

Efficacy and safety of cap-assisted endoscopic mucosal resection for superficial duodenal epithelial neoplasia ≤ 10 mm



Authors

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ABSTRACT

Background and study aims Endoscopic treatment strategies for small superficial duodenal epithelial neoplasia (SDET) have not been established, and the R0 resection rates of all previously reported endoscopic techniques are somewhat low. Furthermore, no reports of cap-assisted endoscopic mucosal resection (EMRC), which is reportedly associated with a relatively high R0 resection rate, have been evaluated in sufficient numbers of patients. Therefore, we assessed the efficacy and safety of EMRC for SDETs ≤ 10 mm in a retrospective cohort study.

Patients and methods We examined a prospectively maintained database and identified 248 consecutive patients (248 lesions) who had undergone endoscopic resection for SDETs ≤ 10 mm between January 2017 and June 2022. Our treatment strategy was consistent, with EMRC indicated for all SDETs ≤ 10 mm without non-lifting signs. The primary endpoint was the R0 resection rate.

Results Overall, 20 lesions had non-lifting signs and were selected for endoscopic submucosal dissection, while the remaining 228 lesions were treated with EMRC. As a result of EMRC, the median tumor size was 5 mm, and the mean procedure time was 5 minutes. Most of the lesions (89.2%) were located in the descending part. The R0 resection rate was 97.4% (222/228 cases), and the en bloc resection rate was 99.6%. Only seven patients (3.1%) experienced adverse events (6 patients, delayed bleeding; 1 patient, acute pancreatitis), which were successfully managed without surgical intervention. Furthermore, no recurrences were observed.

Conclusions We have demonstrated that EMRC is an effective and safe treatment for SDETs ≤ 10 mm that do not have non-lifting signs.

Introduction

Recent advances in endoscopic technology have increased the ability to detect superficial duodenal epithelial neoplasia (SDET) [1, 2, 3, 4]. Endoscopic resection (ER) is an alternative treatment for SDET that is less invasive than surgery and, moreover, maintains the patient's postoperative quality of life [5, 6]. Several resection methods have been reported for ER of the duodenum, including conventional endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), underwater EMR (UEMR), cold snare polypectomy (CSP), and cap-assisted EMR (EMRC) [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17].

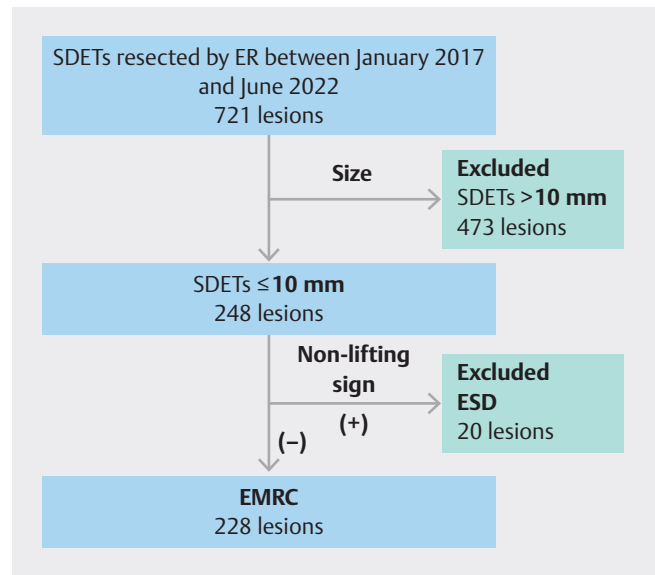
However, various problems have been reported with new endoscopic treatment techniques such as UEMR and CSP. The R0 resection rate for UEMR is reported to be lower than that for conventional EMR because the omission of submucosal injection increases the risk of positive margins [10, 11, 12, 13]. Furthermore, water can be difficult to retain in some areas of the duodenum, making UEMR itself difficult in some cases and causing the procedure to be less stable. As for CSP, resection of only the muscularis mucosae and very shallow submucosa has been reported in the colon [18]. Furthermore, in many cases, the resected specimens are broken into pieces during collection by suctioning, and the lack of a burn effect can make accurate pathological evaluation difficult. Endoscopic diagnosis in the duodenum is less established than that in the colon, and the features of SDET malignancies have not been clarified, making the decision to perform CSP uniformly for all small SDETs controversial.

