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**Safety of endoscopic mucosal resection using a bipolar snare for superficial
non-ampullary duodenal epithelial tumors and the predictive factors of
piecemeal resection**

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Abstract

Introduction: Endoscopic mucosal resection for small superficial non-ampullary duodenal epithelial tumors is a non-invasive treatment, however, perforations can occur. Bipolar snares can reduce the risk of perforation due to small tissue damage. Currently, only a few studies have reported endoscopic mucosal resection for small superficial non-ampullary duodenal epithelial tumors using a bipolar snare and the effect of preoperative findings.

Objective: To investigate (1) resectability and adverse events of endoscopic mucosal resection using a bipolar snare for small superficial non-ampullary duodenal epithelial tumors and (2) the predictions of piecemeal resection.

Methods: Between 2007 and 2017, 89 patients with 107 lesions underwent endoscopic mucosal resection using a bipolar snare. Among them, 88 lesions of 77 patients were evaluated. The primary outcome was the incidence of en bloc resection and R0 resection, and adverse events. Risk factors associated with piecemeal resection, including preoperative lesion findings, were also examined.

Results: The incidence rates of en bloc and R0 resections were 85.2% and 48.9%, respectively. Neither intraoperative or delayed perforations nor procedure-related mortality was noted. The non-lifting sign after submucosal injection was associated with

an increase in piecemeal resection (odds ratio, 20.3, 95% confidence interval, 2.53-162; $p=0.005$).

Conclusion: Endoscopic resection for small superficial non-ampullary duodenal epithelial tumors can cause perforation; however, endoscopic mucosal resection using a bipolar snare can be a safe treatment option as it does not cause perforations. The non-lifting sign after submucosal injection is a predictive factor for piecemeal resection.

Introduction

Recently, the number of detected superficial non-ampullary duodenal epithelial tumors (SNADETs) is increasing due to the development of endoscopic technique and equipment. SNADETs are considered to be precancerous lesions.[1] Recently, various studies have shown that endoscopic resection (ER) is a non-invasive treatment option for SNADETs. However, there are two types of ER – endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). ER for SNADETs has not been standardized. Recently, ESD has increased en bloc resection, regardless of the lesion size; whereas, ESD for SNADETs has a higher incidence of serious adverse events.[2-7] Thus, conventional EMR is widely used for small lesions.

Bipolar snare use leads to lower tissue damage than monopolar snare because the former has less energy, and thus, the use of bipolar snare is associated with a low incidence of perforation.[8-11] EMR using a bipolar snare for colorectal polyps was found to be as safe as EMR using a monopolar snare.[12] Many studies have reported the use of EMR for SNADETs, and in most of these studies, a monopolar snare was used. In contrast, only a few studies showed the use of EMR with a bipolar snare for SNADETs.[11, 13] Moreover, local recurrence may occur if piecemeal resection is performed for SNADETs.[14-16] Piecemeal resection, as well as preoperative findings,

such as the presence of fold convergence of the lesion, the relationship between lesions and the fold, and the vertical or tangential visibility of the lesion during snaring have not been examined in previous studies. Therefore, the purpose of this study was to investigate the resectability and adverse events of EMR using a bipolar snare for SNADETs as well as the predictions of piecemeal EMR.

Materials and Methods

Patients

This retrospective, single-center observational study enrolled patients with SNADETs who underwent EMR using a bipolar snare between July 2007 and December 2017. Patients with familial adenomatous polyposis (FAP) were excluded because the treatment indications of SNADET with FAP were based on the Spigelman classification, which differed from sporadic SNADETs.[17] Additionally, because patients with FAP have multiple SNADETs, it can be difficult to evaluate R0 resection, local recurrence, and bleeding source. Moreover, patients who had undergone precutting EMR or hybrid ESD, and patients with local recurrent lesions were excluded from this study.

Written informed consent was obtained from each patient who underwent EMR. The study protocol was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (approval number: 3989; approval date: February 27, 2018). Furthermore, the study conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in *a priori* approval by the institution's human research committee. All subjects had the opportunity to decline their participation in this study.

