Endoscopic mucosal resection using a ligation device for duodenal neuroendocrine tumors: a simple method

Yasuhiro Inokuchi (iD)**, Kei Hayashi, Yoshihiro Kaneta, Yoichiro Okubo, Mamoru Watanabe, Mitsuhiro Furuta, Nozomu Machida and Shin Maeda**

Abstract

Introduction: Duodenal neuroendocrine tumors (DNETs) smaller than 1 cm in diameter, without invasion to the muscularis propria, have a low risk of metastasis. Therefore, DNETs are frequently resected endoscopically. However, among the various procedures, the best fit for DNET in terms of feasibility, effectiveness, and simplicity is unclear.

Methods: Patients with DNET who underwent endoscopic submucosal resection using a ligation device (ESMR-L) at Kanagawa Cancer Center between May 2003 and December 2020 were studied retrospectively to evaluate clinical characteristics and short-term and long-term outcomes.

Results: Eleven consecutive patients with 12 lesions were treated with 12 sessions of ESMR-L. Lesions were discovered in patients at a median age of 68 (range, 50–83) years. One patient had two lesions at the time of the initial ESMR-L session. Eleven of the 12 lesions (91.7%) existed in the duodenal bulb, of which 10 (83.3%) were in the anterior wall, and the remaining one (8.3%) existed in the descending part of the duodenum. The *en bloc* and R0 resection rates were 100% and 75%, respectively. The rates of bleeding and perforation were both 0%. Among the four patients who had non-curative resections, two patients underwent additional surgery after ESMR-L. One patient had a local remnant tumor, and the other had lymph node metastasis. In cases of local remnant tumors, the vertical margin was positive in the ESMR-L specimen. In that case, ligation by the O-ring was insufficient, retrospectively. All patients had no recurrence during the median follow-up period of 5.7 years.

Discussion: ESMR-L was the best fit for DNET within the indications for endoscopic resection. It is a simple procedure that enables easy and complete resection of DNETs without complications.

Keywords: duodenal neuroendocrine tumor, endoscopic resection, endoscopic submucosal dissection, endoscopic submucosal resection using ligation device

Correspondence to:
Yasuhiro Inokuchi
Chief Doctor, Department of Gastroenterology, Kanagawa Cancer Center, 2-3-2 Asahi-ku, Nakao, Yokohama 241-8515, Kanagawa, Japan.
inokuchiy@kcch.jp

Kei Hayashi
Yoshihiro Kaneta
Mamoru Watanabe
Mitsuhiro Furuta
Nozomu Machida
Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan

Yoichiro Okubo
Department of Pathology, Kanagawa Cancer Center, Yokohama, Japan

Shin Maeda
Department of Gastroenterology, Yokohama City University, Yokohama, Japan

Introduction

Neuroendocrine tumors (NETs) are rare tumors that develop in whole body organs, approximately 70% of which are found in the gastrointestinal tract.[1,2] The most common site for gastrointestinal NET (GI-NET) is the rectum (55.7%), followed by the duodenum, which accounts for 16.7% of all GI-NETs in Japan.[3] Duodenal neuroendocrine tumors (DNETs) smaller than 1 cm in diameter and without invasion to the muscularis propria have a low risk of metastasis.[4,5] Therefore, these lesions are often resected endoscopically using various methods;[6–14] there are also reports of laparoscopic and endoscopic cooperative surgery.[15,16] Although the utility and safety of endoscopic resection (ER) of submucosal tumors (SMTs), including NETs in the esophagus and stomach, have been described

frequently,[17–21] there are only a few reports with a limited number of lesions concerning ER for DNET.[6–14,22–29] Moreover, the best treatment method for DNET in terms of feasibility, effectiveness, and simplicity remains unclear.

In the present study, we aimed to assess the efficacy and safety of endoscopic submucosal resection using a ligation device (ESMR-L) for DNET. In addition, we provide tips for using ESMR-L, which may contribute to better outcomes than previous reports.