While EMRC has been widely reported as a useful and safe treatment in the esophagus and stomach, there have been very few reports in the duodenum [19, 20]. Furthermore, previous reports of EMRC in the duodenum included lesions that were small to large in size and, moreover, the number of cases in the reports was quite small [16, 17]. Most of the large lesions that exceeded the cap size were resected piecemeal. Unlike adenomas of the colon, duodenal adenomas reportedly have a high malignancy rate and very rapid malignant progression [21, 22]. Therefore, complete resection is very important, and techniques with a high R0 resection rate are required. While there have been many reports showing that ESD is useful for large SDET, there have been no reports evaluating treatment strategies focused on smaller SDETs (especially ≤ 10 mm). Furthermore, the R0 resection rates for EMRC in the duodenum in previous reports were low, and predictors of RX/1 and piecemeal resection were reported to be EMR and lesion size ≥ 11 mm [16, 17]. Therefore, our group considers EMRC to be the first choice of ER for SDETs ≤ 10 mm. In the present study, we assessed the efficacy and safety of EMRC for treatment of SDETs ≤ 10 mm.

Patients and methods

Study design

This study was designed as a retrospective cohort study to investigate the efficacy and safety of EMRC for the treatment of SDETs ≤ 10 mm. All procedures were performed at NTT Medical



► **Fig. 1** Flowchart of patient enrollment. SDET, superficial duodenal epithelial neoplasia; ER, endoscopic resection; EMRC, cap-assisted endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

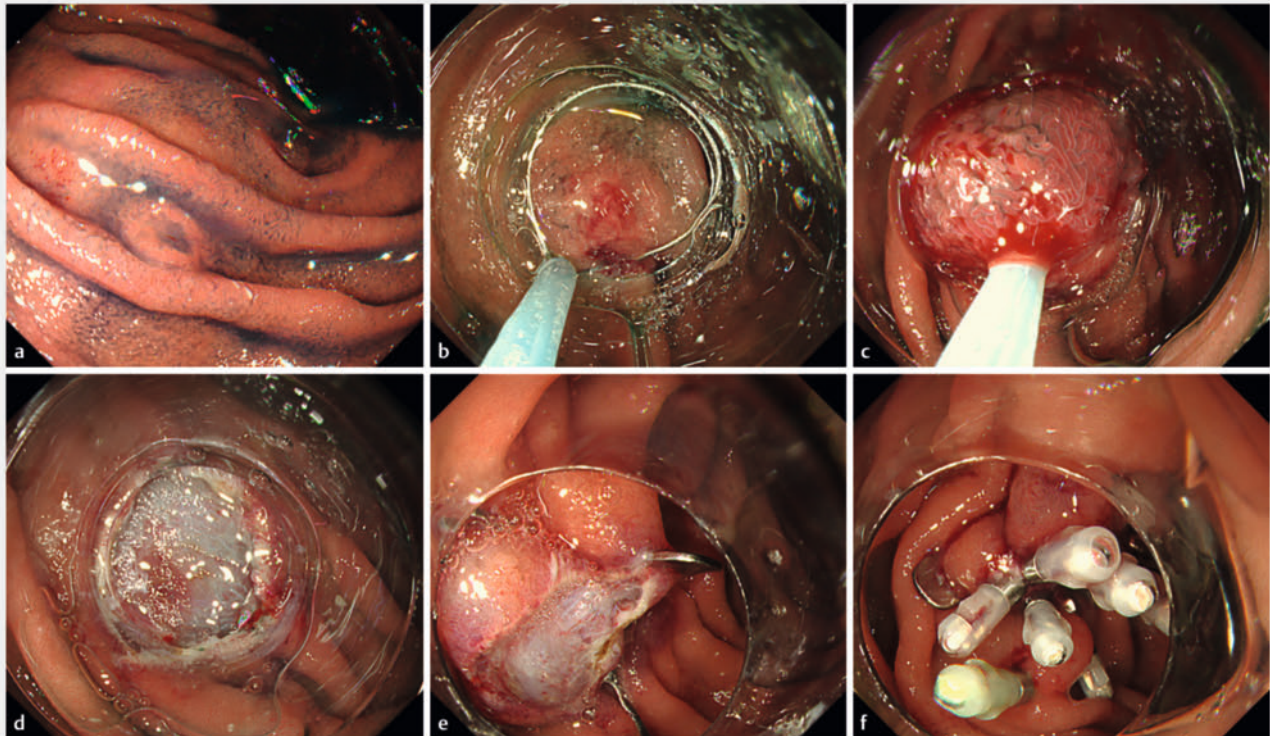
Center Tokyo. Written informed consent was obtained from each patient. This study was approved by the ethics committee at each institute (NTT Medical Center Tokyo; No. 19–63) and was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials (www.umin.ac.jp/ctr/; identification No. UMIN 000050919). All authors had access to the study data and reviewed and approved the final manuscript.