EMR procedure

EMR was indicated for SNADETs with a preoperative size ≤ 20 mm. The lesion's circumference was measured as a proportion of the duodenum circumference, based on its division into 12 equal parts. The EMR procedure was performed using a therapeutic endoscope (GIF-Q260J, Olympus Medical Systems, Tokyo, Japan) and a bipolar snare (13- or 26-mm) (Dragonare™; Zeon Medical Inc., Tokyo, Japan). In cases where it was difficult to treat using the abovementioned scope, we used a lower gastrointestinal endoscope with a narrow diameter or a therapeutic duodenoscope (PCF-PQ260, TJF-260 V, Olympus Medical Systems, Tokyo, Japan). After injecting a 10% glycerine solution (Glyceol, Taiyou Pharma Co, Ltd, Tokyo, Japan) or hyaluronate sodium (Mucoup, Boston Scientific Japan, Tokyo, Japan) into the submucosa, the elevated lesion was electrosurgically resected. A standard electrosurgical generator (ICC 200 or VIO300D; ERBE Elektromedizin GmbH, Tübingen, Germany) was set to Auto Cut mode and 30 W of coagulation. In cases where en bloc resection cannot be performed successfully, an endoscopic piecemeal resection or argon plasma coagulation (APC) was performed. After resection, post-EMR artificial ulcers were closed as much as possible with clips to prevent delayed bleeding or perforation (Figure 1). Fasting and intravenous hydration were performed since the day of treatment, and oral intake was initiated on the second day post-treatment, provided there were no adverse events. Proton pump inhibitors and/or Rebamipide were administered eight weeks post-treatment.

Endoscopic surveillance

Follow-up endoscopy was performed 2 months post-treatment to monitor ulcer healing and residual tumor. Additionally, surveillance endoscopy was performed 1 year post-treatment and every year thereafter. Biopsy specimens were obtained, if endoscopy suggested local recurrence. In patients who did not undergo follow-up endoscopy 1 year post-treatment at our hospital, we conducted a telephone survey to obtain necessary information from the patient or the hospital visited by the patient.

Histological assessment

All lesions were assessed microscopically as reported elsewhere.[18]

Definition of adverse event

Delayed bleeding was defined as (1) overt hematemesis or melena that occurred after EMR, and (2) a decrease in the hemoglobin concentration ($>2\text{-g/dL}$) and bleeding that required emergent endoscopic hemostasis treatment within 30 days of EMR.

Perforation was defined as the presence of free air detected with abdominal computed tomography.

Outcomes

Primarily, the outcome measures were the incidence of en bloc and R0 resections as

well as adverse events. Secondly, the predictions of piecemeal resection were also examined. We assessed variables including age, gender, lesion location, macroscopic lesion type, lesion diameter, and the luminal circumference of the lesion. Furthermore, we assessed the presence of lesion fold convergence, the lesion's location within a duodenum fold (across or between folds), the presence of the non-lifting sign after submucosal injection, the vertical or tangential visibility of the lesion during snaring, and the presence of biopsy before treatment (Figure 2). Whether patients underwent biopsy before treatment was determined by reviewing patients' charts as well as previous endoscopy reports from our and/or patients' previous hospitals. All other variables related to endoscopic images were evaluated by a specialist affiliated with the Japan Gastroenterological Endoscopy Society.

Statistical analyses

Continuous variables were compared using Student's *t*-tests and are presented as mean and standard deviation. Fisher's exact test was used to compare categorical variables. Risk factors for piecemeal resection were assessed with logistic regression analysis; the odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Generalized estimating equations (GEEs) were used to analyze repeated measures data.

All statistical analyses were performed with the IBM® SPSS® software, version 23.0

for Windows (IBM Corporation Armonk, NY, USA). P -values < 0.05 were considered statistically significant.

Results

Clinicopathological characteristics of the study subjects

EMR using a bipolar snare was performed for 107 SNADETs (89 patients). Ten lesions in 5 patients with FAP, 7 lesions in 7 patients who had undergone precutting EMR or hybrid ESD, and 2 local recurrent lesions in 1 patient were excluded. As such, 88 lesions from 77 patients were finally evaluated (Figure 3).