Methods

Patients

We retrospectively investigated patients with DNET who underwent ESMR-L at the Kanagawa Cancer Center between May 2003 and December 2020. A total of 13 patients had 14 lesions during this period. These patients underwent endoscopy and computed tomography (CT) before the treatment to confirm a lesion size smaller than 10 mm and no metastasis. In addition, they underwent an endoscopic ultrasound to confirm that the lesion was limited to the submucosal layer and did not invade the muscularis propria. Two lesions were observed in two patients resected using ESMR-L with mucosal circumferential pre-incision. These cases were excluded from the analysis.

As a result, 11 patients with 12 lesions were retrospectively analyzed including the characteristics of the patients and lesions, short-term outcomes, and long-term outcomes. This study was approved by the Research Ethics Committee of the Kanagawa Cancer Center (Approval Number: 2021-Epidemiology Research 61), which complies with the international guidelines for the ethical review of epidemiological studies. Written informed consent for endoscopic treatment was provided by all recruited patients before each treatment. We also uploaded study information to the Kanagawa Cancer Center website to allow patients to withdraw from the study.

ESMR-L procedure

The perimeter of the lesion was marked using small multiple cautery units made by the tip of a high-frequency snare to clarify the range. After a submucosal injection of normal saline was administered to lift the mucosal layer, endoscopic submucosal resection using a ligation device (ESMR-L) was performed as previously reported.[30] Briefly, the endoscope was attached with a cap specific for the ligation device (Pneumo-activate EVL Device, Sumitomo Bakelite Co. Ltd., Tokyo, Japan), the tumor was sucked into the cap, the lesion was ligated with an O-ring, and then the tumor was resected using a high-frequency snare. We ensured sufficient time (>1 min) for complete ligation by the O-ring to avoid a positive vertical margin and extended the duodenal wall, by filling it with enough air to force out unwilling portions, such as part of the muscular layer beneath the lesion, to prevent perforation. The high-frequency generators used were the ICC200 or the VIO300D (ERBE Elektromedizin GmbH, Tübingen, Germany). After resection, the wound was closed using hemoclips (Olympus, Tokyo, Japan) to prevent postoperative perforation and bleeding (Figure 1).

Short-term outcomes

The short-term outcomes of our study included the *en bloc* resection rate, the rate of adverse events, the complete resection (R0 resection) rate, the pathological complete resection rate evaluated according to histopathological assessment, and the rate of post-ESMR-L additional surgery. R0 resection was defined as *en bloc* resection with negative horizontal and vertical margins. A pathological complete resection was defined as satisfying all the following conditions: *en bloc* resection, negative horizontal and vertical margins, and no lymphovascular infiltration. Resection was judged as non-curative by histopathology when at least one of the following conditions was observed: tumor size was 10 mm or more, fractional resection, positive/inconclusive horizontal margin (HM1/HMX), positive/inconclusive vertical margin (VM1/VMX), and positive lymphatic or vascular infiltration (ly1, v1). Lymphatic infiltration and vascular infiltration were assessed not only by HE stain but also immunohistochemically using D2-40 and EVG, when a pathologist deemed necessary.

