adenocarcinoma that meets the expanded Japanese criteria, given the demonstrated low risk of lymph node metastasis for these select lesions. The expanded criteria for ESD in the stomach includes differentiated-type cancers up to 3 cm that involve the superficial submucosa, non-ulcerated differentiated-type mucosal cancers of any size, ulcerated differentiated-type mucosal cancers up to 3 cm, and undifferentiated mucosal cancers up to 2 cm.²⁶

Endoscopic submucosal dissection in duodenum

Published data on duodenal ESD in the West is extremely limited. Pérez-Cuadrado-Robles et al²⁷ published a metaanalysis and systematic review of the current published literature that included 14 studies, but only 2 were from the West. Similar rates of bleeding and perforation were found in the East and West. However, higher rates of local recurrence were seen in both Western studies (5/34 and 5/13) with no reports (0/163) in any of the Eastern studies likely due to the much higher rates of complete (145/167 vs 7/36) and *en bloc* resections (182/192 vs 19/50) in the Eastern

Fig. 1. (A) Endoscopic submucosal dissection is used for staging and treatment of a superficial cancer in Barrett's esophagus. (B) Resection site. The final staging was T1a cancer with an R0 resection.

Fig. 2. (A) Endoscopic submucosal dissection is used for treatment of a cecal polyp. Biopsies by the referring physician demonstrated at least intramucosal cancer; submucosal invasion could not be assessed on the biopsies. (B) The lesion was removed *en bloc* and pathological examination showed an intramucosal cancer with an R0 resection.

studies.

The difference in resection rates may be secondary to the difficulty of submucosal dissection in the duodenum and the significant technical expertise required to sufficiently ensure complete resection without perforation. Anatomic factors such as a highly vascular duodenal wall, a thin muscularis propria, and constant exposure to gastric acid, bile, and pancreatic secretions all may contribute to procedural complexity, leading to difficulty in achieving *en bloc* or complete resection and promoting procedural complications.

Endoscopic submucosal dissection in the colon

ESD provides a unique opportunity for definitive cure for the treatment of early stage colorectal adenocarcinoma, as cancer with limited submucosal involvement can be curatively resected without a significant risk of lymph node metastasis (Fig. 2).

As of such, current European guidelines recommend consideration of ESD for removal of neoplastic lesions in the colon if they possess high suspicion of limited submucosal invasion. Limited submucosal invasion is suggested based on two main criteria: depressed morphology and irregular or nongranular surface pattern, particularly if the lesions are larger than 20 mm. Additional caveats for consideration of ESD in the colon are if the endoscopist feels that the lesion cannot be optimally and radically removed by (EMR) snare-based techniques as other oncologic guidelines^{7,8} recommend definitive surgical resection should the endoscopically resected specimens possess extensive fragmentation or additional artifact that hinders definitive assessment of margin status.

In the most comprehensive review of colonic ESD to date, Fuccio et al¹⁸ demonstrated that compared to Eastern operators, Western ESD was associated with significantly lower levels of R0 (71.3% vs 85.6%) and *en bloc* resections (81.2% vs 93%) with higher 12-month recurrence rates (5.2% vs 1.1%), although high levels of heterogeneity were reported across the studies.

Similar rates of perforation and bleeding complications were noted. However, Western studies demonstrated a higher rate of adverse events ultimately requiring surgery (3.1% vs 0.8%).

The etiology for the differences in procedural outcomes and complications is unclear, but when excluding studies that included a hybrid ESD technique, the median number of patients per study in the West was 43 compared to 104 in the East. This finding highlights that any potential differences in resection outcomes and complication rates identified in this study may be secondary to a failure to account for the learning curve necessary to perform ESD proficiently. Current case estimates prior to developing technical expertise vary, but some authors have noted an estimate of 80 cases in order to achieve sufficient technical expertise.²⁴ While the article attempted to correct for 'high' and 'low volume centers' the cut off for determining high volume centers was determined arbitrarily and was rather low, with only > 24 ESD per year determining a high volume center.

Additional considerations

Endoscopic closure of the dissection site

While endoscopic repair of perforations is essential, the need for closure of a non-perforated post ESD resection bed is controversial and is largely performed at the behest of the operating endoscopist. A recent report in abstract form concluded that there was no significant difference in adverse events when ESD defects in Western centers were closed or left unclosed.²⁸ The widespread availability in the West of endoscopic suturing, which can be

utilized to effectively close large ESD defects that are difficult to manage with clips, may affect the decision to perform closure but more studies are needed to define the optimal clinical scenarios for its application and demonstrate a clinical benefit.

