

Endoscopic submucosal dissection (ESD) for Barrett's esophagus (BE)-related early neoplasia after standard endoscopic management is feasible and safe




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ABSTRACT

Background and study aims There is little data on the feasibility and safety of endoscopic submucosal dissection

(ESD) as a salvage treatment for Barrett's esophagus (BE)-related neoplasia after standard endoscopic treatments.

Patients and methods A multicenter retrospective analysis on patients who underwent ESD for BE was performed. The primary endpoint was effectiveness of obtaining en-bloc resection in salvage as compared to non-salvage treatments.

Results Median age was 71 (IQR 55–79) years. Twelve (37%) of 32 patients underwent salvage ESD. Median resection time was 100 (IQR 60–136) minutes. En-bloc resection was achieved in 31 patients (97%). Complete R0 resection was obtained in 75% in the salvage group and 80% in the non-salvage group ($P=1.00$). In seven patients (22%), the pre-ESD diagnosis was upgraded on post-ESD histopathology (1 low-grade dysplasia to high grade dysplasia [HGD], 4 HGD to early esophageal carcinoma (EAC), and 2 intramucosal EAC to invasive EAC). No perforations occurred in either group. Two late adverse events occurred, both in the salvage group ($P=0.133$). Delayed bleeding occurred in a patient who had just resumed warfarin and stricture occurred in a patient who had a circumferential resection requiring serial dilation and stent placement.

Conclusions Our cohort study demonstrated that ESD as salvage therapy for BE related neoplasia is feasible and safe, achieving similar high rates of en-bloc resection and complete R0 resection as in treatment-naïve patients. Referral to an expert center performing ESD should be considered for patients with recurrence or progression following endoscopic mucosal resection or ablation therapy.

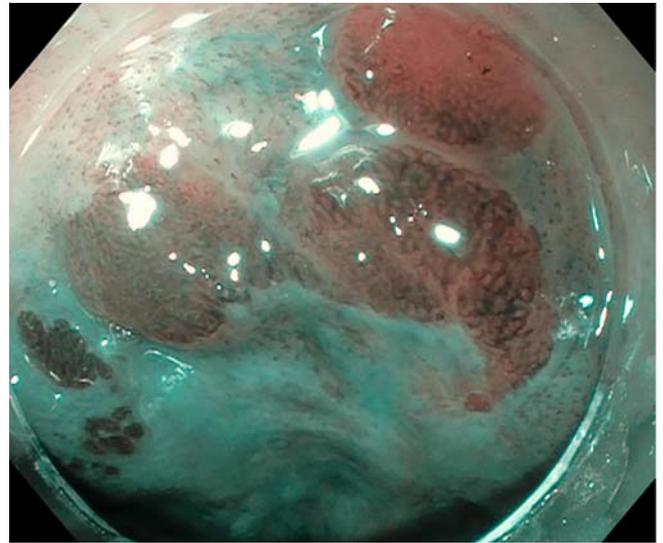
Introduction

Patients with nodularity in the Barrett's esophagus (BE) segment should undergo endoscopic resection of the nodular lesion(s) as the initial diagnostic and therapeutic maneuver as precise histologic assessment of the resected specimen is crucial to guide further therapy. In subjects with resected specimens that demonstrate high-grade dysplasia (HGD) or early esophageal adenocarcinoma (EAC), radio frequency ablation (RFA) of the remaining BE should be performed [1]. Endoscopic mucosal resection (EMR) is a widely available and practically

preferred method to remove visible nodular lesions within BE. The limitation with regard to EMR is the resection size. Multiple EMRs are frequently required to achieve complete EMR and endoscopic submucosal dissection (ESD) is an alternative to EMR. As compared to EMR, ESD has been demonstrated to carry higher rates of en-bloc resection and complete target resection in the gastrointestinal tract [2, 3]. A recent meta-analysis has shown that ESD for early BE neoplasia is associated with a high en-bloc resection rate and acceptable safety profile [4]. Prior endoscopic therapy (e. g. EMR or RFA) often causes submucosal fibrosis and makes subsequent endoscopic therapy difficult.