Adverse events and complications, including bleeding and perforation, were assessed. Bleeding was defined as follows: (1) discontinuance or postponement of the ESMR-L due to severe hemorrhage; (2) severe active hemorrhage during the procedure, resulting in low visibility with unstable vital signs; (3) the occurrence of melena or hematemesis; or (4) the detection of an ongoing hemorrhage, or the presence of coagulated
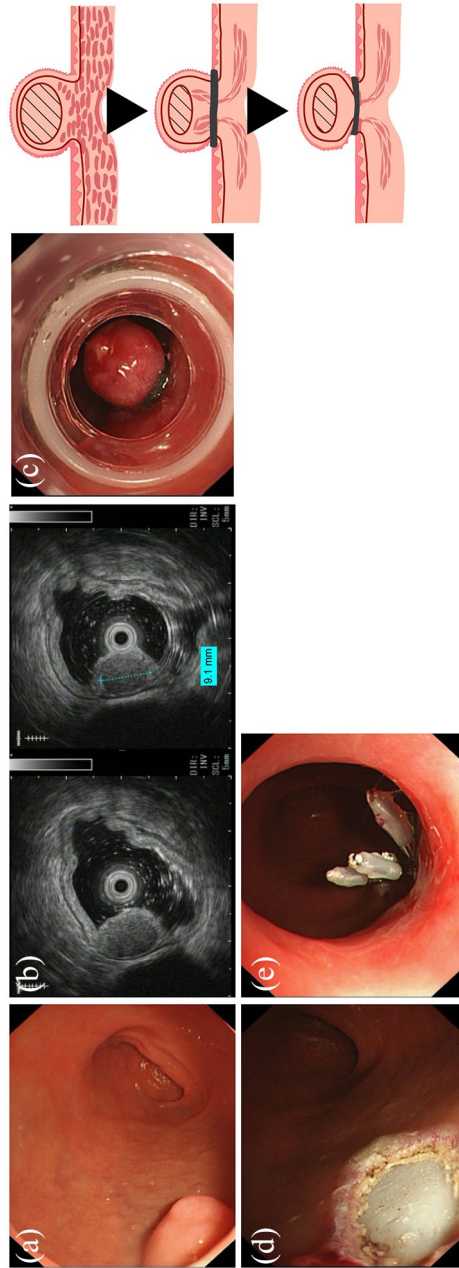
Figure 1. Outline of endoscopic mucosal resection using a ligation device. (a) White-light appearance of the DNET. A submucosal tumor covered by normal mucosa at the anterior wall of the duodenum. (b) Endoscopic ultrasound showing the tumor located at the submucosal layer without invasion to the muscularis propria. (c) Ligation by O-ring. The O-ring is ligated at the base of the tumor. (d) The wound is small and circular. There is no damage at the muscular layer. (e) The small wound left by ESMR-L is completely closed using hemoclips.
DNET, duodenal neuroendocrine tumor; ESMR-L, endoscopic submucosal resection using a ligation device.

blood in the stomach or duodenum with apparent bleeding spots on endoscopy on another day. (1) and (2) were defined as intraoperative bleeding, and (3) and (4) were defined as postoperative bleeding. Perforation was confirmed by observation of mesenteric fat during ESMR-L or by detection of free air or retroperitoneal air on X-ray films or CT scans.

Long-term outcomes

The long-term outcomes of our study included local recurrence, 5-year overall survival (OS) rate, disease-specific survival (DSS) rate, and cause of death. The presence or absence of recurrence was evaluated by endoscopy and CT scans which were performed once a year after the ESMR-L procedure. The period of survival was measured starting from the date of ESMR-L to the date of death or the last verified date of survival.

Endpoints

The primary endpoint was the R0 resection rate. The secondary endpoints were the rates of complications, recurrence rates, and 5-year DSS rate.

Statistical analysis

Categorical variables were expressed as frequencies and proportions. Quantitative data were expressed as medians [ranges (maximum–minimum)].

Results

Patient characteristics and endoscopic findings

The clinical characteristics of the recruited patients and the endoscopic findings from the lesions are shown in Table 1. Among the 11 patients, one patient had two different lesions, which were independently resected in two sessions. Therefore, a total of 11 consecutive patients with 12 lesions were treated in 12 ESMR-L sessions. Of the 11 patients, 6 (54.5%) were men and 5 (45.5%) were women. The median age of the 11 patients was 68 years (range, 50–83 years) at the date of the initial ESMR-L procedure to treat DNET. Of the 12 lesions, 11 (91.7%) existed in the duodenal bulb, of which 10 (83.3%) were in the anterior wall, and the remaining one (8.3%) existed in the descending part of the duodenum. All lesions were diagnosed as NETs by forceps biopsy before treatment. These lesions

Table 1. Patient characteristics and endoscopic findings.