Patients and lesions

We examined the prospectively maintained databases of NTT Medical Center Tokyo and identified 721 consecutive patients who underwent ER between January 2017 and June 2022. Regarding the resection method for SDETs ≤ 10 mm, EMRC was mainly selected as the treatment of first choice. Only lesions with poor lifting by submucosal injection (non-lifting sign), which appeared to be due to obvious submucosal fibrosis, were excluded and treated using ESD instead. Two hundred twenty-eight lesions (of 248 SDETs ≤ 10 mm) that met the study criteria were enrolled. A flow diagram of the enrolled patients is presented in ► **Fig. 1**. Clinical data, including patient characteristics, lesion characteristics, and therapeutic outcomes were collected from our database.

EMRC procedure and perioperative management

► **Fig. 2** shows the EMRC procedure. We performed the EMRC procedures using mainly upper gastrointestinal endoscopes (GIF-Q260J; Olympus, Tokyo, Japan); however, at the discretion of the operator, a lower gastrointestinal scope (PCF-Q260JI; Olympus, Tokyo, Japan) was used to treat lesions located in the third portion of the duodenum. The size of the lesion was measured using a cap, and the morphology was classified according to the Paris classification. When lesion margins were



► **Fig. 2** Cap-assisted endoscopic mucosal resection (EMRC). **a** 5-mm IIA lesion in the second anal side of the major papilla. **b** The snare was set around the inside of the cap and submucosal injection was performed. **c** After half-suction, snaring was performed. **d** The defect after resection. There was no residual tumor and perforation endoscopically. **e** The defect was closed completely with an over-the-scope clip (OTSC). **f** Additional clips were used to cover the inverted submucosa after closure of the defect using the OTSC.

unclear, narrow band imaging or chromoendoscopy with 0.2% diluted indigo carmine was performed. Most of the patients had been referred to our institution from other hospitals, and a preoperative biopsy had already been performed. We performed biopsies during preoperative endoscopy examinations in cases where biopsies had not been performed at other hospitals. The EMRC procedure was the same as previously reported [16, 17]. After submucosal injection of saline solution, the target lesion was aspirated into the distal attachment and strangulated with a snare (SD-7P; Olympus, Tokyo, Japan) that was opened within the transparent cap (MH-592; outer diameter of 13.9 mm; Olympus, Tokyo, Japan). Two locations were marked using the snare: one on the oral side of the lesion and the other on the anal side. The snare was set around the inside of the cap. After submucosal injection, half-suction was performed to check the demarcation line and to prevent suctioning of the muscularis propria. Once the lesion was suctioned into the cap, the assistant closed the snare. The suction was then released, and once the snared mucosa was identified, the lesion was resected using a VIO300D electrical unit (Erbe, Tübingen, Germany) in Endo Cut mode Q (effect 2, 45W). Our strategy for managing postoperative mucosal defects was to attempt closure using an over-the-scope clip (OTSC) and additional clips, because these clips were used to cover the inverted submucosa after closure of the defect using the OTSC [23].

All the procedures were performed under general anesthesia. Insufflation was performed using carbon dioxide. For patients who underwent antithrombotic therapy, the drug withdrawal periods were determined in accordance with the Japan Gastroenterological Endoscopy Society (JGES) guideline [24]. The administration of antithrombotic drugs was resumed within 24 hours after the procedure in all patients. The EMRC procedures were performed by endoscopists each of whom had performed at least 10 esophageal EMRC procedures. A second-look endoscopy scheduled for the day after EMRC was performed according to endoscopist recommendation but was not routinely performed. The patients fasted for 2 days, including the day of EMRC, and were given intravenous hydration. After evaluation of blood test results, a liquid diet was started on the third postoperative day, and patients were generally discharged on the fifth day. There was no difference in the timing of allowing drinking and eating, even if there was a perforation, as long as no symptoms were present.