► **Fig. 1** Residual nodular lesion under high-definition white light. (These images are from a 55-year-old man with BE with HGD status post-multiple RFAs. Surveillance EGD showed residual lesions with biopsy demonstrating HGD. EMR was attempted at the outside institution, however, the lesion could not be adequately raised with submucosal injection. Therefore, the patient was referred for ESD.)



► **Fig. 2** Residual nodular lesion under narrow-band imaging.

Recurrent neoplastic often can't be suctioned into a cap or can't be lifted for EMR due to fibrosis, especially when the recurrent neoplasia is located within the scar of a previous treatment zone. While technically challenging, ESD may offer definitive staging and treatment of patients who have recurrent BE-related neoplasia after prior endoscopic therapy. There is little data on the safety and efficacy of ESD as a salvage treatment for patients with recurrence or progression of BE-related dysplasia and EAC. In this study, we aimed to analyze the feasibility, safety, and effectiveness of ESD as salvage therapy for those who previously underwent standard endoscopic therapy of BE-related early neoplasia.

Patients and methods

Patients

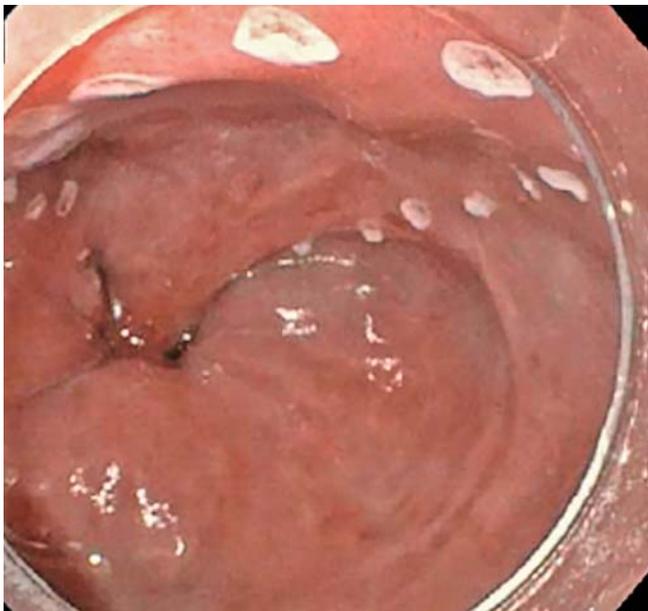
This study was approved by the institutional review board for human research at each participating institution. We conducted a retrospective cohort study and reviewed a database of all the patients who were referred for ESD for BE-related dysplasia or neoplasia from August 1, 2015 to October 31, 2017. We included patients with macroscopic abnormality within BE segment and pathologically confirmed BE-associated dysplasia or neoplasia who were referred for ESD. We did not set up any predetermined number of sessions of RFA. If EMR was performed before ESD, recurrent neoplastic areas often could not be suctioned into a cap or could not be lifted for repeat EMR due to fibrosis, especially when the recurrent neoplasia was located within the scar of a previous treatment zone. This situation prompted ESD. Prior endoscopic therapy including both EMR and RFA often causes submucosal fibrosis, which makes subsequent endoscopic therapy difficult. This situation also prompt-

ed ESD. Patient demographics, histories of prior endoscopic therapy, lesion characteristics (i.e. Paris classification), pre-ESD histologic assessment, and procedural description were extracted from the existing database and electronic medical records (EMRs). Medications were obtained from the reconciliation list in the EMR. Use of antiplatelet or antithrombotic medication and non-steroidal anti-inflammatory drugs (NSAIDs) was captured for analysis. Follow-up visit or endoscopy was performed at the participating centers where ESD had been performed. The follow-up interval was defined from the time of ESD to the time of event (recurrence, death, or loss follow-up). If none of these events was documented, the end of the follow-up period was defined as the last time of patient contact prior to November 30, 2017.