Patients/lesions/ESMR-L sessions, no.	11/12/12
Age at the date of initial ESMR-L, median (range), years old	68 (50-83)
Gender, no. (%)	
Male	6 (54.5%)
Female	5 (45.5%)
Location of the lesions, no. (%)	
Bulb	11 (91.7%)
Anterior wall	10 (83.3%)
Posterior wall	1 (8.3%)
Descending part	1 (8.3%)

ESMR-L, endoscopic submucosal resection using a ligation device.

were all judged to be smaller than 10 mm by endoscopy or endoscopic ultrasound.

Short-term outcomes

The short-term outcomes of the ESMR-L are shown in Table 2. All 12 lesions were resected *en bloc*. Nine *en bloc* resections had tumor-free margins (R0 resections, 75%), and eight lesions (66.7%) were judged to be pathologically completely resected. The overall curability was 66.7%.

Within 12 sessions of ESMR-L, there were no adverse events, including intraoperative or delayed bleeding, and perforations.

Among the four patients who had non-curative resections, three were judged as non-curative because of a positive vertical margin. Two patients underwent additional surgery after the ESMR-L procedure was performed. The clinical characteristics of the lesions in these patients and the pathological diagnoses of additional surgery are summarized in Table 3. One lesion was judged to be non-curative due to lymphovascular involvement. Histological assessment of the surgically resected specimen in this patient revealed lymph node metastasis around the common hepatic artery.

The other resection was noncurative for vertical margin involvement. The ESMR-L procedure for

Table 2. Short-term outcomes of ESMR-L.

Size, median, mm (range)	6 (5–10)
Depth	
Limited within submucosa, no. (%)	12 (100%)
Invasion to muscularis propria, no. (%)	0
Histology	
NET G1, no. (%)	12 (100%)
NET G2, G3, no. (%)	0
En bloc resection, no. (%)	12 (100%)
R0 resection, no. (%)	9 (75%)
Pathological complete resection, no. (%)	8 (66.7%)
Curability	
Curative, no. (%)	8 (66.7%)
Non-curative, no. (%)	4 (33.3%)
Adverse event, no. (%)	
Bleeding	0
Perforation	0

ESMR-L, endoscopic submucosal resection using a ligation device; NET, neuroendocrine tumor; G1/2/3, grade 1/2/3; R0 resection, complete resection.

this resection is shown in Figure 2. Ligation by the O-ring was insufficient, which resulted in a positive margin. Additional surgery revealed that the tumor remained at the ESMR-L site.

Long-term outcomes

The long-term patient outcomes after resection are presented in Table 4. There were no local recurrences or metastases during a median follow-up period of 5.7 years. Of the 11 patients, 2 (18.2%) died of benign diseases. The 5-year OS and 5-year DSS rates were both 100%.

Discussion

Historically, ER has been developed to resect mucosal tumors; endoscopic mucosal resection (EMR) is a conventional method used to resect small lesions.[31] On the contrary, endoscopic submucosal dissection (ESD) is an innovative technique developed to enable the resection of lesions without limitations in shape or size, regardless of the presence of ulceration and fibrosis in the submucosal layer under the lesion.[32] Both endoscopic procedures are also used to resect SMTs, including DNET.

The use of ESD for DNET is attractive, as it provides a direct view of the distant side of the tumor when dissecting the deep submucosal layer under the tumor, which may achieve a high incidence of negative vertical margins. The rate of R0 resection was 67–100% in previous reports, although each study contained an extremely small number (3–8) of lesions.[6,9,11–14,22–24] It is important to note that it is technically difficult, because the wall of the duodenum is thin, which may result in perforation, and the working space is small due to the narrow duodenal lumen. In fact, perforations occurred in most studies on ESD for DNET with an incidence of 25–67%.[9,13,14,23] Moreover, Kim *et al.*[6] reported that the rate of bleeding is higher in ESD cases than in conventional EMR or ESMR-L.

