

[ORIGINAL ARTICLE]

Treatment Results of Endoscopic Mucosal Resection with a Ligation Device for Duodenal Neuroendocrine Tumors

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Abstract:

Objective The vertical margin of neuroendocrine tumors (NETs) removed by endoscopic mucosal resection (EMR) is often tumor-positive. We examine the treatment results of endoscopic mucosal resection with a ligation device (EMR-L) for the removal of duodenal NETs located in the submucosal layer without metastasis. EMR-L can be performed with less technical skill, and the ligation device reduces the rate of positive vertical margin.

Methods Ten consecutive patients with 10 duodenal NETs resected by EMR-L were enrolled. All of the lesions were located in the submucosal layer, were assessed to be free of metastasis, and were confirmed to be NETs pathologically by an endoscopic biopsy. The endoscopic results, pathological results, and prognosis were all examined.

Results The *en bloc* resection rate and endoscopic complete resection rate were both 100%. Complete resection was achieved pathologically in 7 lesions (70.0%). The vertical margins were negative in all cases. Lymphatic vessel invasion was observed in three patients, all of whom underwent additional surgery with lymph node dissection (one of them also exhibited blood vessel invasion and a positive horizontal margin). No evidence of residual tumors or lymph node metastasis was observed in any of the patients. No recurrence was observed in any of the 10 patients (mean follow-up period: 18.6 months). One patient (10.0%) experienced intraoperative bleeding. Perforation occurred in 1 patient (10.0%), but the condition was managed well by conservative therapy.

Conclusion EMR-L was an acceptable method for endoscopically resecting submucosal duodenal NETs, and the NETs resected by EMR-L were tumor-negative in the vertical margins.

Key words: duodenal neuroendocrine tumor, endoscopic mucosal resection with a ligation device, treatment results, vertical margin

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Introduction

The treatments for duodenal neuroendocrine tumors (NETs) have included conventional surgical resection (1), resection by laparoscopic-endoscopic cooperative surgery (2, 3), endoscopic submucosal dissection (ESD), endoscopic mucosal resection (EMR), and endoscopic mucosal

resection with a ligation device (EMR-L) (4, 5). Endoscopic resection is a good choice for duodenal G1 NETs, as the tumors are less than 10 mm in diameter, confined to the submucosal layer, and show low rates of lymph node and distance metastasis (6). Duodenal NETs removed by EMR are prone to have positive vertical margins, although the EMR procedure itself is simple, safe, and time-saving (4). ESD achieves a higher margin-free resection rate than EMR, but

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the procedure poses a high risk of perforation when performed by endoscopists with less experience or skill in endoscopy (7).

Given these risks, our group recommends resection by EMR-L for small duodenal NETs without metastasis. In EMR-L, the submucosal layer is cut by suction with a ligation device to ensure a safe margin. EMR-L requires less technical skill, and snare resection below the band ligation is effective in achieving a negative vertical margin. Earlier evaluations have attested to the acceptable safety and outcomes of EMR-L treatment for rectal NET (8-10). The procedure can be performed safely within a short period of time and allows for a relatively precise histological assessment of the resected margin (11, 12). However, the safety and curative reliability of duodenal EMR-L remain unclear. Osera et al. reported a 100% margin-free rate for the resection of duodenal NET by EMR-L, but only in a population of 5 cases (13). Kim GH et al. and Kim TW et al. reported the treatment outcomes of more than 15 duodenal EMR-L procedures, but they provided no clear data on the margin-free rate in their cases (4, 5).

In this study, we examined the treatment results of duodenal NETs by EMR-L with a close focus on complications and the margin-free rate.

Materials and Methods

Study design

Ten consecutive patients with 10 duodenal NETs who underwent EMR-L from October 2013 to September 2017 at Keio University Hospital were enrolled retrospectively. All lesions were confirmed as NETs pathologically by a biopsy. An assessment by ultrasonic endoscopy [EUS; 20-MHz catheter probes (UM3R, Olympus, Tokyo, Japan)] confirmed the size of each duodenal NET and its localization in the submucosal layer. Computed tomography (CT) confirmed the absence of lymph node and distant metastasis. Tumors measuring more than 13 mm in diameter were excluded from this study, as the maximum diameter of the ligation devices was 13 mm. The indication for EMR-L was a non-functional G1 NET of less than 13 mm in diameter with localization in the submucosal layer and no detectable metastasis according to the guideline for NET (14).

All aspects of this study were approved by the ethical committee of Keio University, School of Medicine.