The case characteristics of all participants are presented in Table 1. The median tumor size across all procedures was 8 (range, 1-25) mm. Most lesions (71.6%) were located in the second part of the duodenum. Furthermore, a biopsy before the procedure was performed for most lesions (94.3%), and post-EMR artificial ulcers of 82 lesions (93.2%) were closed using clips.

Twenty lesions (22.7%) were histologically diagnosed as duodenal carcinoma post-EMR. Of these lesions, three lesions were submucosal invasive cancers; however, no additional treatment was performed based on patients' preference. These patients are still alive without any recurrence.

The en bloc and R0 resections

The incidence of en bloc and R0 resections was 85.2% and 48.9%, respectively. Moreover, six lesions had added coagulation by APC (Table 2). Two cases of local recurrence were found (2.3%) during the median surveillance period of 427 (interquartile range (IQR), 66-1086) days, and the follow-up rate was 86%. R0 resection was not achieved for a few adenomas and thus, additional EMR was required; however, no recurrence post-retreatment was observed. Based on the Hematoxylin-Eosin staining of specimens post-resection, submucosal fibrosis was observed in 20% (15/75 cases) of flat lesions with a biopsy. Among them, the non-lifting sign was observed in 6 cases, and 4 of these 6 cases (66.7%) had submucosal fibrosis.

Adverse events

Table 2 shows the incidence rates of adverse events. Neither intraoperative or delayed perforation nor procedure-related mortality occurred. Delayed bleeding occurred in 8 (9.1%) lesions (7 patients). Among them, only one patient received antithrombotic treatment (i.e. warfarin). Two post-EMR artificial ulcers could not be closed using clips. All cases of delayed bleeding were controlled by endoscopic hemostasis. None of the patients required blood transfusion. Piecemeal resection was an independent risk factor of delayed bleeding in our multivariate analysis (OR, 5.21: 95% CI, 1.01-27.0: $p=0.049$), and all cases of delayed bleeding in the second part of the duodenum had lesions

located on the same side of the papilla.

Risk factors associated with piecemeal resection

The piecemeal resection rate was 14.8% (Table 2). Tumor size (OR, 1.18; 95%CI, 1.04-1.34; $p = 0.009$), tumor circumference (OR, 1.28; 95%CI, 1.10-1.49; $p = 0.001$), and the presence of the non-lifting sign after submucosal injection (OR, 16.2, 95%CI, 2.58-101; $p = 0.003$) were predictions of piecemeal resection (Table 3). The presence of the non-lifting sign after submucosal injection was an independent prediction of piecemeal resection in our multivariate analysis with GEEs (OR, 20.3; 95%CI, 2.53-162; $p = 0.005$).

Discussion

The results obtained in this study suggest that EMR using a bipolar snare is a safe treatment method for SNADETs; resection rates were reasonable while intraoperative and delayed perforations were absent. Additionally, we showed that the non-lifting sign after submucosal injection was a predictive factor for piecemeal resection. This is the first study to examine the use of EMR using a bipolar snare for SNADETs in the general population.

EMR using a bipolar snare is potentially safe as neither intraoperative or delayed perforations nor procedure-related mortality was observed. The ER for SNADETs has a frequent risk of intraoperative and delayed perforation because the duodenum has a very thin muscle layer, and post-ER artificial ulcers are exposed to bile and pancreatic fluids.[19, 20] Therefore, it is considered important to manage the flow direction of electric current and to close post-ER artificial ulcers. Delayed perforations of ESD can be associated with the use of electrical cautery, which induces ischemic changes in the muscle layer during submucosal dissection.[21] The electric current flows from the monopolar device throughout the body of the patient. In contrast, in bipolar devices, the electric current flows primarily across the tissue segment between the two electrodes, thereby, minimizing tissue damage.[10, 12, 11, 13] Delayed perforation was observed in