In contrast, EMR is a simple procedure that does not require a high level of technique.[6,25,29] Nevertheless, the problem is that the rate of R0 resection is often insufficient in resection for SMT, including DNET; achieving negative vertical margins is especially difficult.[25,29] Therefore, EMR has been modified to improve the rate of vertical margin negativity by adding a pre-procedure circumferential mucosal incision (EMR-P)[6,7] or using a cap (EMR-c)[25,26] or ligation device.[6,8,10] EMR-c seems feasible, considering a review by Brito *et al.*,[33] which described the incidence of perforation and bleeding in EMR-c as 8% and 12%, respectively. Regardless, EMR-c is not sufficient for achieving complete pathological resection.[25] The effectiveness of EMR-P in improving margin involvement is still controversial.[6,7] Although achieving R0 resection is the ultimate goal for ER, there is a report that argues that margin involvement is not related to recurrence because the remnant tumor cells might be coagulated by the heat of the snare during endoscopic removal.[29] In contrast, Ragheb *et al.*[34] recently reported that a positive margin was a statistically significant risk factor for recurrence. Moreover, the tumor remained at the local site in a positive margin case in the present study, which was surgically resected after ESMR-L. Therefore, we believe that DNET must be resected without margin involvement.

Table 3. Histopathological findings of non-curative ESMR-L specimens.

	Location	Size	Depth	Diagnosis	LY	v	HM	VM	Surgery	Residual tumor at primary site	Lymph node metastasis
Case 1	Bulb AW	10	SM	NET G1	0	0	X	1	Yes	+	−
Case 2	Bulb AW	4	SM	NET G1	1	1	0	0	Yes	−	+
Case 3	Descending part	5	SM	NET G1	0	1	0	1	No		
Case 4	Bulb AW	6	SM	NET G1	0	0	X	1	No		

AW, anterior wall; ESMR-L, endoscopic submucosal resection using a ligation device; G1, grade 1; HM, horizontal margin; LY, lymphatic invasion; NET, neuroendocrine tumor; SM, submucosa; VM, vertical margin.

ESMR-L, a simple method for resecting DNET, is the best option among various ER procedures, as DNET with indication for ER is restricted in tumors smaller than 10 mm and limited within the submucosal layer.[35,36] Furthermore, ESD, a high-risk procedure for DNET[6,9,11,13,14,23] that requires a high level of technique, is not essential. Recently, endoscopic full-thickness resection (EFTR) has been useful for resecting gastrointestinal lesions. EFTR is an endoscopic procedure that allows the removal of a whole layer of the gastrointestinal tract wall. However, there are only few reports used for DNET with limited number of cases.[35–37] Although successful negative margins seem high by EFTR, extraintestinal structures adjacent to the site of lesions such as vessels, bile duct, and small intestine might be damaged. In contrast, ESMR-L is undoubtedly safe. EFTR would be an alternative for additional surgery, when margin involvement was revealed by other ER procedures. The advantages of ESMR-L compared to other procedures are as follows: a high rate of R0 resection,[8,10,27,28] rare occurrence of perforation,[6,8] small wounds that can easily be closed by clipping (Figure 1), and simple procedure.[8,10] Conversely, Kim *et al.*[6] reported that the pathological complete resection rate was only 25% in ESMR-L for DNET, which was significantly lower than that of rectal NET, thus speculating that this was caused by insufficient suction due to the fear of perforation. Similarly, we also performed resection with vertical margin involvement, which seemed to be caused by insufficient suction and inappropriate ligation by the ring (Figure 2). Therefore, it is important to ensure that the whole tumor is completely included in the ring and confirm that the base of the lesion is thoroughly ligated before resection. The core tip for adequate ligation is to provide sufficient time for the ring to completely shrink to avoid a positive vertical margin. If the ring is located at the side of the tumor and is not completely shrunk, pushing the ring toward the base of the tumor using the tip of a snare or injection needle is helpful. Ligating again with another ring is an alternative.