Endoscopic resection by EMR-L

Endoscopic resection was performed under intravenous sedation (flunitrazepam and pethidine). A conventional endoscope (GIF-Q260J; Olympus, Tokyo, Japan) with a disposable 23-gauge injection needle catheter (Olympus) was used. After submucosal injection of glycerol (10% glycerol and 5% fructose; Chugai Pharmaceutical, Tokyo, Japan) with a small amount of indigo carmine and 0.1% epinephrine, EMR-L was performed by aspirating the lesion into the ligation

device (pneumatic EVL device; Sumitomo Bakelite, Tokyo, Japan), deploying the elastic band, and performing snare resection (SD-210L-10; Olympus, Tokyo, Japan) below the elastic band using a blended electrosurgical current (Endo Cut Q, effect 3, cut duration 1, cut interval 3, VIO 300D; ERBE Elektromedizin, Tübingen, Germany). Mucosal defects remaining after EMR-L were closed using conventional hemoclips (EZ Clip™; Olympus) to prevent any delayed bleeding or perforation (Fig. 1).

Histopathological examinations

The resected specimens were fixed with formalin and serially sectioned at 2-mm intervals for an assessment to determine tumor involvement in the horizontal and vertical margins. The histopathological type, tumor size, depth of invasion, and lymphatic and blood vessel invasion were evaluated microscopically.

Definitions of the treatment results

En bloc resection was defined as resection of the lesion in one piece as opposed to piecemeal resection of the lesion in multiple segments. Endoscopic complete resection was defined as the absence of an identifiable residual tumor on the EMR-L scar by endoscopy, irrespective of *en bloc* resection. Pathological complete resection was defined when the following conditions were met: (i) *en bloc* resection, (ii) G1 NET according to the World Health Organization classification (15), (iii) tumor located to the submucosal layer, (iv) negative horizontal or vertical margin, and (v) no lymphatic or blood vessel invasion.

Evaluations

The endoscopic and pathological results were both assessed. The endoscopic parameters assessed included the *en bloc* resection rate, bleeding rate, perforation rate, delayed bleeding rate, delayed perforation rate, and recurrence rate.

Results

Characteristics of duodenal NETs

The patient characteristics and outcomes of the 10 resected tumors in the 10 patients (7 men and 3 women; mean age, 55.5 years) treated by EMR-L were analyzed. Of the 10 lesions, 6 were located in the duodenal bulb, and 4 were located in the second portion of the duodenum. The mean size of the resected tumors was 7.0 mm (3-12 mm). Endoscopic ultrasonography (EUS) was performed for 10 lesions, all of which extended into the submucosal layer (Table 1).

Overall outcomes of EMR-L for duodenal NETs

All 10 tumors (100%) were removed by *en bloc* endoscopic complete resection. All of the tumors were G1 NETs. The tumors were located in the submucosal layer in every case. Horizontal margin involvement occurred in 1 patient, and the vertical margins were negative in all 10 patients.

