Short- and long-term outcomes of endoscopic submucosal dissection for non-ampullary duodenal neuroendocrine tumors

Masafumi Nishio[a], Kingo Hirasawa[a], Yuichiro Ozeki[a], Atsushi Sawada[a], Ryosuke Ikeda[a], Takehide Fukuchi[a], Ryosuke Kobayashi[a], Makomo Makazu[a], Chiko Sato[a], Shin Maeda[b]

Yokohama City University Medical Center; Yokohama City University Graduate School of Medicine, Japan

Abstract	**Background** Endoscopic resection is recommended for non-ampullary duodenal neuroendocrine tumors (NAD-NETs) ≤10 mm in diameter and confined to the submucosal layer, without lymph node or distant metastasis. However, the efficacy and safety of endoscopic submucosal dissection (ESD) for NAD-NET remains unclear. The aim of this study was to assess the short-term efficacy and safety and the long-term outcomes of ESD for NAD-NET.

Methods Eight patients with 8 NAD-NETs who underwent ESD between 2015 and 2018 were included. The indications for ESD were: i) tumor ≤10 mm in diameter; ii) NET G1; iii) confined to the submucosal layer; and iv) without lymph node or distant metastasis. We retrospectively assessed the short- and long-term outcomes and safety.

Results The median patient age was 69 (48-76) years. All tumors were located in the duodenal bulb and showed 0-Is morphology. The median size was 6.4 (3-9.3) mm. The rates of *en bloc* resection, histologically free horizontal and vertical margins, and curative resection were 100%, 88%, and 88%, respectively. Intraoperative and postoperative perforation each occurred in 13% of patients, all of whom were treated conservatively and avoided emergent surgery. Delayed bleeding was not observed. No local, lymph node or distant recurrence was observed during a median follow-up period of 34 (18.5-62.5) months.

Conclusions The rates of *en bloc* and curative resection, and histologically free margins were sufficiently high. Although intraoperative and postoperative perforations occurred, emergency surgery was not needed. The results show that ESD is an efficacious and safe treatment for NAD-NET.

Keywords Duodenum, endoscopic resection, endoscopic submucosal dissection, neuroendocrine tumor, treatment outcome

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Introduction

The gastrointestinal tract is the most frequent site of neuroendocrine tumors (NETs) [1]. Duodenal NETs occur less frequently than gastric and rectal NETs, accounting for <5% of the total number [1,2]. However, these tumors are being recognized at an increasing frequency with the widespread use of gastrointestinal screening endoscopy [3].

According to the European Neuroendocrine Tumor Society guidelines, endoscopic resection is recommended for non-ampullary duodenal neuroendocrine tumors (NAD-NET) ≤10 mm in diameter and confined to the submucosal layer, without lymph node or distant metastasis [4,5]. Various methods of endoscopic resection, including endoscopic mucosal resection (EMR), EMR with ligation device (EMR-L), EMR with circumferential precutting (EMR-P), cap-assisted EMR (EMR-C), and endoscopic submucosal dissection (ESD), have been reported in previous studies [6-18]. However, there is no consensus regarding the preferred method of endoscopic resection for NAD-NET.

Previous studies have reported that ESD was superior to EMR for achieving *en bloc*, R0 and curative resections of rectal NETs [19-21]. ESD for NAD-NETs is reportedly technically difficult and associated with a high frequency of complications;

[a]Division of Endoscopy, Yokohama City University Medical Center (Masafumi Nishio, Kingo Hirasawa, Yuichiro Ozeki, Atsushi Sawada, Ryosuke Ikeda, Takehide Fukuchi, Ryosuke Kobayashi, Makomo Makazu, Chiko Sato); [b]Department of Gastoenterology, Yokohama City University Guradate School of Medicine (Shin Maeda), Japan

however, it achieves better *en bloc* and curative resection rates than EMR [13-18]. Since there are only a few published studies with a very small number of patients, we aimed to assess the efficacy and safety of ESD for NAD-NET over a longer period and with a slightly higher number of cases.