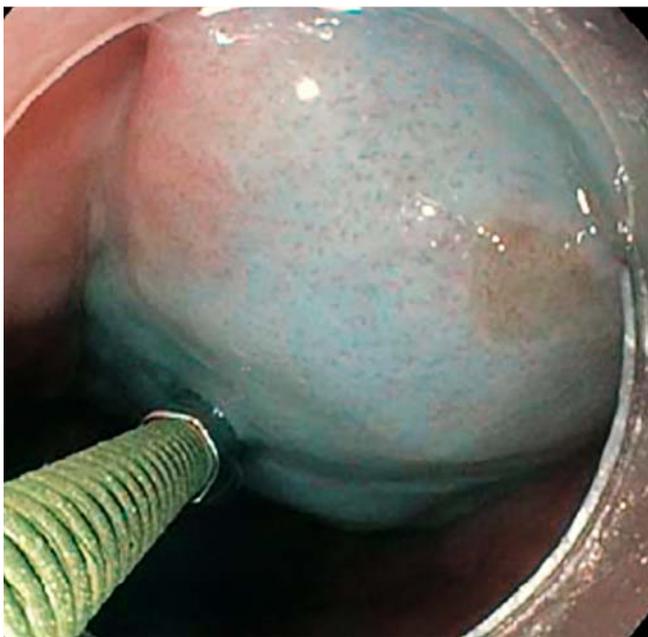
Endoscopic procedure

Patients who take antiplatelet or antithrombotic medication were instructed to consult their prescribing physicians for permission to hold medications prior to the ESD. We followed society guidelines with regard to the duration of holding medications [5]. All ESD procedures were performed by the authors, who are experienced interventional endoscopists. ESD procedures were performed under general anesthesia with carbon dioxide routinely used for insufflation. EMR was determined based on the endoscopic appearance, using high-definition white light (HWL) endoscopy and narrow-band imaging (NBI). Lesions with endoscopic features of advanced cancer were deemed unsuitable for EMR. Endoscopic ultrasound was not performed as routine examination before ESD [6, 7].

A transparent cap was fitted to the end of the endoscope. The ERBE VIO 300D electrosurgical generator (Erbe, Tübingen Germany) was used to deliver electrosurgical current. ESD knives used were the Hook, IT-2, TT, IT-nano, and Dual (Olympus Corporation, Tokyo), Clutch Cutter (Fujifilm, Tokyo) and SB knife (BVM Medical, Tokyo). Before placing perimeter markings, we precisely evaluated the lateral extent of the disease

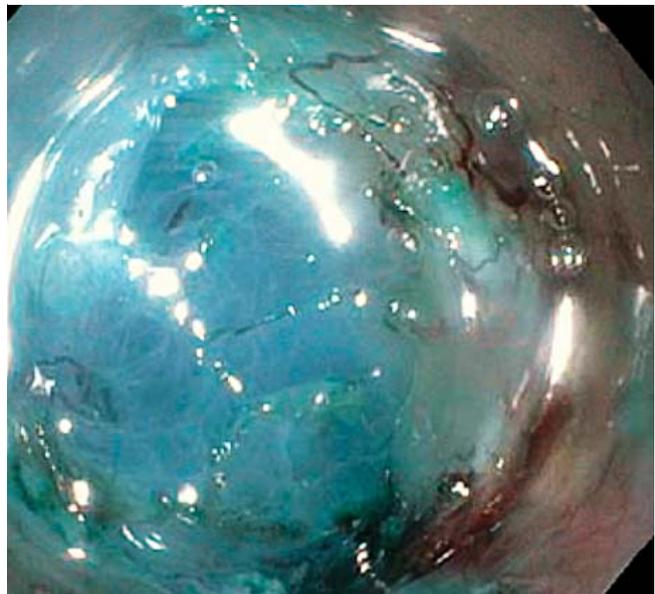


► Fig. 3 Perimeter marking.



► Fig. 4 Initial submucosal injection.

and then the lesions were marked at approximately a 2-mm distance from the edge with the knife tip in soft coagulation mode. After perimeter marking, a mixture of normal saline solution/methylene blue/ +/- diluted epinephrine, or 6% hetastarch in normal saline solution/indigo carmine/diluted epinephrine was injected into the submucosal space to expand the layer between the mucosa and muscle layer. The decision as to which ESD knife or submucosal lifting solution used was at the discretion of the endoscopist. Mucosal incision was performed in Endocut mode and ESD was performed using a combination of coagulation and cut currents (forced coagulation, swift coagulation,



► Fig. 5 Submucosa exposed during ESD.

on, spray coagulation, or Endocut modes) (► Fig. 1–8). Submucosal fibrosis encountered during ESD was defined as visible fibrotic tissue. High-dose proton pump inhibitor (PPI) was universally prescribed for at least 12 weeks after ESD. Patients underwent first surveillance endoscopy in 3 to 6 months after ESD for inspection and repeat biopsy. If no recurrence was present, further surveillance was performed at expanding intervals thereafter. If recurrence was suspected, forceps tissue sampling, snare resection or ablation was performed at the discretion of the endoscopist. Residual flat BE was ablated on follow-up procedures (RFA or cryoballoon treatment).