2 out of 55 patients (3.6%) who underwent EMR for SNADETs; both patients underwent piecemeal resection and their post-ER artificial ulcers could not be closed.[20] In the present study, 13 (14.8 %) lesions underwent piecemeal resection; of these, one lesion with post-ER artificial ulcers could not be closed, but there were no cases of delayed perforation. Delayed perforation did not occur in EMR using a bipolar snare, even in cases with post-EMR ulcers that could not be closed by clips, if the diameter of the lesion was less than 10 mm.[13]

Delayed bleeding can occur in 3.1% to 11.6% of cases that underwent EMR for SNADETs.[22, 23, 14, 24, 15] Exposure of the post-EMR artificial ulcers to biliary and pancreatic fluids can also contribute to delayed bleeding, [25] and prophylactic endoscopic clips reduce delayed bleeding after EMR.[23, 15] In this study, we found that delayed bleeding is likely to occur in piecemeal resection cases and bleeding lesions that are located on the same side of the papilla. While the use of bipolar snare can minimize deep tissue damage, the longer coagulation time associated with this method can lead to a strong burning effect on the mucosa and submucosa layers. Therefore, it was speculated that the size of the post-EMR ulcer in piecemeal resection cases was larger than that of en bloc cases and an incomplete closure of post-EMR ulcer was more likely to occur in such cases. These post-EMR ulcers were likely to be exposed to biliary and pancreatic fluids on the same side of the papilla, resulting in

further delayed bleeding. Inoki et al. reported that no patient had delayed bleeding after EMR using a bipolar snare for SNADETs.[13] However, this previous study only included 11 FAP patients who were approximately 40 years old. In contrast, the present study included 77 elderly patients (mean age, 63 years), many of whom had a variety of diseases and some were taking antithrombotic drugs. Hamada et al. reported that no delayed bleeding was observed with cold snare polypectomy for SNADETs in 332 lesions of 10 FAP patients.[26] Considering that delayed bleeding was also not observed in the excluded FAP patients (10 lesions of 5 patients) in our study, the rate of delayed bleeding may be lower in FAP patients than in the general population. Therefore, our study population was more representative of the general population, and it is better to evaluate them separately from the FAP cases.

The en bloc and R0 resection rates of EMR using a bipolar snare for SNADETs (≤ 20 mm in diameter) in the present study were similar to those reported in a previous study on EMR using a monopolar snare – 69%-82% and 30%-59%, respectively [2, 15, 16, 7]. Given that SNADETs may be malignant, resection in a single piece is recommended.[27] Moreover, the probability of local recurrence is 25%-33% in piecemeal resection cases.[28, 29] In underwater EMR (UEMR), the digestive tract is in a relaxed state, so it can grasp a wider range of mucosa than conventional EMR.[30] Although one single-center study showed that UEMR and EMR using monopolar had a

high en bloc and R0 resections rate, some difficult and large cases were converted to ESD by endoscopists in that study.[31] On the other hand, cases that had the non-lifting sign or large size lesions underwent EMR in our study, which can be attributable to the lower resection rate observed in this study than in previous studies. The R0 resection rate was 48.9% in this study, and the local recurrence rate was also low. Because a bipolar snare has a stronger lateral burning effect than a monopolar snare for colon polypectomy, it can make the lateral margin more difficult to assess[12], and therefore, the local recurrence may decrease.

We elucidated the prediction of piecemeal resection including preoperative findings, such as the presence of fold convergence of the lesion, the relationship between lesions and fold, and the vertical or tangential visibility of the lesion during snaring. The presence of the non-lifting sign after submucosal injection was found to be the only independent risk factor of piecemeal resection. Some studies reported that SNADETs >10-15 mm was associated with piecemeal resection; however, these studies did not consider the abovementioned preoperative findings.[15, 20, 32] Regarding preoperative findings, Minamino et al. reported that the colon polyp located across a fold increases the frequency of incomplete resection.[18] However, the present study did not show a similar result. The folds of the duodenum may be lower in height than those of the colon. The biopsy procedure may induce fibrosis, which may further complicate endoscopic