Are all perforations the same?

While the overall perforation rate is significantly higher with ESD compared to EMR, the perforations in ESD are usually small and easily amendable to endoscopic treatment with clips, while perforations occurring during EMR are typically much larger and more difficult to manage endoscopically. Adoption of ESD in the West may be hampered by classification of small perforations or muscle injuries as severe complications, even when they are effectively treated by intraprocedural clipping without much impact on the remainder of the procedure or patient outcomes.

Training in the West

As the use of ESD expands throughout the west, it calls for a standardized training regimen to meet demand. However, initial Eastern training of ESD typically utilizes smaller gastric antral lesions, which require substantially less expertise to resect safely. As the West does not have the amount of early stage gastric neoplasia to enable adequate wide spread ESD training, there have been three recommended training avenues: direct supervision at an Eastern center with significant ESD exposure, indirect training using animal models, or a hybrid animal and direct supervision training program. Coman et al²⁹ highlighted an example of a 5-phase hybrid training model for ESD in the West. The recommended initial phase includes accumulation of basic knowledge of procedural indication and patient selection followed by observation of experts in action in phase 2. Phase 3 includes directly assisting (via technical support or operation of the needle knife devices) the experts performing the procedure. Only after completion of phase 3 should the trainee begin working on simulator models (*ex-vivo* and *in-vivo* animal models; or synthetic models of organ of interest). While procedural familiarity and skill will largely be unique to each trainee, a minimum of 30 resections, reaching an adequate resection speed, and management of complications were suggested as aims of animal model training. After formal completion of phases 1 to 4 the trainee could then begin to perform ESD procedures under direct expert supervision in phase 5. In phase 5 the authors recommend initial cases to include small lesions in the stomach or rectum prior to initiation of more difficult lesions such as those found in the upper stomach, esophagus or colon.

In the United States, the most recent available data from the American Society of Gastrointestinal Endoscopy³⁰ listed a total of 47 advanced endoscopy training programs in which ESD was actively being performed, with a median of 30 procedures/year. We expect that as ESD becomes more widely adopted, endoscopy trainees at these programs will have better access to supervised training.

Conclusion

As screening protocols continue to expand, early identification of superficial neoplastic lesions will continue to become an increasing part of gastroenterological practice, and precise identification of the most appropriate resection technique is paramount. While adoption of ESD in the West has been slow, ESD represents an excellent opportunity for a minimally invasive curative resection of early luminal cancers throughout the GI tract. While still early in the application of ESD in the West, there exists significant enthusiasm among practitioners and the procedure is now being

performed throughout the West. As the Western experience with ESD grows, there will be more opportunity for training at centers with significant clinical volumes and an opportunity to conduct high quality randomized trials comparing ESD to alternative treatments such as surgery or EMR.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