To prevent perforation, sending air to extend the duodenal wall after ligation is important to exclude the undesired involvement of the muscular layer in the ring. Indeed, there are a few reports of ESMR-L for DNET that experienced a case of perforation.[27,28] As for submucosal injection before ligation, Oono *et al.*[10] reported that it could be omitted without additional complication rates
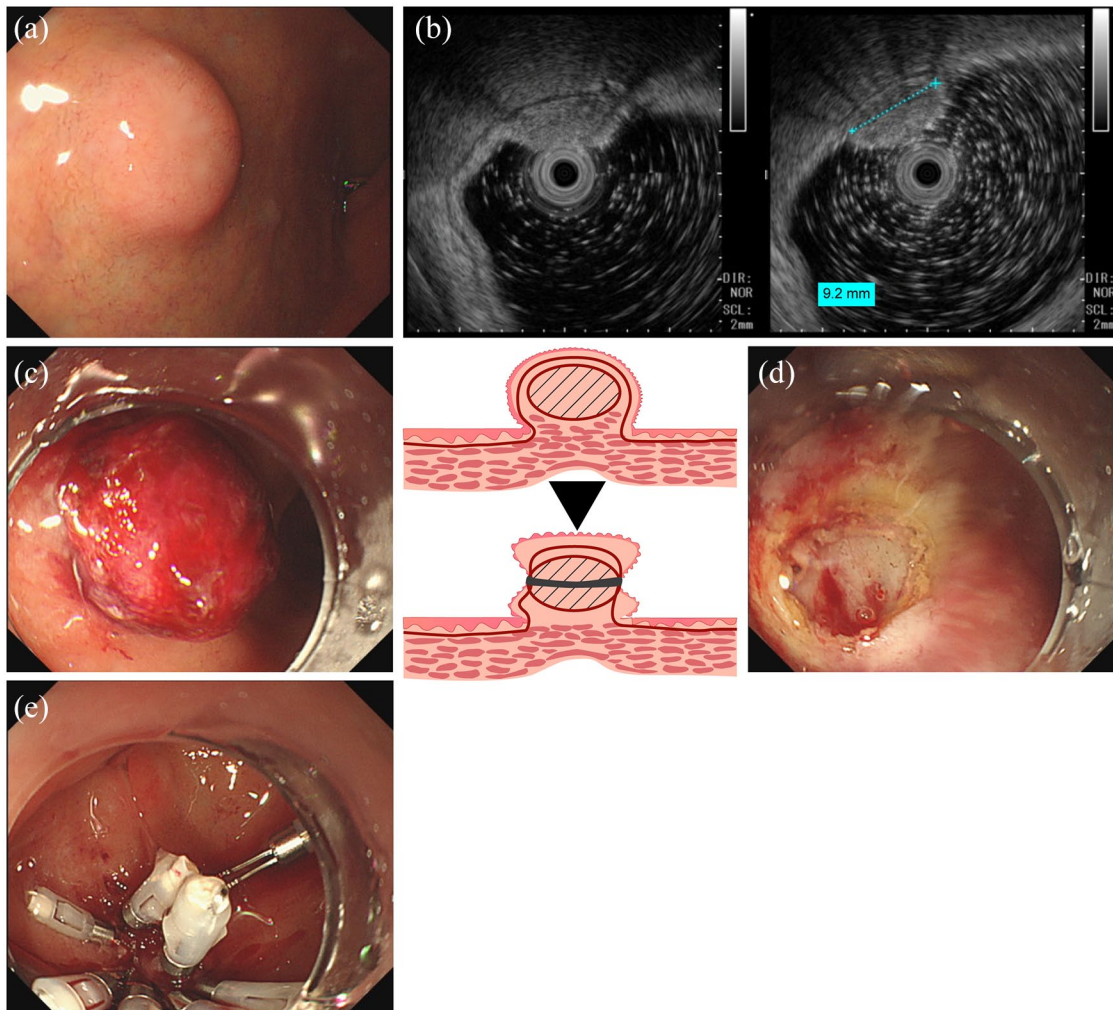
Figure 2. A case of ESMR-L with a positive vertical margin. (a) The tumor is located at the anterior wall of the duodenum. (b) EUS shows the tumor located at the submucosal layer, without invasion to the muscularis propria, with a diameter of 9.2 mm. (c) Ligation by O-ring. The O-ring is ligated to the side of the tumor. (d) After resection, there is no damage to the muscular layer. (e) The wound is completely closed using hemoclips. ESMR-L, endoscopic submucosal resection using a ligation device; EUS, endoscopic ultrasound.