Patients and methods

Enrolled patients and tumors

Between January 2015 and September 2018, 8 consecutive patients with 8 NAD-NETs underwent ESD at Yokohama City University Medical Center. In all cases, esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS; high-frequency miniprobe, UM-2R, 20MHz; Olympus, Tokyo, Japan), and computed tomography (CT) were performed before ESD. We confirmed that all patients met the following criteria before ESD: i) histological diagnosis of NET G1 via endoscopic biopsy; ii) tumor ≤10 mm in diameter on EUS; iii) confined to submucosal layer on EUS; and iv) no regional lymph node enlargement or distant metastasis on CT. The procedures were performed in accordance with the Helsinki Declaration of the World Medical Association.

ESD procedures

All patients underwent ESD under sedation with intravenous propofol (0.8-2.0 mg/kg/h) administered using an exclusive pump (Telfusion pump; TERUMO, Tokyo, Japan) and pentazocine (15 mg). A single-channel upper gastrointestinal endoscope with a water-jet system (GIF-Q260J; Olympus) was used. Several spots were marked at least 5 mm outside the border of the lesion with the Dual knife (Olympus). After injection of 0.4% hyaluronic acid solution (MucoUp; Johnson & Johnson Medical Co., Tokyo, Japan) into the submucosa, the mucosal incision was performed outside of the markings using the Dual knife to achieve negative horizontal margins. After mucosal incision, submucosal dissection was also performed using the Dual knife (1.5 mm). To achieve negative vertical margins, submucosal dissection was performed as close to the muscle layer as possible. A high-frequency generator (VIO 300D; ERBE, Tübingen, Germany) was used during mucosal incision and submucosal dissection: mucosal incision was performed using ENDO CUT I mode (Effect 2), and submucosal dissection was performed using SWIFT COAG mode (Effect 3, 40W). Carbon dioxide insufflation was used during all ESD cases. In 7 cases, the artificial ulcer that developed after ESD was covered with a polyglycolic acid (PGA) sheet (Neoveil; Gunze Co., Kyoto, Japan) and fixed in place with fibrin glue (Beriplast P Combi-Set; CSL Behring Pharma, Tokyo, Japan) to prevent delayed perforation. All procedures were performed by an experienced endoscopist who had previously performed more than 20 duodenal ESDs for epithelial tumors (Fig. 1).

Histological evaluation

After fixing in 10% formalin and serial sectioning at 2-mm intervals, the resected specimens were assessed
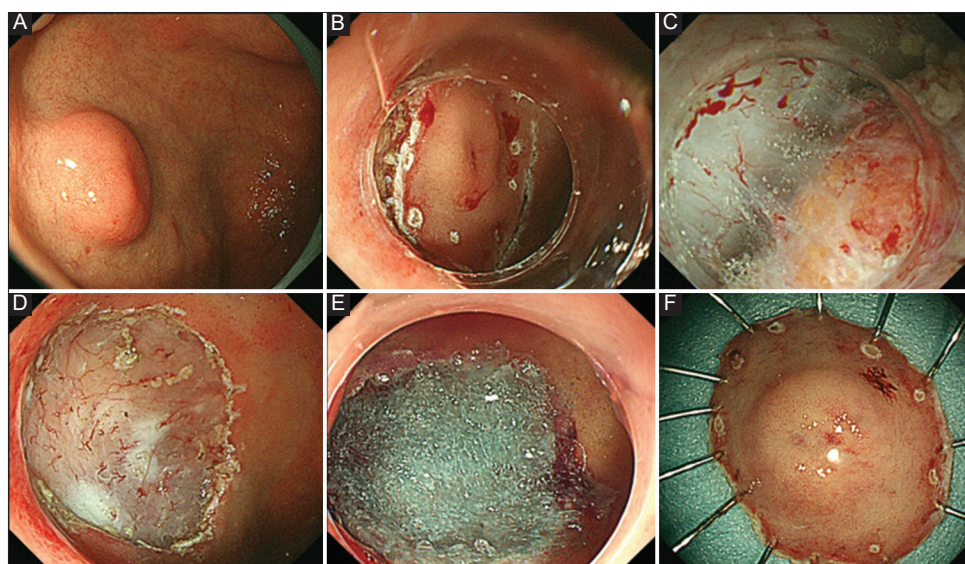

