Endoscopic Mucosal Resection Using Band Ligation (EBL) Will Serve Two Ends in the Treatment for Small Rectal Neuroendocrine Tumors? A Multicenter Retrospective Study

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ABSTRACT

Background: Rectal neuroendocrine tumor (NET)s that are <10mm in diameter can be treated with local excision including endoscopic resection. Endoscopic mucosal resection (EMR) of rectal NETs is often associated with involvement of the resection margin. Endoscopic submucosal dissection (ESD) has more histologically complete resection. However, ESD can lead to more serious complications and longer procedure time than EMR. Endoscopic mucosal resection using band ligation (EBL) is a new technique for eliminating the rectal NET. The aim of this study is to evaluate the therapeutic efficacy and convenience of EBL with that of EMR or ESD for the endoscopic therapy of rectal NET.

Methods: From March 2013 to February 2018, we enrolled consecutive patients with rectal NETs less than 15mm in diameter and without lymph node enlargement. The histologic complete resection rate, length of procedures, and post-procedure complications were retrospectively analyzed.

Results: Twelve NETs were excised by EBL, and 43 lesions were removed by EMR and 20 lesions were resected using ESD. The histologic complete resection rate was 66.7% in the EBL group, 74.4% in the EMR group, and 90.0% in the ESD group ($P=0.249$). The tumor-free deep and lateral resection margins of EBL group were greater than in the EMR group ($P<0.001$ and $P=0.093$, respectively). There was no perforation in any group. Post-procedure bleeding occurred in three cases of EBL and was controlled endoscopically. Additionally, the mean procedure time was significantly longer in ESD than EBL ($p<0.001$). During the follow-up period, two local recurrence and two distant metastasis were detected in the EMR group only.

Conclusions: Compared to EMR, EBL showed similar procedure time and complication rate, lower recurrence rate, lower lymphatic invasion, and deeper tumor free resection margin. EBL is technically easy to perform and can be safely performed in less time than ESD. EBL enables deep vertical resection margins and high complete resection rate comparable to ESD. Considering the benefits of ease, efficiency, and short procedure time, EBL could be considered either an alternative to ESD or an optional therapy for small rectal NET.

Key words: rectal neuroendocrine tumor (NET), endoscopic mucosal resection using band ligation (EBL), endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD)

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INTRODUCTION

Rectal neuroendocrine tumors (NET) comprise 1.1% to 1.3% of all rectal tumors and account for 12.6% of all NETs (1,2). Rectal NET is a subepithelial tumor covered with yellow-discolored mucosa. It is usually found incidentally during diagnostic endoscopy (3). Rectal NET present a wide range of behavioral aspect, from asymptomatic or benign to metastatic or disseminated. Rectal NET increases the likelihood of metastasis in proportion to tumor size. Rectal NETs that are less than 10 mm in diameter and confined to the subepithelial layer represent 3% of metastasis (4-6). Therefore, in small rectal NETs less than 10 mm in diameter, endoscopic resection is a possible therapy and improves quality of life compared to operation (7,8). Rectal NETs more than 2 cm are usually treated surgically. However, no consensus has yet been reached for the treatment of 1 to 2 cm sized rectal NET.

Conventional endoscopic mucosal resection (EMR) is a popularly used and simple procedure to treat small rectal NET. However, most rectal NETs are not limited to the mucosa, but rather invade the submucosal layer. Therefore, EMR frequently produce frequent involvement of the resection margin (14% to 62%). Thus, additional treatment is often required after incomplete tissue resection (9-11).

Endoscopic submucosal dissection (ESD) for rectal NET therapy has the merit of producing a higher complete resection rate than EMR because ESD contains dissection of submucosal tissue just below the lesion (7,8, 12-15). However, ESD is a technically complex and difficult procedure that needs skilled endoscopic techniques. Compared to EMR, ESD may cause higher risk of bleeding or perforation, higher cost, and longer procedure time.

Endoscopic mucosal resection using band ligation (EBL) is another available novel technique for the complete resection of rectal NET. EBL is technically easier than ESD (9,16,17). Compared to EMR, EBL can resect deeper submucosal layer (9,17). There are few studies comparing EBL, EMR, and ESD as endoscopic treatments for rectal NET.

The purpose of this study is to evaluate the therapeutic efficacy and convenience of EBL in relation to EMR or ESD as endoscopic treatment of rectal NET.