Table 4. Long-term outcomes after initial ESMR-L.

Follow-up period, median (range), years	5.7 (1.9–16.9)
Local recurrence, *n* (%)	0
Lymph metastasis, *n* (%)	0
Distant metastasis, *n* (%)	0
Death	
Due to other malignancies, *n* (%)	0
Due to benign diseases, *n* (%)	2 (18.2%)
ESMR-L, endoscopic submucosal resection using a ligation device.	

compared to ESMR-L with submucosal injection, to shorten the ESMR-L procedure time from 15 to 10 min; they also described that omitting submucosal injection could make it easy to notice a small DNET lesion before ligation, which could become indistinguishable after submucosal injection. A preliminary study using dogs' stomachs reported that ESMR-L without submucosal saline injection resulted in damage to the muscularis propria or perforation in 4 of 15 (26.7%) procedures.[30] Moreover, the duodenal wall is thinner than the gastric wall, which may be associated with a high risk of perforation. These results lead us to believe that submucosal injection of saline must be performed before ESMR-L to prevent perforation, as the advantage of

omitting it is very small (shortening by only 5 min) and the disadvantage (making a small lesion difficult to notice) may be replaced by pre-procedure perimeter marking.

There are some limitations to the present study. First, because it was a single-center, retrospective study, a bias for selecting treatment for each lesion might exist. Second, as DNET within indications for ER are relatively rare, and as this was a single-center study, a small number of lesions were assessed as in previous reports. To reconfirm the usefulness of ESMR-L for treating DNET among various endoscopic procedures, a multicenter study with a large number of lesions is desirable.

To conclude, the tips for ESMR-L are as follows: the perimeter of the lesion must be marked, normal saline should be injected into the submucosal layer, sufficient time (>1 min) should be taken after ligation, the duodenal wall should be extended by filling it with enough air before snaring, the ring should then be appropriately ligated at the base of the lesion, and cutting by snare must be done beneath the O-ring. After resection, the wound should be closed using hemoclips. In keeping with these strategies, DNET within the indication for ER[35,36] is easily and completely resected without complications. ESMR-L seems to be the best-fit procedure for DNET within indications of ER.

Author contribution(s)
Yasuhiro Inokuchi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.
Kei Hayashi: Conceptualization; Writing – review & editing.
Yoshihiro Kaneta: Conceptualization; Writing – review & editing.
Yoichiro Okubo: Conceptualization; Investigation; Writing – review & editing.
Mamoru Watanabe: Conceptualization; Writing – review & editing.
Mitsuhiro Furuta: Conceptualization; Writing – review & editing.
Nozomu Machida: Conceptualization; Writing – review & editing.
Shin Maeda: Conceptualization; Supervision; Writing – review & editing.

ORCID iD
Yasuhiro Inokuchi https://orcid.org/0000-0003-1890-3470

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