Complex early Barrett's neoplasia at 3 Western centers: European Barrett's Endoscopic Submucosal Dissection Trial (E-BEST)

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Background and Aims: Endoscopic submucosal dissection (ESD) is an effective technique to resect early Barrett's neoplasia and has advantages over conventional EMR in that it enables en-bloc resection and accurate histopathologic analysis of cancer resection margins. However, its long learning curve and higher adverse event rate have tempered its uptake in the West. We aimed to analyze the safety and efficacy of ESD when used to resect complex Barrett's neoplasia. The primary endpoint was the en-bloc and R0 resection rate.

Methods: This was a retrospective analysis of 143 ESDs for Barrett's neoplasia performed in 3 tertiary referral centers from 2008 to 2016.

Results: The mean lesion size was 31.1 mm (range, 5-90) and median follow-up time 21.6 months (interquartile range, 11.0-32.6). In total, 24.5% of lesions (35/143) were scarred after previous endoscopic resection, surgery, or radiotherapy. The en-bloc resection rate was 90.8% and R0 resection rate 79% in this series. The overall adverse event rate was 3.5% (1.4% bleeding, 0% perforation, and 2.1% stricture formation). The expanded curative resection rate was 65.8%, reflecting the R0 resection rate and proportion of cases with more advanced disease. Submucosal cancer was identified as a significant factor affecting the R0 resection rate.

Conclusion: We demonstrated the feasibility and safety of ESD in the West for resection of complex Barrett's neoplasia including large, nodular, or scarred lesions. This is a safe and effective technique with a low adverse event rate when performed by an experienced operator. The en-bloc resection rate reached a plateau once 30 procedures had been performed. (Gastrointest Endosc 2017;86:608-18.)

Barrett's esophagus is a preneoplastic condition caused by GERD,[1] with the risk of malignant progression between .07% and .82%.[2,3] Until relatively recently, esophagectomy was seen as the criterion standard treatment for Barrett's high-grade dysplasia (HGD) or early adenocarcinoma. However, esophagectomy can be associated with a high mortality and morbidity.[4-6] EMR is an effective treatment for HGD and intramucosal cancer (IMC) with 5-year survival rates well above 90% and low major adverse event rates (1.5%-3%).[7,8] It is the advocated first-line therapy for early neoplasia[9] because the risk of lymph node metastases is low. There is good evidence that the combination of EMR followed by

Abbreviations: ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; IMC, intramucosal cancer; Sm, submucosal; LVI, lymphovascular invasion.

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radiofrequency ablation is a safe and effective method of treating Barrett's neoplasia and subsequent eradication of intestinal metaplasia.[10] However, the main limitation of EMR is that en-bloc resection is only possible for lesions less than 2 cm, with larger lesions requiring piecemeal resection.[11] This is acceptable if the lesion histology is at its worst (ie, HGD), but if adenocarcinoma is found, then information about cancer clearance at the resection margin (R0) and depth of invasion is crucial.[12,13] Emerging data suggest that cancer with invasion limited to the first third of the submucosa (Sm1) has a low risk of lymph node metastases and may not require surgery, but the determination of the exact depth of invasion of cancer in the submucosa requires a very good quality specimen.[14-16]

Endoscopic submucosal dissection (ESD) allows resection of much larger lesions in an en-bloc fashion, meeting the principles of oncosurgery. This provides the ideal specimen to obtain all the relevant histopathologic details required to determine a curative resection. ESD also enables resection of scarred and submucosally invasive lesions that would otherwise be difficult to resect by EMR.[17] Despite a meta-analysis demonstrating the superiority of ESD over EMR for the resection of GI neoplasia,[18] its uptake has been tempered by higher adverse event rates, technical difficulties, and its time-consuming nature. Although ESD is widely practiced in Japan for the treatment of squamous neoplasia, uptake in the West has been limited, largely because of a lack of individuals trained in the technique and of a reimbursement tariff. Data now support the potential role of ESD in Barrett's neoplasia,[11,17,19-22] although research is limited, and much of the data are limited to HGD rather than superficially invasive cancer. Furthermore, little data have examined ESD in scarred lesions. This is unfortunate because this is where EMR struggles, and the technique of ESD is of potentially the greatest value. The aim of our study was to explore the feasibility, safety, and efficacy of ESD in resection of suspected superficial Barrett's cancers $\geq$2 cm in size or lesions that could not be resected by conventional EMR because of scarring-related poor lifting.

METHODS

Setting

This is a retrospective analysis of a prospectively registered patient cohort at 3 tertiary referral centers (Queen Alexandra Hospital, Portsmouth, UK; Humanitas Research Hospital, Milan, Italy; and Gastrozentrum Hirslanden, Zurich, Switzerland). All patients referred for endoscopic resection of Barrett's neoplasia were prospectively recorded on an electronic database.

Selection criteria

Inclusion criteria were nonscarred endoscopically suspected (nodular appearance and/or abnormal mucosal pattern) or histologically proven Barrett's neoplasia $\geq$2 cm in size or scarred (defined by poor lift after submucosal injection or previous history of EMR, chemoradiotherapy, ablation, or surgery) neoplasia of any size. All patients were over 18 years of age, with American Society of Anesthesiologists class 1 to 3. Written, informed consent for the procedure was obtained from all patients. Exclusion criteria included flat dysplastic lesions where no previous intervention had been performed, lesions with suspected deep submucosal invasion (>Sm2 or T2), American Society of Anesthesiologists class >3, evidence of distant or nodal disease on EUS or CT, or patients unable to consent. Local institutional review board approval was obtained for the study (PHT/3556).

Diagnostic workup

All lesions underwent endoscopic assessment before ESD. The Barrett's segment was examined with high-definition white light and 2.5% acetic acid chromoendoscopy. Prague classification was used to describe the Barrett's segment.[23] The size and type of neoplastic lesions were described according to the Paris classification.[24] The lesion underwent repeat biopsy sampling if there was a suspicion of more advanced neoplasia or multifocal areas of neoplasia had not undergone previous biopsy sampling. Where deep submucosal invasion was suspected on endoscopy (depressed lesions with an irregular or absent mucosal surface pattern), further staging investigations (EUS) were performed at the discretion of the tumor board meeting, comprising endoscopists, surgeons, oncologists, radiologists, and pathologists. All patients had a baseline staging chest and abdomen CT to exclude nodal or metastatic disease before endoscopic resection.

ESD training details

All 3 endoscopists performing ESD in this study (P.B., A.R., and S.S.) had initial training in the technique under direct supervision from an expert using animal models. Subsequently, they performed ESD for gastric and rectal lesions in humans. All endoscopists had performed over 50 gastric/rectal ESDs and were proficient in the technique before embarking on ESD in the esophagus. Esophageal ESD was not directly supervised, and learning was self-directed using growing endoscopy experience.

ESD procedure

An anesthetist administered full general anesthetic with tracheal intubation. Carbon dioxide was used for insufflation. Both conventional and magnification high-definition video endoscopes (EG-L590ZW, EG-530FP, and EG600-WR [Fujifilm Europe, Düsseldorf, Germany] or GIF-H260 and GIF-HQ290 [Olympus Medical, Hamburg, Germany]) were used. A distal transparent cap was fitted to the end of the endoscope (D-206; Olympus). The Erbe VIO 300D electrosurgical generator (Erbe, Tubingen, Germany) was used for each step of the ESD. The ESD knives used