PATIENTS AND METHODS

Patients and lesions

A total of 75 patients with rectal NETs who underwent endoscopic treatment from March 2013 to

February 2018 at Eulji University Hospital in Daejeon, Eulji General Hospital in Seoul, and Kyung Hee University Hospital at Gangdong in Seoul, Korea were retrospectively reviewed. No patient had symptoms of carcinoid syndrome. All rectal NETs were found accidentally on screening endoscopy and pathologically confirmed by endoscopic biopsy prior to planned endoscopic therapy. There is still no consensus on the proper therapy for 10-19 mm sized rectal NET (18). But, the Japanese multi-center survey suggests endoscopic resection as first action for rectal NETs 11 to 15 mm in size that are localized to the submucosal layer (19). Therefore, if there was no depression or ulceration, we performed endoscopic resection for rectal NETs estimated to be less than 15 mm in diameter. The gross tumor size was measured using fully open biopsy forceps during endoscopy (6mm in width, FB-25K-1; Olympus Optical Co, Tokyo, Japan). The types of resection methods, such as EBL, EMR, and ESD, were chosen according to the preference of the endoscopist. All patients underwent computed tomography (CT) to assess the extent of pararectal lymph nodes metastasis. In CT scans on patients, all tumors did not have pararectal lymph node metastasis or distant metastasis. Endoscopic observations, procedure time, pathologic complete resection rate, complications, and follow-up findings were analyzed retrospectively.

The ethics committee of Kyung Hee University Hospital at Gangdong approved the study design. Informed consent was gained from each patient (IRB No. KHNMCM 2015-07-012-001, Clinical trial registration No. KCT 0002303).

Endoscopic procedures

Endoscopic mucosal resection (EMR)

We performed EMR with a single-channel endoscope (GIF-Q260, Olympus Medical Systems Corporation, Tokyo, Japan). A mixture of 0.9% saline solution, a small quantity of indigocarmine, and 0.001% diluted epinephrine was injected into the submucosal layer under the NET to reduce resection margin involvement and the risk of perforation. Then, the tumor was caught by the snare and resected using an Endocut Q current (effect 2, cut duration 1, cut interval 4) which was generated by using a VIO300D electrosurgical unit (ERBE Elektromedizin GmbH, Tübingen, Germany). The resected tissue was retrieved by a grasping forcep (Olympus, Optical Co.).

EMR using a band-ligation device (EBL)

A single-channel endoscope (GIF-Q260, Olympus

Medical Systems Corporation, Tokyo, Japan) with a band ligation device (MD-48710 EVL Device; Sumitomo Bakelite Co. Ltd, Tokyo, Japan) mounted on the tip was used. Similar to EMR, the solution described above was injected into the submucosal layer. Then, the tumor was drawn into a band-ligation before the elastic band was deployed. Snare resection was performed under the band in the same way as EMR (fig. 1). To prevent post-procedure bleeding and perforation, the lesion floor was sealed with clip after resection. The resected specimen was aspirated into the cap and then retrieved.

Endoscopic submucosal dissection (ESD)

ESD was carried out using previously mentioned endoscope. To obtain a steady endoscopic vision and to provide countertraction for submucosal dissection to the connective tissue, a transparent hood was

mounted on to the tip of the endoscope. Similar to EBL and EMR, the solution described above was injected into the submucosal layer. After lifting the tumor, a Dual Knife (KD-650 L; Olympus Medical Systems Corporation, Tokyo, Japan) was used to incise the surrounding mucosa of NET. In order to create a sufficient lateral resection margin without a tumor, mucosal incisions were made at least 2 to 3 mm apart around the lesion.

After the mucosal incision, the submucosal tissue under the tumor was dissected step by step from the muscle layer. NET was completely isolated after sufficient submucosal dissection. All mucosal incisions and submucosal dissections were performed using an Endocut Q current (effect 2, cut duration 3, cut interval 4) and a Swift coagulation current (effect 4, 40 W) generated by previously mentioned VIO300D electro-surgical unit. Hemostatic forceps (SDB2422; Pentax HOYA, Tokyo, Japan) were used to control visible

Figure 1 - Endoscopic submucosal resection with a ligation device
(a) A yellowish small NET was noted. (b) Submucosal saline solution is being injected beneath the NET
(c) An elastic band was deployed. (d) Snare resection is being carried out below the band.

Figure 1 - Endoscopic submucosal resection with a ligation device
 (e) Clear resection surface is observed.
 (f) The resection specimen was retrieved.
 (g) The resected floor was endoscopically closed with clips.

bleeding in soft coagulation mode (output 80W). After the NET was removed, endoscopic clipping for the lesion floor was performed in the same way as EBL. The resected specimen was retrieved by suction into the cap or by grasping with a net (Olympus, Optical Co.).