treatments.[33, 34, 27] Fukunaga et al. reported that a preoperative biopsy caused severe submucosal fibrosis in 20.6% of laterally spreading colorectal tumors.[35] The duodenum has a thinner wall than the gastric antrum, as seen via transabdominal ultrasonography.[36] Therefore, fibrosis of the duodenal wall is more likely to occur due to a preoperative biopsy than fibrosis of the gastric wall; thus, the non-lifting sign during submucosal injection may likely occur.[35] Kinoshita et al reported that 24.6% of the SNADETs that underwent EMR were converted to ESD because the non-lifting sign was observed due to fibrosis caused by a preoperative biopsy.[27] In the present study, submucosal fibrosis was observed histologically in 20% of flat lesions with a biopsy, and in 66.7% of cases with the non-lifting sign. Recently, UEMR was reported to be useful for en bloc resection even in cases with recurrent lesions or fibrosis.[37] Thus, UEMR and ESD may be considered as the first choice of treatment for lesions suspected to have the non-lifting sign during treatment.

Our study has a few limitations. First, because this was a retrospective study with a small sample size conducted at a single-center with a single arm, the statistical power of the present study may be low. However, the present study has the largest sample size compared to previous studies on EMR using a bipolar snare for SNADETs, excluding patients with FAP. Second, the visibility of preoperative findings was assessed by a single gastrointestinal endoscopist. There is a possibility that a difference exists in the

appearance of lesions of the same type. Third, data on the location, such as anterior, posterior, medial, and lateral walls, were not available, which may affect complication-related results. Yahagi et al. reported that delayed bleeding often occurred in lesions on the medial wall.[38] Finally, because 14% of cases could not be followed, local recurrence could have been underestimated in this study. Given these limitations, the results of the present study may be interpreted carefully.

In conclusion, EMR using a bipolar snare for SNADETs is a safe treatment option. No patients developed perforations in this study. In future studies, we would like to compare the effectiveness of EMR using a monopolar snare with EMR using a bipolar snare for the treatment of SNADETs. In cases of SNADET that are suspected to have the non-lifting sign during treatment, another treatment option, such as UEMR or ESD, can be considered instead of conventional EMR.

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None.

Statement of Ethics

This study was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (approval number: 3989; approval date: February 27, 2018).

Written informed consent was obtained from each patient who underwent EMR.

Subjects had the opportunity to decline participation in this study on our homepage on the Internet.

Disclosure Statement

The authors declare that there is no conflict of interest.

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Author Contributions

MY analyzed and interpreted the data and drafted the article. YN designed the protocol, analyzed and interpreted the data, and clinically revised the article for important intellectual content. TS, HM, MO, FS, KO, SH, FT, KT, HY, TT, TW, and YF revised the article for important intellectual content. All authors read and approved the final manuscript.

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Figure legends

Figure 1. EMR procedure for SNADETs

a, Before EMR. **b**, After the submucosal injection. **c**, **d**, Grasped by the snare. **e**, **f**, Post-EMR artificial ulcers which were closed by clips. *SNADETs*, superficial non-ampullary duodenal epithelial tumors; *EMR*, endoscopic mucosal resection.

Figure 1

Figure 2. Preoperative lesion characteristics

a, Lesion with fold convergence. **b**, Lesion located across a fold. **c**, Lesion with the non-lifting sign after submucosal injection. **d**, Tangentially visible lesion at EMR. **e**, Vertically visible lesion at EMR. *EMR*, endoscopic mucosal resection.

Figure 2

Figure 3. Study enrollment

EMR, endoscopic mucosal resection; *SNADETs*, superficial non-ampullary duodenal epithelial tumor; *ESD*, endoscopic submucosal dissection; *FAP*, familial adenomatous polyposis.