Histopathologic assessment

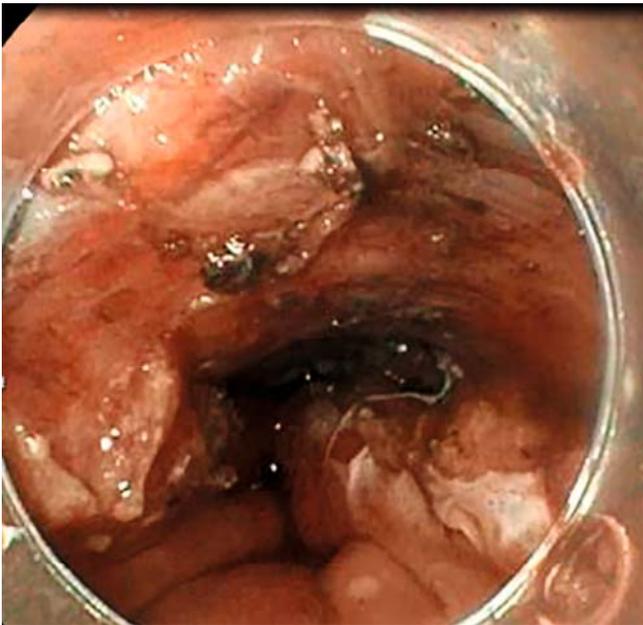
All ESD-resected specimens were pinned, fixed in formalin and oriented to allow accurate assessment of resection margin. All specimens were reviewed by an experienced gastrointestinal pathologist and confirmed by two gastrointestinal pathologists. Histologic grading was the most advanced grade in the sample specimen. For those who previously underwent EMR or ESD, pre-ESD histologic grading was the grade seen on the EMR or ESD specimen as biopsy diagnosis of BE is well known to change after assessment of an EMR specimen [8].

Outcome of interest and adverse events

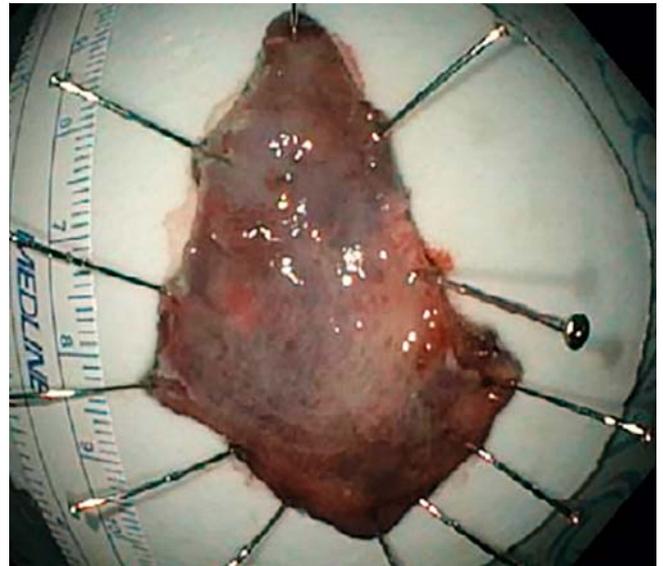
Complete (R0) resection was defined as neither endoscopic evidence nor histologic evidence of BE-associated dysplasia or neoplasia on both lateral and vertical margin after ESD. The primary endpoint of this study was the rate of en-bloc resection in salvage vs. non-salvage treatments. Secondary endpoints were the rate of complete (R0) resection, a proportion of cases where the pathology was upgraded on post-ESD pathology from the pre-ESD pathology, and procedure-related adverse events (AEs). We categorized ESD-related bleeding as intra-procedural or delayed bleeding that required directed intervention. Intra-procedural bleeding was defined as persistent arter-



► Fig. 6 Fibrosis encountered during ESD.



► Fig. 7 Post-resection.