Histopathologic evaluation

The histologic size was assessed as the largest diameter in the freshly removed specimen. All resected samples were fixed in 10% formalin, cut into 2-mm slices, and stained with hematoxylin-eosin. The depth of invasion, vertical and lateral resection margins, and lymphovascular invasion were determined by histologic examination. Histologic complete resection was defined as an en bloc resection without tumor involvement in the lateral and vertical margins of the resected sample and no invasion of the lymphovascular vessels. Resection margin involvement was defined as the presence of a microscopic tumor at the connected cutting edge or thermal distortion that interferes with the evaluation of this section.

Data collection and assessment

The data including histologic complete resection rate, procedure time, and procedure-related complications such as bleeding and perforations were assessed. The procedure time was defined as the time from the beginning of the submucosal injection until the completion of the tumor resection. Bleeding control time after resection was not included.

Complications

Post-procedure bleeding was defined as bleeding requiring hemostasis by endoscopy, radiologic intervention, or surgery, or bleeding with hemoglobin level dropping by 2 g / dL (20). Post-procedure perforation was diagnosed if mesenteric fat or intraperitoneal space was directly observed during the procedure (frank perforation), or free air was detected in the simple chest X-ray after resection without obvious intestinal wall defect identified during the procedure (micro-perforation).

Follow-up evaluation

All patients underwent sigmoidoscopy or colonoscopy, chest CT scan, abdominopelvic CT scan every 6 months for the first 3 years and then every year for 2 years to detect local recurrence, lymph node swelling and distant metastasis after endoscopic resection.

Statistical analysis

The Mann-Whitney or Kruskal-Wallis test was used as a continuous variable. Data analysis was performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). All tests were 2-tailed and P value less than 0.05 was considered statistically significant.

RESULTS

Profiles of patients and tumors

Of the 75 patients included in this study, 12 were treated with EBL, 43 were managed with EMR, and 20 underwent ESD. The baseline characteristics of patients and tumors are shown in *table 1*. The mean age was similar among the EBL, the EMR, and ESD groups (48.1 years, 46.9 years, 50.9 years, respectively, $P=0.439$). The male to female ratio was also similar in the EBL, EMR, and ESD groups (6:6, 25:18, 11:9, respectively, $P=0.878$). Evidence of metastasis to lymph nodes or other organs was not found in the initial evaluation of the patient. The mean diameter of the tumors estimated by endoscopy was 8.42 mm in the EBL, 7.53 mm in the EMR, and 9.45 mm in the ESD group, respectively ($P=0.328$). The mean

pathologic tumor size in the three groups was similar (EBL: 5.20 mm, EMR: 5.86 mm, ESD: 8.90 mm; $P=0.440$). The mean tumor size assessed by endoscopy was larger than the mean tumor size based on pathologic evaluation.

Endoscopy showed that the tumor in the lower rectum was 25.0 % in the EBL group, 53.5 % in the EMR group, and 55.0 % in the ESD group. All tumors showed elevated lesion with a smooth surface. No depressed lesions were observed. There was no difference in the tumor location or tumor size depending on each treatment group.

Clinical results according to endoscopic treatment

The clinical outcomes of the three groups are summarized in *table 2*. All tumors were resected in an en bloc fashion. Pathologically, the tumors were found in the submucosal layer in 100.0% of the EBL group, 97.7% in the EMR group, and 100.0% in the ESD group. Mitosis was observed 75.0% in the EBL group, 11.6% in the EMR group, and 10.0% in the ESD group. Lymphatic invasion was observed 0.0% in the EBL group, 4.7% in the EMR group, and 0.0% in the ESD group. Vascular invasion was not found in any group. Tumor-free lateral resection margin was observed 0.22 mm in the EBL group, 0.31 mm in the EMR group, and 1.56 mm in the ESD group. The tumor-free deep and lateral resection margins of EBL group were greater than in the EMR group ($P<0.001$ and $P=0.093$, respectively).