Figure 1 Endoscopic submucosal dissection technique. (A) A non-ampullary duodenal neuroendocrine tumor is observed in the anterior wall of the duodenal bulb. (B) Mucosal incision is performed using the Dual knife after marking with dots around the tumor. (C) Submucosal dissection is performed using the Dual knife (1.5 mm) as close to the muscle layer as possible. Since few Brunner's glands exist just below the tumor, we should be careful not to injure the tumor when submucosal dissection is at that site. In contrast, when the lifting of the submucosal injection around the tumor is insufficient because of abundant Brunner's glands, we should be careful not to injure the muscle layer to avoid intraoperative perforation. (D) The tumor is completely removed with no intraoperative perforation. (E) The artificial ulcer after endoscopic submucosal dissection is covered with a polyglycolic acid sheet, fixed in place with fibrin. (F) The tumor is resected *en bloc*

histologically. Experienced gastrointestinal pathologists assessed the histological type, macroscopic appearance, tumor size, depth of invasion, lymphatic and vascular involvement, and horizontal and vertical margins. For classification of histological type, the World Health Organization (WHO) 2010 classification of tumors of digestive system was used [22]. Immunohistochemical analysis with 2 well-characterized neuroendocrine markers, chromogranin A and synaptophysin, was performed to reach an accurate diagnosis. In addition, the Ki-67 index was assessed in all cases to classify tumors as G1, G2, or G3 according to the WHO classification.

Definition

En bloc resection was defined as resection of the lesion in a single piece with no endoscopically visible residual tumor. R0 resection was defined as *en bloc* resection with histologically free horizontal and vertical margins. Curative resection was defined as *en bloc* resection of tumor ≤10 mm in diameter confined to the submucosal layer, and without lymphovascular invasion. According to the time of onset, bleeding was subdivided into intraoperative and delayed bleeding [23]. Delayed bleeding was defined as hematemesis or melena that required an endoscopic hemostatic procedure using hemostatic forceps or clips [24]. Intraoperative perforation was defined as perforation occurring during the procedure. Delayed perforation was diagnosed when sudden high fever with peritoneal or retroperitoneal free air on CT occurred postoperatively, in the absence of intraoperative perforation and signs of free air on CT immediately after tumor removal [25].

Follow up

All patients received a standard intravenous dose of proton pump inhibitors (PPIs) for 3 days and were switched to oral PPIs for 4 weeks after the ESD procedure. All patients were followed-up by an annual EGD to check for local recurrence and an annual CT to identify lymph node and distant metastases.

Statistical analysis

Statistical analysis was performed using JMP Pro 12 software (SAS Institute, Cary, NC). Continuous variables are presented as median and range, and categorical variables are presented as percentage. The Kaplan-Meier method was used for the analysis of long-term outcomes.

Ethical approval

This study was approved by the Institutional Review Board of Yokohama City University Medical Center (D1602024). All patients were informed of the risks and benefits of treatment before they underwent the procedure. Informed consent or alternative versions were obtained from all patients included in the study.

Result

Clinicopathological characteristics

The clinicopathological characteristics of the study cohort are summarized in Table 1. Five (63%) of the 8 patients were men. The median age at the time of diagnosis was 69 (range 48-78) years. All patients were asymptomatic, and the tumors were detected incidentally during a screening EGD. All tumors were located in the duodenal bulb and showed 0-Is endoscopic morphology. The median tumor diameter on EUS was 6.4 (range 3-9.3) mm. During the study period, all NAD-NETs were included in the indication of endoscopic resection (ESD or EMR) and none was treated by surgery.