► Fig. 8 Resected specimen.

ial bleeding requiring repeated endoscopic hemostatic attempts. Delayed bleeding was any bleeding that prompted any medical intervention beyond the initial ESD session.

Statistical analysis

For descriptive analysis, approximately normally distributed data were reported as mean \pm standard deviation (SD), and skewed data as median and interquartile range (IQR). We summarized data using the Student's *t*-test for continuous variables, and the chi-square test and Fisher exact test for categorical variables when appropriate. Based on the hypothesis test with a two-sided *P* value, $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using STATA, version 14 (STATA Corp LP, Texas, United States).

Results

Patient and ESD characteristics

A total of 32 patients (median age 71 years [IQR 65–76]; 91% male) underwent ESD for BE-related early neoplasia. Eleven patients were enrolled at University of Washington Health System and all ESDs were performed by one endoscopist (J.H.). The other 21 patients were enrolled at Stanford University Health System and all ESDs were performed by one endoscopist (S.F.). Six patients (19%) took at least one antiplatelet medication and one (3%) patient took antithrombotic medication prior to ESD. Twelve patients (37%) received prior endoscopic treatment (i.e. EMR, RFA and ESD) for BE before ESD. One patient with a long-segment BE (Prague Classification C5M6) was found to have two separated BE-related neoplastic lesions 2 cm apart and

► **Table 1** Characteristics of study patients.

Characteristics	N = 32
Age [years] (IQR)	71 (65–76)
Male	29 (91%)
BMI [kg/m ²] (IQR)	30.2 (25.5–40.4)
ASA class	
▪ II	9 (28%)
▪ III	22 (69%)
▪ IV	1 (3%)
Use of antiplatelet or anticoagulant	
▪ Aspirin	6 (19%)
▪ Warfarin	1 (3%)
Baseline pre-ESD histopathology	
▪ Low-grade dysplasia	5 (16%)
▪ High-grade dysplasia	11 (34%)
▪ Intra-mucosal adenocarcinoma (t1a)	16 (50%)
Previous endoscopic therapy before ESD	
▪ Endoscopic mucosal resection	3 (9%)
▪ Radiofrequency ablation	5 (16%)
▪ Combination	3 (9%)
▪ Endoscopic submucosal dissection	1 (3%)

IQR, interquartile range; BMI, body mass index; ASA, American Academy of Anesthesiologists; ESD, endoscopic submucosal dissection

this patient had undergone ESD 6 months before the second ESD procedure, and the first ESD was performed during the study period. The majority (84%) of pre-ESD pathology of the target lesions was either HGD or intramucosal (T1a) EAC (► **Table 1**). Median size of resected specimens was 32 mm (range 15–70, IQR 20–40) in diameter and 95% of patients had lesions with a diameter greater than 20 mm. Endoscopic appearance (i. e. Paris classification) of the lesion was classified as Ila in 20 (63%), Ila+Is in two (6%), Ila+Ilc in one (3%), I Ib in seven (22%), and Ilc in two patients (6%). Submucosal fibrosis was encountered in 16 patients (50%). Median resection time was 100 minutes (IQR 60–136). En-bloc resection was achieved in 31 patients (97%) and complete R0 resection was obtained in 25 patients (78%) (► **Table 2**).

Pre-ESD vs. post-ESD pathological diagnosis comparison

In seven patients (22%), pre-ESD diagnosis was upgraded on post-ESD histopathology. One low-grade dysplasia was diagnosed as high-grade dysplasia (HGD) and four cases with HGD were diagnosed as EAC. Two intramucosal (T1a) EACs diagnosed on previous EMR histology before ESD were diagnosed as invasive (T1b) EAC on post-ESD histology. The majority of

► **Table 2** Characteristics of ESD procedures.

Characteristic	N = 32
Resected specimen size [mm] (IQR)*	32 (20–40)
Paris classification	
▪ Ila	20 (63%)
▪ Ila+Is	2 (6%)
▪ Ila+Ilc	1 (3%)
▪ I Ib	7 (22%)
▪ Ilc	2 (6%)
Presence of submucosal fibrosis	16 (50%)
Resection time [min] (IQR)	100 (60–136)
En-bloc resection	31 (97%)
R0 resection	25 (78%)

ESD, endoscopic submucosal dissection; IQR, interquartile range

► **Table 3** Comparison of pathological diagnosis pre- and post-ESD.