Involvement of the lateral resection margin was observed 8.3% in the EBL group, 2.3% in the EMR group,

Table 1 - Baseline characteristics of the study groups

Variable	EBL group (n=12)	EMR group (n=43)	ESD group (n=20)		P-value		
					1 vs. 2	1 vs. 3	2 vs. 3
Age, years	48.1±9.5	46.9±10.7	50.9±12.7	0.439	0.582	0.585	0.214
Male, n (%)	6 (50)	25 (58.1)	11 (55.0)	0.878	0.618	0.787	0.816
Tumor size							
Endoscopically estimated tumor size, mm	8.42±3.08	7.53±3.39	9.45±4.97	0.328	0.333	0.953	0.175
Pathologic tumor size, mm	5.20±2.61	5.86±3.54	8.90±7.16	0.440	0.728	0.365	0.228
Tumor location ^a				0.187	0.083	0.103	0.911
Upper rectum	9 (75.0)	20 (46.5)	9 (45.0)				
Lower rectum	3 (25.0)	23 (53.5)	11 (55.0)				

All results are presented as numbers (%) or means ± SDs. EBL: endoscopic submucosal resection with a ligation device; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection.

^aTumor location was defined as lower portion (≤ 7.5 cm from the anal verge) and lower portion (7.6-15 cm from the anal verge).

Table 2 - Clinical outcomes according to endoscopic treatment modality

Variable	EBL group (n=12)	EMR group (n=43)	ESD group (n=20)	P-value		
				1 vs. 2	1 vs. 3	2 vs. 3
Pathologic results						
Depth				0.689	0.597	1.000
Submucosa	12 (100.0)	42 (97.7)	20 (100.0)			0.495
Mucosa	0 (0.0)	1 (2.3)				
Mitosis (/10 HPF)					<0.001	<0.001
0.828						
	0 (3 (25.0))	0 (38 (88.4))	0 (18 (90.0))			
	1 (7 (58.4))	1 (4 (9.3))	1 (2 (10.0))			
	2 (1 (8.3))	4 (1 (2.3))				
	20 (1 (8.3))					
Lymphatic invasion	0 (0.0)	2 (4.7)	0 (0.0)	0.470	0.451	1.000
Vascular invasion	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000	1.000
Tumor-free lateral resection margin, mm	0.22±0.41	0.31±0.64	1.56±1.36	<0.001	<0.001	0.003
Tumor-free deep resection margin, mm	0.19±0.42	0.11±0.12	0.30±0.17	0.001	0.903	0.014
Lateral margin involvement	1 (8.3)	1(2.3)	3(15.0)	0.170	0.330	0.587
Deep margin involvement	4 (33.3)	10(23.3)	3(15.0)	0.487	0.483	0.232
Complete resection	8 (66.7)	32 (74.4)	18 (90.0)	0.249	0.597	0.107
Salvage operation	0 (0.0)	1 (2.3)	0 (0.0)	0.689	0.597	1.000
Complication						
Perforation	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000	1.000
Bleeding	3 (25.0)	0 (0.0)	0 (0.0)	<0.001	0.001	0.021
Procedure time, min	9.63±5.89	3.90±1.21	22.80±2.96	<0.001	<0.001	<0.001
Local recurrence during follow-up	0 (0.0)	2 (4.7)	0 (0.0)	0.470	0.451	1.000
Distant metastasis during follow-up	0 (0.0)	2 (4.7)	0 (0.0)	0.470	0.451	1.000
Follow-up period, month	22.8±10.9	56.3±33.5	47.3±43.3	0.005	<0.001	0.436

All results are presented as numbers (%) or means ± SDs. EBL: endoscopic submucosal resection with a ligation device; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection

and 15.0% in the ESD group ($P=0.170$). The rate of lateral resection margin involvement was higher in the ESD group than in the EBL and EMR groups. Involvement of the deep resection margin was observed 33.3% in the EBL group, 23.3% in the EMR group, and 15.0% in the ESD group ($P=0.487$). The rate of deep resection margin involvement was lower in the ESD group than in the EBL and EMR groups.

The histologic complete resection rate was [66.7%; (8 of 12)] in the EBL group, [74.4%; (32 of 43)] in the EMR group, and [90.0%; (18 of 20)] in the ESD group ($P=0.249$). Only one patient (2.3%) who did not undergo endoscopic complete resection after EMR received additional surgery. The remaining patients who underwent histologically incomplete resection did not

undergo additional surgery because they underwent endoscopic complete resection (R1 resection). No patient underwent additional surgical resection after EBL and ESD.

Procedure times and procedure-related complications

The procedure related bleeding occurred in the EBL group only (three cases (25.0%)). All bleeding was controlled endoscopically using clips. There was no perforation in the all three groups. The mean procedure time was significantly longer in the ESD group than in the EBL and EMR groups (22.8 minutes vs. 9.6 and 3.9 minutes, $P < 0.001$).