Short-term outcome and pathological findings

The short-term outcome and pathological findings of all cases is summarized in Table 2. The median ESD procedural time was 43 (range 25-98) min. *En bloc*, R0 and curative resection were achieved in 100% (8/8), 88% (7/8), and 88% (7/8) of tumors, respectively. In the single case in which an R0 resection was not achieved, the horizontal margin was negative but the vertical margin of the specimen was positive. All tumors were confined to the submucosal layer and were positive for chromogranin A and/or synaptophysin on immunohistochemical staining. The Ki-67 index was less than 2% in all tumors; therefore, all tumors were diagnosed as NET G1 based on the WHO classification. None of the tumors exhibited lymphovascular invasion. Additional surgical resection was offered to the patient in whom a curative resection was not achieved because of positive vertical margins. However, she rejected the additional treatment and underwent careful observation using EGD and CT after the ESD.

Table 1 Characteristics of patients and tumors in the present study

Characteristics	Value
Age in years, median (range)	69 (48-78)
Sex, n (%)	
Male	5 (63)
Female	3 (37)
Tumor location, n (%)	
Bulb	8 (100)
Descending part	0 (0)
Tumor morphology, n (%)	
0-Is	8 (100)
Tumor size on EUS, median, mm (range)	6.4 (3-9.3)

EUS, endoscopic ultrasound

Long-term outcome

The details of all patients in the present study are shown in Table 3. Patients were followed up for a median of 34.0 (range 18.5-62.5) months after ESD. None of the patients showed evidence of local recurrence, metachronous lymph metastasis, or distant metastasis during the follow-up period. Based on the Kaplan-Meier survival analysis, both the estimated overall survival and progression-free survival rates were 100% (Fig. not shown).

Table 2 Short and long-term outcome of patients with non-ampullary duodenal NETs who underwent ESD

Outcome	Value
Procedural time, median, min (range)	43 (25-98)
Pathological type, n (%)	
NET G1	8 (100)
Tumor size on pathology, median, mm (range)	6.5 (4-9.5)
Invasive depth, n (%)	
submucosal layer	8 (100)
En bloc resection, n (%)	8 (100)
R0 resection, n (%)	7 (88)
Curative resection, n (%)	7 (88)
Complication, n (%)	
delayed bleeding	0 (0)
intraoperative perforation	1 (13)
delayed perforation	1 (13)
Follow-up time, median, months, (range)	34.0 (18.5-62.5)
Local recurrence, n (%)	0 (0)
Lymph metastasis, n (%)	0 (0)
Distant metastasis, n (%)	0 (0)

ESD, endoscopic submucosal dissection; NET, neuroendocrine tumor

Complications

Intraoperative perforation occurred in 1 patient (13%). Stitching using an endoscopic clip was performed immediately after removing the tumor and emergent surgery was avoided. Delayed perforation occurred in 1 patient (13%) on the day following ESD. In this case, free air around the duodenum was found on emergency CT. Since there was no obvious perforation site and the artificial ulcer was fully covered by the PGA sheet during emergency EGD, she was treated conservatively and avoided emergent surgery. Notably, this patient showed positive vertical margins. None of the patients developed belayed bleeding.

Discussion

In the present study, we assessed the short- and long-term treatment outcomes of ESD for NAD-NET in 8 consecutive patients; to the best of our knowledge, this is the largest number reported to date. Soga *et al* reported that metastasis was found in 9.8% of patients with duodenal NET larger than 10 mm in diameter [26]. Therefore, several guidelines recommend endoscopic resection, rather than significantly more invasive open surgery, for duodenal NETs ≤10 mm in diameter and confined to the submucosal layer, with no evidence of lymph node or distant metastasis on CT [4,5,27,28]. Various endoscopic resection methods, such as EMR, EMR-L, EMR-P, EMR-C, and ESD, have been reported in the treatment of duodenal NETs [7,11-14,16-18,29,30]. However, there is no consensus regarding the preferred method of endoscopic resection. We have employed ESD for NAD-NET since 2015 for the following reasons: i) intraoperative perforation requiring emergent surgery occurred in one patient who underwent EMR-L for NAD-NET in 2015; and ii) as we had previously reported, ESD was significantly superior to EMR-L for rectal

Table 3 Clinicopathological characteristics of patients with NAD-NET underwent ESD