Pathological assessment

Histological assessments were made by pathologists who were board-certified by the Japanese Society of Pathology. The lesions were classified according to the revised Vienna classification (VCL) [25]. Considering the low accuracy of histopathological diagnoses made from biopsy specimens, VCL C2/3 lesions

were also regarded as therapeutic targets, in addition to VCL C4/5 lesions. VCL C2 lesions were targeted for resection when those lesions were strongly suspected endoscopically to be tumors. Resected specimens were stretched, pinned to a cork board, and placed in a 10% formalin container. If the lesion was resected en bloc and the lateral and vertical margins were tumor negative, the specimen was defined as an “R0 resection.”

Outcome measurements and definition of adverse events

The primary outcome of this study was the R0 resection rate. The secondary outcomes were the en bloc resection rate, complete defect closure rate, procedure time, rate of adverse events (AEs), number of days in hospital after procedure, and the recurrence rate based on surveillance endoscopy findings. We scheduled an interval surveillance endoscopy examination within 18 months after EMRC. We defined AEs as delayed bleeding, intraoperative/delayed perforation, acute pancreatitis, or death. Delayed bleeding was defined as a hemorrhage requiring an endoscopic hemostatic procedure and occurring within 28 days after EMRC. Intraoperative perforation was defined as presence of an obvious defect in the intrinsic muscles on endoscopic observation of the peri-duodenal space or the peritoneal cavity. Delayed perforation was diagnosed when computed tomography showed free air or contrast extravasation. Pancreatitis was defined as a serum lipase level more than three times the upper limit of normal combined with typical clinical symptoms. All the patients were hospitalized for at least one postoperative day and also underwent follow-up outpatient visits within 30 days after EMRC to check for presence of AEs.

Results

We successfully treated 248 consecutive SDETs \leq 10 mm (248 patients). Of these, 20 cases (8.1%) had non-lifting signs and were treated using ESD, while the other 228 lesions were treated using EMRC. The clinicopathological characteristics of the lesions resected by EMRC are shown in ► **Table 1**. Median patient age was 59 years, and 154 patients (67.5 %) were male. Sixteen of the enrolled patients (7.0%) were receiving antithrombotic therapy. Mean lesion size was 5.9 mm. The majority of lesions (90.3%) were located in the 2nd portion. Morphologically, most of the lesions (60.0%) were flat elevated. Isochromatic or white colors were more frequently observed (67.5%). Most of the preoperative biopsy findings showed VCL C2/3 (97.8%).

Efficacy

Treatment outcomes are summarized in ► **Table 2**. The R0 resection rate was 97.4% (222/228 cases), and the en bloc resection rate was 99.6% (227/228 cases). The post-EMRC mucosal defect was completely closed by OTSC in 90.4% of patients (206/228 cases). The number of OTSC was one in all cases. Eighteen cases (7.8%) were closed with clips alone. Four cases (1.8%) were not closed because they were located in the bulb. The histological diagnoses of these lesions were as follows: adenoma 188 (82.5%), carcinoma 26 (11.4%), and all cancer lesions

► **Table 1** Clinicopathological characteristics of lesions resected with EMRC.

Patients, n	228
Median age, years (range)	59 (34–85)
Sex, male/female	154/74
Antithrombotic therapy, n (%)	16 (7.0)
Lesions, n	228
Tumor size, mm, mean \pm SD	5.9 (2.3)
Location, n (%)	
▪ 1st portion	14 (6.1)
▪ 2nd portion (oral side of the major papilla)	87 (38.2)
▪ 2nd portion (anal side of the major papilla)	119 (52.1)
▪ 3rd portion	8 (3.6)
Morphology, n (%)	
▪ Protruded	9 (4.0)
▪ Flat elevated	137 (60.0)
▪ Depressed	82 (36.0)
Color, n (%)	
▪ Red	74 (32.5)
▪ Isochromatic or white	154 (67.5)
Preoperative biopsy findings, n (%)	
▪ VCL C2/3	223 (97.8)
▪ VCL C4/5	5 (2.2)

EMRC, cap-assisted endoscopic mucosal resection; VCL, Vienna classification; SD, standard deviation.