Pre-ESD diagnosis	Pathological diagnosis of ESD resected specimen		
	No dysplasia or LGD	HGD	EAC
LGD	4	1	0
HGD	1	6	4
EAC ¹	0	2	14

ESD, endoscopic submucosal dissection; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EAC, early esophageal carcinoma; EMR, endoscopic mucosal resection

¹ 2 intramucosal (T1a) EAC diagnosed on previous EMR histology (not biopsy diagnosis) were diagnosed as invasive (T1b) EAC on post-ESD histology

upgraded histopathology (6 out of 7 patients, 86%) was seen in either HGD or EAC on pre-ESD diagnosis (► **Table 3**).

Salvage vs. non-salvage comparison

There was no significant difference in patient baseline characteristics between the two groups. The interval between initial treatment and salvage treatment was a median of 162 [IQR 70–965] days. Among patients who underwent salvage therapy who did and did not have an upgrade in the final histopathology, there was no statistical difference in interval days ($P=0.51$). En-bloc resection was achieved in all salvage patients (100%) and 95% (19/20) in non-salvage patients. Complete R0 resection was obtained in 80% in the non-salvage group and 75% in the salvage group ($P=1.00$). There was no statistical difference in median resected specimen size (34 mm in the non-salvage group and 29 mm in the salvage group [$P=0.241$]) or in median resection time (90 min in the non-salvage group and 112 min in the salvage group [$P=0.35$]). Submucosal fibrosis was encountered significantly more in the salvage group ($P=0.001$). No statistical difference in the proportion of upgraded pathology between the two groups (low-grade dysplasia to

► **Table 4** Comparison between non-salvage and salvage ESD groups.

Characteristics	Non-salvage ESD (N=20)	Salvage ESD (N=12)	P value
Age [years] (IQR)	68 (59–77)	72 (69–76)	0.877
Male	18 (90%)	11 (92%)	0.876
Use of antiplatelet or anticoagulant	3 (15%)	4 (33%)	0.379
Resected specimen size [mm] (IQR)	34 (20–40)	29 (20–42)	0.241
Resection time [min] (IQR)	90 (60–150)	112 (66–141)	0.35
R0 resection	16 (80%)	9 (75%)	1.00
Submucosal fibrosis	5 (25%)	11 (92%)	0.001
Intra-procedural bleeding	0 (0%)	4 (33%)	0.014

ESD, endoscopic mucosal dissection; IQR, interquartile range

► **Table 5** Patients who failed to achieve R0 resection.

Patient	Type of ESD	Pre-ESD diagnosis	Post-ESD diagnosis	Margin positive
1	Non-salvage	HGD	T1a	HGD (lateral margin)
2	Non-salvage	HGD	T1a	EAC (lateral margin)
3	Salvage	HGD	T1a	EAC (vertical margin)
4	Non-salvage	T1a	T1b	EAC (lateral margin)
5	Non-salvage	T1a	T1b	EAC (vertical margin)
6	Salvage	T1a	T1b	EAC (lateral margin)
7	Salvage	T1a	T1b	EAC (vertical margin)

ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; EAC, early esophageal carcinoma

HGD [$P=1.00$], HGD to ECA [$P=0.620$], respectively) was noted (► **Table 4**).

Adverse events

There were no perforations in either the non-salvage or salvage group. Intra-procedural bleeding occurred more often in the salvage group ($P=0.014$). There were two late AEs, both in the salvage group ($P=0.133$). Delayed bleeding occurred on post-operative Day 12 in one patient who had just resumed warfarin and one stricture occurred in a patient who had a circumferential resection requiring serial endoscopic dilations and stent placement. Both patients were adequately managed without any further surgical interventions.

Follow-up of patients who failed to achieve R0 resection

Seven patients (3 vertical margin-positive and 4 lateral margin-positive) did not achieve R0 resection due to presence of neoplasia on the resected margin and three of the seven patients underwent ESD as a salvage therapy (► **Table 5**). One patient was found to have T1a EAC on ESD specimen with positive lateral margin for HGD and received endoscopic eradication therapy. The other patient who had T1a on ESD specimen with macroscopic lateral-positive margin for EAC underwent EMR of the margin during the same procedure session. All five other pa-

tients with R1 resection were discussed at a multidisciplinary conference with medical oncologists, radiation oncologists, and surgeons, and treatment recommendations were based on consensus opinions for each patient. The five other patients were eventually referred to surgery after discussion at a multidisciplinary conference. During mean follow-up of 197 days, no cancer death or procedure-related deaths occurred. We have not identified buried metaplasia in either the naïve or salvage ESD groups.