Follow-up

Endoscopy and CT scans demonstrated that there were two local recurrence in the EMR group [2 cases (4.7%)] and two distant metastasis in the EMR group [2 cases (4.7%)].

DISCUSSION

Rectal NETs are mostly detected at an early stage by active diagnostic endoscopy (1). Rectal NETs are mostly small, and 66 % of NET are less than 10 mm in diameter (3). Risk factors for metastasis in rectal NET are more than 10 mm in diameter, muscle involvement, poorly differentiated neuroendocrine pathology, and lymphovascular invasion. The size of the tumor is considered to be the most important factor associated with metastasis of rectal NETs (3,8,21). The metastatic potential for rectal NETs smaller than 10 mm is less than 2% (18, 22).

Endoscopic resection is widely accepted as a curative treatment method of rectal NET smaller than 10 mm. However, there is still a debate over what the best endoscopic treatment is to easily and effectively remove the rectal NET. Conventional EMR is a widely used simple method to treat small rectal NET. However, most rectal NETs extend to the submucosal layer, so that conventional EMR can not remove the tumor with sufficient vertical resection margins in many cases, even if the tumor is less than 10mm in diameter (7,8,23,24). In the case of incomplete resection of the tumor, additional endoscopic resection of the residual tumor is difficult due to fibrosis that prevents the lesion from being lifted by submucosal injection after initial incomplete endoscopic resection (25). Therefore, complete resection is technically very important in rectal NET treatment strategies.

ESD technique is superior to conventional EMR in terms of higher en bloc and pathologically complete resection in rectal NET therapy. However, ESD is technically complex and difficult, time-consuming, with a significant risk of perforation or bleeding, and is not yet widely accepted in the treatment of colorectal neoplasms (26, 27). The ESD perforation rate for colorectal neoplasms was much higher than the ESD perforation rate for stomach tumors, so the safety profile related to ESD was not established for colorectal neoplasms (13, 14, 28).

Endoscopic mucosal resection using band ligation (EBL) is proposed as another feasible novel effective treatment for rectal NET to overcome the shortcomings of conventional EMR (9,17). EBL can achieve a higher curative resection rate for NET than conventional EMR

by allowing the entire tumor and adjacent submucosal tissue to be aspirated into a cap to remove significantly deeper vertical portions of the submucosal layer below the tumor (9, 16, 17, 29). Compared to ESD, EBL is technically easy and has significantly shorter processing times.

This study shows that EBL is as effective as ESD for rectal NET smaller than 10 mm in complete histologic resection rate (66.7% vs. 90.0%, $p=0.107$). The tumor-free lateral and deep resection margins of EBL group were larger than those of the EMR group ($P<0.001$ and $P=0.093$, respectively). Lymphovascular invasion in rectal NET is known to be associated with poor prognosis and an elevated mitotic rate (30). In this study, invasion of lymphatic vessels occurred only in the EMR group (4.7%). If endoscopists are not experts for colorectal ESD, many complications can occur (12,14). There was no perforation in this study. In this study, the procedure time of ESD was significantly longer than EBL (22.80 vs. 9.63 min; $P<0.001$). EBL, a modified EMR technique, is very easy and simple for endoscopists who have colorectal EMR experience and is a time-saving method compared to ESD. Until now, no lymph node, local, or distant metastases have been found in the EBL or ESD group. During the follow-up period, two local recurrence and two distant metastasis were found in the EMR group. With respect to local recurrence and distant metastasis, EBL is superior to conventional EMR and comparable with ESD.

The advantage of this study is that relatively large numbers of patients with rectal NETs 15 mm in diameter or less were consecutively enrolled. Another strength of this study was a relatively long follow-up period.

The limitation of present study is that this study was not a randomized prospective control study and procedures were performed according to the preference of each endoscopist.

CONCLUSIONS

Compared with EMR, EBL showed similar procedure time, similar complication rate, lower recurrence rate, less lymphatic invasion, and deeper tumor free resection margin. EBL enables a deep vertical resection margin and a high complete resection rate comparable to ESD. In addition, EBL is technically easy to perform and can be safely performed in less time than ESD. Considering the benefits of ease, efficiency, and short procedure time, EBL could be considered either an alternative to ESD or an optional therapy for small rectal NET.

Conflicts of interest

The authors state that there is no interest in the manuscript, including financial, consultants, institutions and other relationships that could lead to prejudice or conflicts of interest.

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