Table 1. Patient and lesion's characteristics

Patients / Lesions, no.		77 / 88
Age, years, Mean $\pm$ SD		63.2 $\pm$ 10.5
Gender	Female	28 (36.4%)
	Male	49 (63.6%)
ASA-PS	1	21 (27.3%)
	2	49 (63.6%)
	3	7 (9.1%)
Antithrombotic drug	No	80 (90.9%)
	Yes	8 (9.1%)
Location	Bulbs	8 (9.1%)
	SDA	10 (11.4%)
	Second part	63 (71.6%)
	IDA	5 (5.7%)
	Third part	2 (2.2%)
Macroscopic type	0-I	8 (9.1%)
	0-IIa	62 (70.4%)
	0-IIa + IIc	5 (5.7%)
	0-IIc	13 (14.8%)
Size, mm, median (range)		8 (1-25)
Luminal Circumference of tumor, %, Mean $\pm$ SD		9.4 $\pm$ 0.3
Biopsy before treatment	No	5 (5.7%)
	Yes	83 (94.3%)
Closure for post EMR ulcer by clips	No	6 (6.8%)
	Yes	82 (93.2%)
Histology	Adenoma	68 (77.3)
	Adenocarcinoma	20 (22.7%)

SD, standard deviation; ASA-PS, american society of anaesthesiologist physical status

classification; SDA, superior duodenal angle; IDA, inferior duodenal angle; EMR, endoscopic mucosal resection.

Table 2. Clinical outcomes & Adverse events		n=88
Clinical outcomes	En-block resection	75 (85.2%)
	Piecemeal resection	13 (14.8%)
	R0 resection	43 (48.9%)
	Addition of APC ablation	6 (6.8%)
	Local recurrence	2 (2.3%)
Adverse events	Delayed bleeding	8 (9.1%)
	Intra-operative perforation	0 (0%)
	Delayed perforation	0 (0%)
	Aspiration pneumonia	1 (1.1%)

APC, argon plasma coagulation.

Table 3. Risk fator associated with piecemeal resection

		En-block resection	Piecemeal resection	GEE Crude-OR		GEE Multiple-adjusted OR	
		n=75 lesions in 64 patients	n=13 lesions in 13 patients	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
Age, years, Mean ± SD		63.3 ± 10.5	62.7 ± 10.0	0.99 (0.94-1.05)	0.81		
Gender	Female	25 (39.1%)	3 (23.1%)	1.00			
	Male	39 (60.9%)	10 (76.9%)	1.88 (0.47-7.54)	0.38		
Location	Bulbs - SDA	14 (18.7%)	4 (30.1%)	1.00			
	Second - Third part	61 (81.3%)	9 (69.9%)	0.52 (0.14-1.92)	0.32		
Macroscopic type	0-I	6 (8%)	2 (15.4%)	1.00			
	0-IIa/ 0-IIa+IIc	56 (74.7%)	11 (84.6%)	0.48 (0.86-2.66)	0.40		
	0-IIc	13 (17.3%)	0 (0%)	-	-		
Size, mm, Mean ± SD		7.9 ± 4.3	12.1 ± 5.0	1.18 (1.04-1.34)	0.009	1.10 (0.94-1.55)	0.23
Luminal Circumference of tumor, %, Mean ± SD		8.7 ± 2.1	12.2 ± 5.3	1.28 (1.10-1.49)	0.001	1.24 (0.99-1.55)	0.06
Lesion with fold convergence	No	59 (78.7%)	11 (84.6%)	1.00			
	Yes	16 (21.3%)	2 (15.4%)	0.67 (0.14-3.31)	0.62		
Lesion located across a fold	No	30 (40%)	4 (30.1%)	1.00			
	Yes	45 (60%)	9 (69.9%)	1.50 (0.43-5.26)	0.53		
Lesion with non-lifting sign during submucosal injeccion	No	73 (97.7%)	9 (69.9%)	1.00			
	Yes	2 (2.7%)	4 (30.1%)	16.2 (2.58-101)	0.003	20.3 (2.53-162)	0.005
Visibility of a lesion at EMR	Tangentially	59 (78.7%)	9 (69.9%)	0.46 (0.16-2.27)	0.46		
	Vertically	16 (21.3%)	4(30.1%)	1.00			
Biopsy before treatment	No	5 (6.7%)	0 (0%)	1.00			
	Yes	70 (93.3%)	13 (100%)	-	-		

SD, standard deviation; ASA-PS, american society of anaesthesiologist physical status classification; SDA, superior duodenal angle; EMR, endoscopic mucosal resection; GEE, generalized estimating equations; OR, odds ration; CI, confidence interval.