No.	Age, year	Sex	Location	Size, mm	Depth	Pathological Morphology	Procedural time, min	*En bloc* resection	R0 resection	Curative resection	Complication
1	70	M	Bulb, AW	5	SM	NET G1	76	Yes	Yes	Yes	No
2	55	F	Bulb, AW	5	SM	NET G1	98	Yes	Yes	Yes	No
3	48	M	Bulb, AW	6	SM	NET G1	35	Yes	Yes	Yes	No
4	77	M	Bulb, SW	7	SM	NET G1	30	Yes	Yes	Yes	No
5	67	F	Bulb, AW	4	SM	NET G1	57	Yes	No (pVM1)	No (pVM1)	Delayed perforation
6	76	M	Bulb, AW	8	SM	NET G1	31	Yes	Yes	Yes	No
7	78	M	Bulb, AW	7	SM	NET G1	25	Yes	Yes	Yes	Intraoperative perforation
8	66	F	Bulb, AW	9.5	SM	NET G1	50	Yes	Yes	Yes	No

AW, anterior wall; ESD, endoscopic submucosal dissection; NAD-NET, non-ampullary duodenal neuroendocrine tumor; NET, neuroendocrine tumor; SM, submucosal; SW, superior wall; VM, vertical margin

NETs in terms of the *en bloc*, R0 and curative resection rates [19].

In the present study, we observed *en bloc*, R0 and curative resection rates of 100%, 88%, and 88%, respectively, after ESD for NAD-NET; these were similarly favorable compared to the previously reported results for rectal NETs (100%, 100%, and 83%, respectively). Several previous studies have shown that ESD achieves better *en bloc* resection, R0 resection and curative resection rates than EMR [19-21]. We had reported that in rectal NETs, the *en bloc*, R0 and curative resection rates were 73%, 63% and 50%, respectively, in an EMR-L group (n=22), and 100%, 100% and 83% in an ESD group (n=24) [19].

In NAD-NETs, several previous studies have reported that the *en bloc*, R0 and curative resection rates of ESD were higher than those of EMR, EMR-L and EMR-C [13-18]. Kim *et al* reported 38 patients with 41 duodenal NETs treated by EMR (n=18), EMR-L (n=16), EMR-P (n=3), or ESD (n=4). In their study, the *en bloc* resection rates in the EMR, EMR-L, EMR-P and ESD groups were 89%, 100%, 100% and 100%, respectively, while curative resection was achieved in 56%, 25%, 33% and 100% [13]. To avoid an additional, invasive surgical resection, accurate pathological evaluation of horizontal and vertical margins is important. EMR is associated with positive vertical margins, or a crush and burn effect on the resected specimen, which leads to difficulties in performing a precise pathological evaluation. Recently, endoscopic full-thickness resection (EFTR) with the full-thickness resection devise (FTRD; Ovesco Endoscopy, Tübingen, Germany) for duodenal tumors had been reported [31,32]. Bauder *et al* reported that complete resection rates were 80% in five subepithelial tumors treated by FTRD. Their results suggested that EFTR is effective for NAD-NET, but the evidence is insufficient because of the small sample size [32]. Therefore, at the moment, ESD is the preferred method for NAD-NET to ensure accurate pathological diagnosis and avoid additional surgical resection for residual tumor.

We also assessed the long-term outcomes of patients with NAD-NET who underwent ESD. In the present study, none of the patients showed any evidence of local recurrence, or lymph node or distant metastasis, during a median follow-up period of 34.0 (range 18.5-62.5) months. In previous studies, local recurrence occurred in 0-18% of patients with NAD-NET who underwent EMR [7,13,14,29,30,33,34], whereas no local recurrences were observed in patients after ESD [13-15,18]. These studies indicated that *en bloc* resection and R0 resection is important for avoiding local recurrence. Similarly to our own, the results from previous studies suggest that ESD is more effective than EMR for maintaining recurrence-free survival after NAD-NET treatment.