Discussion

This article represents one of a few multicenter studies reported to date on clinical outcomes of ESD as salvage therapy for patients with recurrence or progression of BE-related early neoplasia after initial endoscopic management. These data affirm that ESD as salvage therapy for BE-related dysplasia and early neoplasia is feasible and safe, achieving similar high rates of en-bloc resection and complete R0 resection as in treatment-naïve patients.

Several gastroenterology society guidelines have recommended that patients with focal dysplastic or neoplastic lesions arising in BE should undergo endoscopic resection of the lesions, which serves to provide precise histologic assessment and prognostic information [1, 9, 10]. EMR has been traditional-

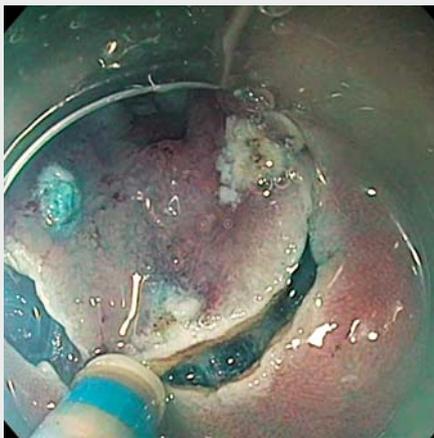
ly performed to remove visible nodular lesions within BE with excellent data on overall safety and efficacy [11]. Aside from the length of BE and absence of subsequent ablative therapy, a long-term follow-up study suggested that risk factors most frequently associated with recurrence were piecemeal resection and multifocal neoplasia [12]. Efficacy of EMR is partially limited by the maximum size for which EMR allows en-bloc resection and it is generally smaller than 15 mm in the diameter. Wide-field EMR has been reported by selected referral centers with efficacy and comparable safety profiles [13], but higher rates of post-EMR stricture remains a concern. ESD was originally developed to enable en-bloc margin-negative resection of early neoplasia and allows for detailed histopathologic assessment that is necessary to confirm curative resection, but it has recently been applied for management of BE-related dysplasia or neoplasia. Two multicenter studies from the United States [14] and Europe [15] reported the utility of ESD in evaluation of HGD and early EAC in BE. Both studies reported higher rates of en-bloc resection (96% and 91%, respectively) and R0 resection (70% and 79%, respectively). The overall safety profile was acceptable in that there were four early AEs with seven strictures requiring dilation in the US study versus two early AEs with three strictures requiring dilation in the European study.

Our study results demonstrate that en-bloc resection and R0 resection was achieved in 97% and in 78%, respectively, showing procedural efficacy comparable with two recently reported multicenter studies [14, 15]. We acknowledge that median resected specimen size in our study (32 mm) was similar to the European study (31 mm) but smaller than the US study (45 mm). Our study safety profiles were confirmed comparable with the two multicenter studies as well as the pooled large-scale data [4]. Although these studies have demonstrated encouraging profiles of efficacy, durability, and safety, the role of ESD as an initial resection tool for management of focal neoplastic lesion in BE remains controversial. One randomized trial assessing the efficacy of ESD vs EMR for focal lesions less than 30 mm in the largest diameter has reported that higher R0 re-

section rates were achieved in the ESD group but there was no statistical significance in terms of complete remission or recurrence rates [16]. Due to the need for advanced skillsets and fairly complex procedure, current societal guidelines in Western countries recommend EMR as the mainstay of initial mucosal resection method and suggest ESD as an alternative for larger lesions (e.g. > 15 mm) or poorly lifting lesions because of scarring or suspicious of submucosal invasion [1, 9, 10].