Note: According to the revised Vienna classification, superficial duodenal epithelial neoplasias (SDETs) were divided into four categories: indefinite for neoplasia (VCL 2); low-grade adenoma (VCL 3); high-grade adenoma/intramucosal carcinoma (VCL 4); and carcinoma with submucosal invasion (VCL 5). The predominant color or macroscopic type was used when the tumor showed multiple colors or macroscopic types. The morphology of the lesions was evaluated according to the Paris classification.

were intramucosal carcinoma. The mean procedure time was 5 minutes, and the mean closure time was 15.6 minutes. Surveillance endoscopy to check for presence of local recurrence showed no local recurrence after EMRC (mean follow-up period; 30.1 months).

Safety

No delayed perforations or deaths were observed as AEs. Although delayed bleeding occurred in six patients (2.6%), it was successfully managed with subsequent clipping or coagulation. Acute pancreatitis occurred in one case, but the patient was successfully managed without surgical intervention. The mean postoperative hospital stay was 4.8 days.

► **Table 2** Treatment outcomes.

R0 resection rate, n (%)	222/228 (97.4)
En bloc resection rate, n (%)	227/228 (99.6)
Complete closure rate, n (%)	224/228 (98.2)
Final pathological findings, n (%)	
▪ Adenoma	188 (82.5)
▪ Intramucosal cancer	26 (11.4)
▪ Submucosal cancer	0 (0)
▪ Other	14 (6.1)
Adverse events, n (%)	
▪ Delayed bleeding	6 (2.6)
▪ Delayed perforation	0 (0)
▪ Pancreatitis	1 (0.5)
Procedure time, min, mean \pm SD	15.6 (6.8)
Hospital stay after procedure, days, mean \pm SD	4.8 (1.3)
Recurrence rate, n (%)	0 (0)

SD, standard deviation.

Note: Delayed bleeding was defined as a hemorrhage requiring an endoscopic hemostatic procedure and occurring within 28 days after resection. Delayed perforation was diagnosed when computed tomography showed free air or contrast extravasation. Pancreatitis was defined as an elevated serum lipase level more than three times the upper limit of normal combined with typical clinical symptoms.

Discussion

SDET was previously considered a rare disease, but recent advances in endoscopic technology have increased opportunities for detection [1, 2, 3, 4]. Various endoscopic treatments have been used to resect SDET [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17]. While the efficacy of ESD for relatively large lesions has been widely reported, an exact treatment strategy for small SDETs (≤ 10 mm) has not been clearly established [8, 9, 10]. Conventional EMR, UEMR with improved EMR, and CSP without electrocautery have been reported [7, 8, 10, 11, 12, 13, 14, 15]. Several recent reports about UEMR have shown that while the AEs were not significantly different from those with other treatments, the R0 resection rate was lower at 61% to 71% [10, 11, 12, 13]. Reportedly, the R0 resection rate is slightly lower than that for conventional EMR [26]. The main cause of this difference was reported to be the omission of submucosal injection, which increases the risk of a positive lateral margin [26]. CSP has been developed as a minimally invasive treatment for non-pedunculated colonic polyps measuring < 10 mm [27]. First, however, reports have indicated that only the muscularis mucosae and very shallow submucosa can be resected by CSP in the colon [18]. Second, resected specimens are often broken into pieces during lesion sampling, making accurate pathological evaluation difficult because of the absence of a burn effect [18, 27]. Furthermore, because endoscopic diagnosis in the duodenum is less well established than that in the colon and the features

of SDET malignancies have not been clarified, whether CSP should be uniformly performed for all small SDETs remains debatable. On the other hand, conventional EMR has been reported as the standard treatment for relatively small lesions in the gastrointestinal tract, consisting of three steps: submucosal injection, strangulation of the target lesion with snare forceps, and resection with electrocautery [7, 8]. Conventional EMR for SDETs has been reported to result in somewhat piecemeal resection and not very high R0 resection rates, but relatively large SDETs have been evaluated [7, 8, 26].