We next assessed the complications occurring during ESD for NAD-NET. ESD for duodenal tumors was associated with a higher risk of complications, including bleeding and perforation, than EMR [13,35,36]. In the present study, no delayed bleeding occurred; however, intraoperative perforation and delayed perforation each occurred in 1 patient (13%). ESD for duodenal tumors is more technically difficult than for stomach or colon lesions, because the duodenal wall is very thin and the narrow lumen leads to poor endoscopic maneuverability [13,35,36]. This technical difficulty is considered to be associated with the high frequency of intraoperative perforations. Two small case series of ESD for NAD-NET reported a high frequency of intraoperative perforation: 67% (2/3) [18] and 29% (2/5) [17]. Therefore, ESD for duodenal NETs should be performed by experienced endoscopists. Although ESD is useful for *en bloc* resection and R0 resection, duodenal ESD is technically difficult and is only performed in a few countries. Therefore, duodenal ESD might be unacceptable in western countries. On the other hand, the efficacy of EFTR using an FTRD for duodenal superficial tumors has been reported [31,32]. Since the evidence of EFTR for duodenal NETs is still unclear, comparative studies of the efficacy and safety of ESD and EFTR are needed. In addition, exposure of the artificial ulcer after ESD to bile and pancreatic juice can also lead to delayed perforation [35]. Closure with an endoscopic clip is commonly used for the mucosal defect after ESD. However, in ESD for duodenal bulbus, closure with the endoscopic clip is technically difficult because of the narrow working space and proximity to the pylorus. Therefore, we selected a PGA sheet with fibrin glue for covering the artificial ulcer after ESD in most cases of the present study. Coverage by a PGA sheet with fibrin glue has been shown to be helpful for prevention of delayed perforation after duodenal ESD [37,38]. However, delayed perforation did occur in 1 patient who received PGA sheet coverage with fibrin glue in the present study. Therefore, careful observation of the clinical course after ESD and rapid assessment with blood tests and CT scan are needed if delayed perforation is suspected.

The patients in the present study were followed-up by CT scan for detecting metastasis. The European Neuroendocrine Tumors Society (ENETS) consensus guideline suggests that somatostatin receptor scintigraphy and 68Ga-DOTA-NOC positron emission tomography/CT are useful for diagnosis; however, this modality can lead to follow-up effectiveness. The evidence for these modalities is still insufficient and a study of a larger cohort over a longer term is needed.

The present study has several limitations. First, it was a single-center, retrospective study that assessed the outcome of ESD for NAD-NET. Second, the present study had a small number of patients. However, to the best of our knowledge, this is the largest number of patients undergoing ESD for NAD-NET reported to date. Third, the follow-up period in the present study is somewhat insufficient for detecting metastasis. Considering the rarity of NAD-NET in the general population, a multicenter study involving a larger number of patients with a long follow-up period is needed.

In conclusion, the present study showed that if there is neither lymph node nor distant metastasis evident on CT, ESD is effective and safe for NAD-NETs measuring ≤10 mm in size and confined to the submucosal layer. *En bloc* resection was achieved in all cases and R0 resection in most cases, and there were no recurrences during the follow-up period. However, further multicenter, prospective studies involving larger numbers of patients are needed to assess the efficacy and safety of ESD and to determine the preferred endoscopic resection method in patients with NAD-NETs.

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│  **Summary Box**                                  │
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│  **What is already known:**                       │
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│                                                   │
│  • Endoscopic resection is recommended for non-   │
│    ampullary duodenal neuroendocrine tumors       │
│    (NAD-NETs) ≤10 mm in diameter without          │
│    lymphovascular invasion                        │
│  • Previous studies have reported that endoscopic │
│    submucosal dissection (ESD) was superior to    │
│    endoscopic mucosal resection for achieving *en │
│    bloc*, R0 and curative resection of rectal NETs│
│  • However, the efficacy and safety of ESD for    │
│    NAD-NETs remains unclear                        │
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│  **What the new findings are:**                   │
│  ─────────────────────────                        │
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│  • In NAD-NETs treated by ESD, the rates of *en   │
│    bloc* and curative resection, and histologically│
│    free margins were sufficiently high            │
│  • Intraoperative and delayed perforation occurred│
│    in a few cases, but no emergency surgery was   │
│    needed                                         │
│  • ESD is an efficacious and safe treatment for   │
│    NAD-NET                                         │
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