One of the advantages of ESD over EMR is the potential to provide more accurate histopathologic assessment. In our study, a total of seven patients (22%) had their pre-ESD diagnoses upgraded on post-ESD histopathology (1 low-grade dysplasia to HGD, 4 HGD to EAC, and 2 intramucosal [T1a] EAC to invasive [T1b] EAC). It is of note that the majority of patients (6 of 7, 86%) with upgraded histopathology were viewed as either HGD or intramucosal (T1a) EAC on pre-ESD diagnosis. This is crucial for treatment decision-making and prognostication. The rate of upgrading diagnosis on post-ESD pathology specimen was comparable to that in the US multicenter study [14].

ESD is uniquely positioned to be used as salvage therapy for patients with recurrence or progression of BE-related early neoplasia. Prior endoscopic therapy (e.g. EMR or RFA) can cause significant submucosal fibrosis and make subsequent endoscopic therapy difficult. The advantage of ESD for achieving en-bloc resection in lesions with fibrosis has been reported in other parts of the gastrointestinal tract [17]. There is little data on the safety and efficacy of ESD as a salvage treatment for patients with recurrence or progression of BE-related dysplasia and EAC. The aforementioned European study included 24.5% of patients who underwent prior EMR (22.4%), esophagectomy (0.7%) and radiotherapy (1.4%) but did not disclose the specific clinical outcomes within these subgroups. Our study included 12 patients (37%) (salvage group) who received prior endoscopic treatment (i.e. EMR, RFA and ESD) before ESD. As expected, submucosal fibrosis was encountered significantly more in this group ($P=0.001$). En-bloc resection was achieved in 97% of patients and no difference was seen in R0 resection rate (80% in the non-salvage group vs 75% in the salvage group [$P=1.00$]). There was no statistical difference in median resection time (90 min in the non-salvage group and 112 min in the salvage group [$P=0.35$]). To our knowledge no head-to-head comparison data of naïve vs. salvage ESD for BE-related neoplasia has been published to date. Our study has demonstrated the comparable efficacy of salvage ESD without longer procedural time. One study recently analyzed safety and efficacy of ablation therapy following ESD as compared to EMR for BE [18]. In the study, no significant difference was seen in total complication rate (7.4% and 9.3%, respectively) and stricture formation rate (3.7% and 9.3%, respectively) between the ESD and EMR groups, and the remission rate for dysplasia was higher in the ESD group (96.3%) compared to the EMR group (88.4%). Our study builds on the aforementioned study that ESD as salvage therapy following endoscopic therapy for BE-related dysplasia and early neoplasia is safe and achieves similarly high rates of complete R0 resection as in treatment-naïve patients. We acknowledge that in our cohort, the number of salvage ESD cases was small and might contribute to type II error.



Video 1 ESD: dysplastic Barrett's esophagus after multiple RFA ablation.

The major strength of our study is the detailed head-to-head comparison data for naïve vs. salvage ESD for BE-related neoplasia. Our findings reinforce that recurrence or progression of BE-related early neoplasia after endoscopic therapy can be successfully managed with ESD without requiring significantly longer resection time.

First among the weaknesses in our study is that it is a tertiary referral center series and therefore, little heterogeneity of technical skillsets or technique are reflected. It is reasonable to expect, however, that these results can be matched by others with sufficient skill and experience in ESD. It is also noted that our study was not a single-operator series and conducted at multiple centers. Having a center focus on ESD increases referrals and operator experience. Second, the follow-up period after ESD was relatively shorter than in the other two studies [14, 15]. However, the follow-up duration of 197 days is sufficient to assess outcomes of interests in this study, including procedural efficacy and safety. We specifically aimed to analyze clinical outcomes of ESD as a salvage treatment for patients with recurrence or progression of BE-related dysplasia and EAC. We acknowledge that the results of this study are in line with those reported in the aforementioned larger scale studies.

Conclusion

In conclusion, in this multicenter cohort, we have demonstrated that ESD as salvage therapy for BE-related dysplasia and early neoplasia is feasible and safe, achieving similar high rates of en-bloc resection and complete R0 resection as in treatment-naïve patients. For patients with recurrent neoplasia or disease progression located within the scar of a previous EMR or ablation therapy when repeat EMR is difficult due to fibrosis, referral to an expert center performing ESD should be considered for salvage therapy.

Competing interests

Yutaka Tomazawa – No conflicts. Shai Friedland – No conflicts.
Joo Ha Hwang – Consultant to Olympus, Medtronic, Micro-Tech.

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