- SEER. SEER preliminary cancer incidence rate estimates for 2016, and diagnosis years 2000 to 2016, SEER 18. NIH SEER Website. Available from: <https://seer.cancer.gov/statistics/preliminary-estimates/>. Published 2019. Accessed June 12, 2019.
- Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol*. 2016;111:30-50; quiz 51.
- Kim GH, Liang PS, Bang SJ, Hwang JH. Screening and surveillance for gastric cancer in the United States: is it needed? *Gastrointest Endosc*. 2016;84:18-28.
- Davila RE, Rajan E, Baron TH, Adler DG, Egan JV, Faigel DO, et al.; Standards of Practice Committee, American Society for Gastrointestinal Endoscopy. ASGE guideline: colorectal cancer screening and surveillance. *Gastrointest Endosc*. 2006;63:546-57.
- Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. *Endoscopy*. 2001;33:367-73.
- Guideline Committee of the Korean Gastric Cancer Association (KGCA); Development Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. *J Gastric Cancer*. 2019;19:1-48.
- NCCN. Colon cancer (version 2.2018). NCCN clinical practice guidelines in oncology 2018. NCCN Website. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed June 12, 2019.
- NCCN. Rectal cancer (version 1.2018). NCCN clinical practice guidelines in oncology 2018. NCCN Website. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed June 12, 2019.
- Podboy AJ, Louie C, Kolahi K, Friedland S. Endoscopic submucosal dissection is associated with less pathologic uncertainty than endoscopic mucosal resection in diagnosing and staging Barrett's related neoplasia. *Gastrointest Endosc*. 2019;89(6 Suppl):AB469-70.
- Moss A, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut*. 2015;64:57-65.
- Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut*. 2001;48:225-9.
- Draganov PV, Wang AY, Othman MO, Fukami N. AGA institute clinical practice update: endoscopic submucosal dissection in the United States. *Clin Gastroenterol Hepatol*. 2019;17:16-25.e1.
- Yang D, Coman RM, Kahaleh M, Waxman I, Wang AY, Sethi A, et al. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. *Gastrointest Endosc*. 2017;86:600-7.
- Subramaniam S, Chedgy F, Longcroft-Wheaton G, Kandiah K, Maselli R, Seewald S, et al. Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST). *Gastrointest Endosc*. 2017;86:608-18.
- Emura F, Mejía J, Donneys A, Ricaurte O, Sabbagh L, Giraldo-Cadavid L, et al. Therapeutic outcomes of endoscopic submucosal dissection of differentiated early gastric cancer in a Western endoscopy setting (with video). *Gastrointest Endosc*. 2015;82:804-11.
- Probst A, Schneider A, Schaller T, Anthuber M, Ebigo A, Messmann H. Endoscopic submucosal dissection for early gastric cancer: are expanded resection criteria safe for Western patients? *Endoscopy*. 2017;49:855-65.
- Pimentel-Nunes P, Mourão F, Veloso N, Afonso LP, Jácome M, Moreira-Dias L, et al. Long-term follow-up after endoscopic resection of gastric superficial neoplastic lesions in Portugal. *Endoscopy*. 2014;46:933-40.
- Fuccio L, Hassan C, Ponchon T, Mandolesi D, Farioli A, Cucchetti A, et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. *Gastrointest Endosc*. 2017;86:74-86.e17.
- Sung JJ, Lau JY, Goh KL, Leung WK; Asia Pacific Working Group on Colorectal Cancer. Increasing incidence of colorectal cancer in Asia: implications for screening. *Lancet Oncol*. 2005;6:871-6.
- Guo HM, Zhang XQ, Chen M, Huang SL, Zou XP. Endoscopic submucosal dissection vs endoscopic mucosal resection for superficial esophageal cancer. *World J Gastroenterol*. 2014;20:5540-7.
- Yang D, Zou F, Xiong S, Forde JJ, Wang Y, Draganov PV. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. *Gastrointest Endosc*. 2018;87:1383-93.
- Terheggen G, Horn EM, Vieth M, Gabbert H, Enderle M, Neugebauer A, et al. A randomised trial of endoscopic submucosal dissection versus endoscopic mucosal resection for early Barrett's neoplasia. *Gut*. 2017;66:783-93.
- Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015;47:829-54.
- Bourke MJ, Neuhaus H, Bergman JJ. Endoscopic submucosal dissection: indications and application in Western endoscopy practice. *Gastroenterology*. 2018;154:1887-1900.e5.
- NCCN. Gastric cancer (version 1.2018). NCCN clinical practice guidelines in oncology 2018. NCCN Website. Available from: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed April 12, 2018.
- Ono H, Yao K, Fujishiro M, Oda I, Nimura S, Yahagi N, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc*. 2016;28:3-15.
- Pérez-Cuadrado-Robles E, Quénéhervé L, Margos W, Moreels TG, Yeung R, Piesseaux H, et al. ESD versus EMR in non-ampullary superficial duodenal tumors: a systematic review and meta-analysis. *Endosc Int Open*. 2018;6:E998-1007.
- Mehta A, Ngamruengphong S, Hajifathalian K, Shah SL, Dawood E, Ferri LE, et al. Prophylactic endoscopic closure does not reduce adverse events following endoscopic submucosal dissection: a case-matched multicenter study. *Gastrointest Endosc*. 2019;89(6 Suppl):AB97.
- Coman RM, Gotoda T, Draganov PV. Training in endoscopic submucosal dissection. *World J Gastrointest Endosc*. 2013;5:369-78.
- American Society for Gastrointestinal Endoscopy. ASGE Website. Available from: <https://www.asgmatch.com/Program/List?institution=&stateID=-1>. Accessed June 16, 2019.

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