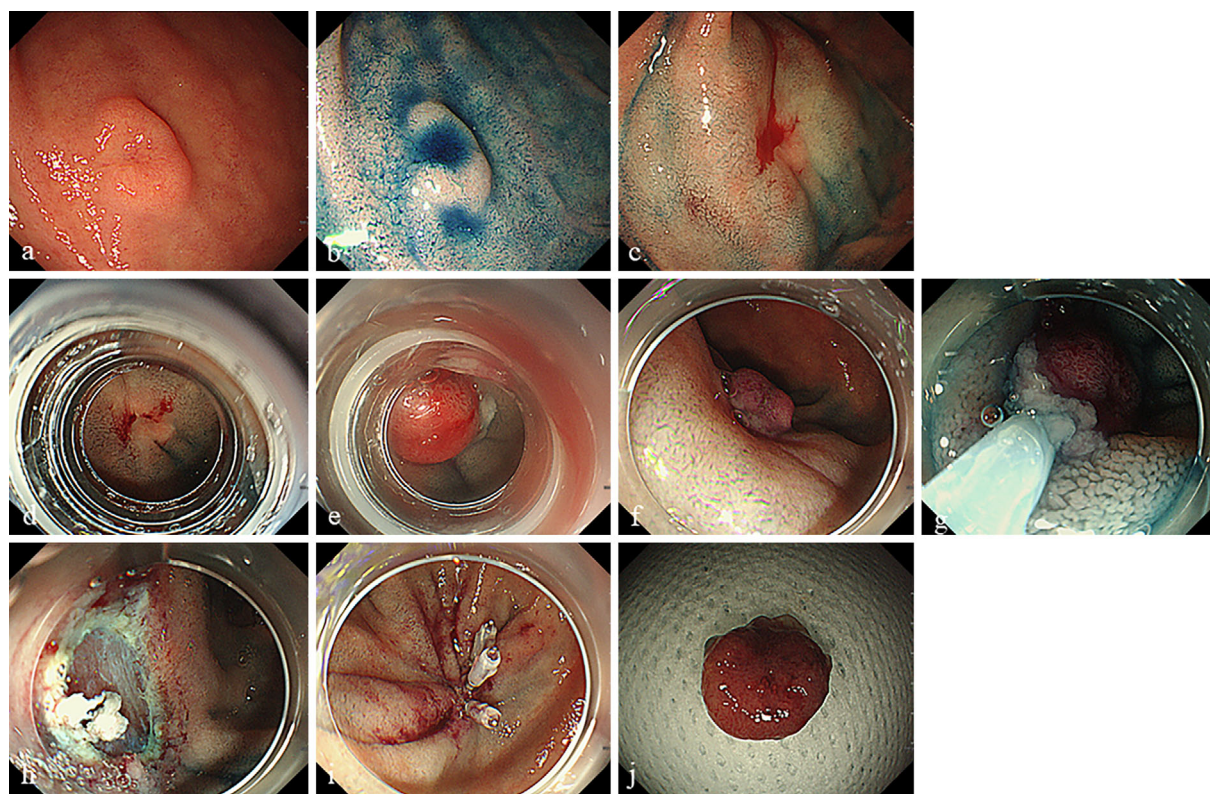


Figure 1. EMR-L procedure. (a) Duodenal NET located in the second portion. (b) Indigocarmine staining revealed a slight depression in the center of the lesion. (c) Injection of glycerol into the submucosal layer. (d) (e) (f) Aspirating the duodenal NET into the ligation device and ligating with the elastic band. (g) (h) *En bloc* resection performed by snaring. (i) Closure of mucosal defects using conventional hemoclips. (j) Resected lesion.

Table 1. Characteristics of 10 Duodenal NETs in 10 Patients who Underwent EMR-L.

Male : Female	7 : 3
Mean age (range, year)	55.5 (39-82)
Location	
Bulb	6
Second portion	4
Tumor size	
≤5 mm	5
5-10 mm	3
>10 mm	2

Lymphatic vessel invasion was observed in three patients, all of whom underwent additional surgery with lymph node dissection: pylorus-preserving pancreaticoduodenectomy with lymph node dissection. No evidence of residual tumor or lymph node metastasis was observed after the surgery (one case also exhibited blood vessel invasion and a positive horizontal margin). As a result, pathological complete resection was achieved for 7 lesions (70.0%) (Table 2) (Fig. 2).

Complications

Intraprocedure bleeding was noted in 1 patient (10.0%). Perforation was noted in 1 patient (10.0%). None of the pa-

Table 2. Overall Outcomes of EMR-L for Duodenal NETs.

Histopathological type	
Well-differentiated	10
<i>En-bloc</i> resection rate	100% (10/10)
Endoscopic complete resection rate	100% (10/10)
Pathological complete resection rate	70.0% (7/10)
Causes for pathological incomplete resection	
Horizontal/vertical	1*/0
Lymphovascular invasion	3*

*Involvement of tumors in the horizontal margin and lymphovascular were observed in one lesions.

tients experienced delayed bleeding or delayed perforation.

Follow-up

No recurrence was observed in any of the 10 patients included in the follow-up (mean follow-up period, 18.6 months; range, 6-52 months).

Discussion

Conventional surgical operations may be unduly invasive for duodenal NETs without metastasis, although determining the appropriate extent of resection for duodenal lesions is difficult (1). Less-invasive therapies by endoscopic resection