In contrast, there are very few reports of EMRC for SDET [16, 17]. Jamil et al. reported a high eradication rate and a low recurrence rate after EMRC for treatment of SDET [17]. EMRC was performed for 49 SDETs, with 39 resected piecemeal and only 10 resected en bloc. The reason for these results was that the median size was as large as 25 mm (6–60 mm), and the initial eradication rate for small lesions was higher than that for large lesions (100% vs 87.9%, respectively). Although this study examined the largest number of SDET lesions treated using EMRC to date, the variation in lesion size and the low en bloc resection rate made it difficult to assess the indications for EMRC accurately. Therefore, we considered SDETs ≤ 10 mm and able to fit inside the cap (outer diameter; 13.9 mm, insider diameter; approximately 12 mm) to be eligible for EMRC. In addition, SDETs ≤ 10 mm and that did not have a non-lifting sign were considered candidates for EMRC because approximately 25% of patients with SDET reportedly require conversion from EMR to ESD based on non-lifting signs and approximately 30% of patients undergoing UEMR required conversion to ESD as well [12]. Because of the uniformity of this simple treatment strategy, we were able to examine the efficacy and safety of EMRC in consecutive patients with SDETs ≤ 10 mm in this study.

Our data showed that EMRC for SDET achieved an R0 resection rate of over 97%, which is considerably higher than the rates for other previously reported treatments [28]. This high R0 resection rate suggested that surveillance endoscopy could be reduced. There were no cases of perforation and the incidence of bleeding was low, as in other studies. In addition, there were no recurrences after EMRC during the follow-up period in our study. In the present study, the EMRC procedures were performed by endoscopists who had performed more than 10 cases of esophageal EMRC, including some endoscopists who had never performed duodenal ESD, but the results were good. This outcome suggests that unlike ESD, which requires considerable experience in order to learn the technique, EMRC is a relatively simple procedure.

A strength of this study is that the sample size was very large, compared with previous reports examining the efficacy and safety of ER for SDET. Furthermore, the treatment definition was simple and clear, and the definition was easily applicable to actual clinical practice, because the indications were focused on only two points: size and non-lifting signs. On the other hand, our study had several limitations. First, although the patients in this study were prospectively enrolled into our database, detailed data about them were retrospectively collected from medical records. However, because the lesions were resected using a strategy that has clear criteria regarding

the indications for the procedure and the study was conducted at a single center according to the same criteria, an excessive lesion-by-lesion selection bias is unlikely. Furthermore, the number of cases was quite large, despite being limited to SDETs measuring ≤ 10 mm. Second, because we did not enroll patients who underwent endoscopic treatments other than EMRC, we were not able to assess whether EMRC is superior to other techniques directly in this study. However, because previous reports have shown that the R0 resection rate was not so high and EMRC was clearly more useful in our experience for the lesions that met the present criteria, there is a risk that patients would be disadvantaged by the selection of another technique [26]. Third, the median follow-up period was 30.1 months, and our data were limited by this relatively moderate follow-up period. In a large multicenter retrospective subanalysis of endoscopic treatment for SDET, 80% of all recurrences were seen within 2 years [28]. The 2-year cumulative local recurrence rate for SDETs ≤ 29 mm was 2.8% for non-ESD (conventional EMR, CSP, UEMR) and 0.4% for ESD, with significantly lower rates for ESD. Although there are several reports about endoscopic treatment of SDETs, none of them are limited to SDETs ≤ 10 mm. In the previous large study, the recurrence rate was 2.8% for SDETs ≤ 29 mm, so the recurrence rate is likely to be lower for SDETs ≤ 10 mm, the target in this study [28]. Although direct comparison is difficult because our EMRC results were limited to lesions ≤ 10 mm, the median follow-up period was 30.1 months, which is longer than 2 years, a period during which recurrence is more likely to occur, and no recurrence was observed. The recurrence rate may be lower than that for non-ESD (conventional EMR, CSP, UEMR), but long-term outcome data are needed to be able to determine whether local recurrences are rare after EMRC. Finally, considering the cost-effectiveness and technical simplicity of OTSC, it would be worthwhile to assess whether conventional clips alone are sufficient to achieve defect closure and prevent delayed AEs in patients with small mucosal defects of around 10 mm.

Conclusions

In conclusion, we have demonstrated that EMRC is a fairly effective and safe treatment for SDETs ≤ 10 mm that do not have non-lifting signs.

Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical trial

Trial registry: UMIN Japan (<http://www.umin.ac.jp/english/>)
Registration number (trial ID): UMIN000050919
Type of Study: a retrospective cohort study

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