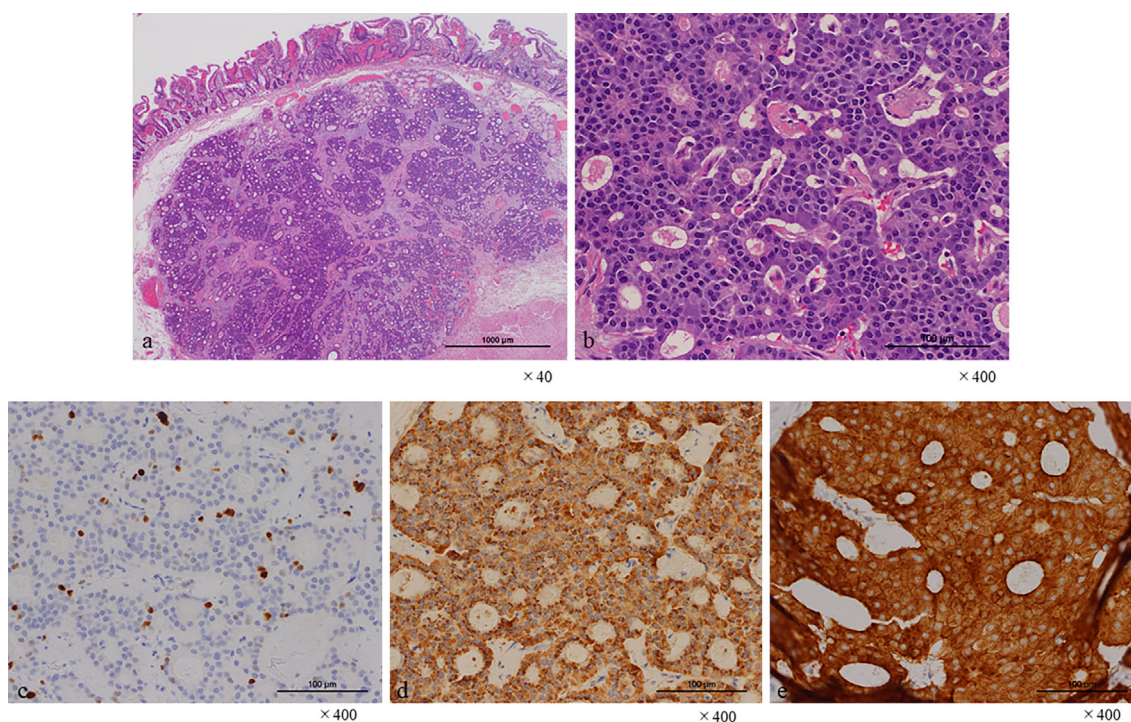


Figure 2. Representative pathological findings of duodenal G1 NET. (a) The tumor was resected from the submucosal layer [$\times 40$, Hematoxylin and Eosin (H&E) staining]. (b) Cells containing round nuclei and pale cytoplasm in ribbon-like arrangements were observed on a histological examination ($\times 400$, H&E staining). (c) The Ki-67 index was $\leq 2\%$ in the duodenal NET ($\times 400$, Ki67 staining). (d) The high expression of chromogranin A in the duodenal G1 NET ($\times 400$, chromogranin staining). (e) The high expression of synaptophysin in the duodenal G1 NET ($\times 400$, synaptophysin staining).

also offer patients an improved quality of life compared with surgical resection. The European Neuroendocrine Tumor Society recommends endoscopic treatment for G1 duodenal NETs that are <10 mm in diameter, limited to the submucosal layer, and have no lymph node or distant metastasis (6). However, the endoscopic treatment strategy for duodenal NETs without obvious metastasis is controversial. ESD may be acceptable for G1 NETs and is more likely to achieve a negative vertical margin just above the muscle layer than EMR. However, reports on ESD for duodenal NET are rare, as the duodenal wall is generally thinner than the wall of the stomach, and the technical difficulty of maneuvering the flexible endoscope in the tiny duodenal lumen heightens the perforation risk (7). When NETs are resected by EMR, the incidence of positive vertical margins is high even though the procedure is far less technically challenging to perform than ESD (4).

In the present study, we used EMR-L to resect duodenal NETs that originated from the submucosal layer, were free from observable metastasis, and were smaller than 13 mm (diameter of the elastic band of the EVL device) upon resection. Instead of normal saline, which is the lifting solution used in previous reports, we used Glycerol[®] as a lifting solution in the expectation that it would provide sufficient lift to prevent perforation (16). We can remove a duodenal NET with a negative vertical margin *en bloc* by resection with snaring under the band. Intraprocedure bleeding was noted

in 1 case (10.0%) and was easily stopped after achieving endoscopic hemostasis with electrocoagulation and hemoclips. Perforation occurred in another case (10.0%), and the perforation site was closed immediately using hemoclips. These two patients recovered non-operatively within four to five days. The perforation rate was lower than that for conventional ESD for duodenal superficial tumors (17-19).

In conclusion, resection by EMR-L for duodenal NET is an acceptable treatment that can be expected to achieve a negative vertical margin if the lesion is located in the submucosal layer, is less than 13 mm in diameter, and is free of metastasis.

The authors state that they have no Conflict of Interest (COI).

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