

Comparison between cap-assisted and ligation-assisted endoscopic mucosal resection for rectal neuroendocrine tumors

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Abstract

Background Modified endoscopic mucosal resection (EMR) is considered a treatment option for rectal neuroendocrine tumors (NETs) <10 mm in diameter. In this study, we evaluated the clinical outcomes of cap-assisted EMR (EMR-C) and EMR with a ligating device (EMR-L).

Methods We retrospectively analyzed 158 patients with 162 rectal NETs treated endoscopically at a single Korean tertiary hospital between March 2010 and November 2017. We evaluated the rates of endoscopic *en bloc* resection, histologic complete resection, and procedural complications according to the treatment method.

Results Among 162 rectal NETs, 42 were treated with EMR-C and 120 with EMR-L. The endoscopic *en bloc* resection rate was higher in the EMR-L group than in the EMR-C group (100% vs. 92.9%, $P=0.003$). A trend was observed towards a superior histologic complete resection rate in the EMR-L group, but it was not statistically significant (92.5% vs. 83.3%, $P=0.087$). There were no significant differences in procedural complications ($P=0.870$). In a multivariate analysis, a tumor located ≥ 10 cm from the anal verge was related to histologic incomplete resection ($P=0.039$).

Conclusion EMR-L may be the preferable treatment method, considering both endoscopic *en bloc* resection rate and histologic complete resection rate.

Keywords Rectal neuroendocrine tumor, endoscopic mucosal resection-ligating device, cap-assisted

Ann Gastroenterol 2020; 33 (4): 385-390

Introduction

Rectal neuroendocrine tumors (NETs) account for roughly one third of all gastrointestinal NETs, with the rectum being the second most common site (34.6%) after the small intestine (36.5%) [1]. Recently, incidences of rectal NETs have been increasing. This may be due to an increase in screening colonoscopies, improvement in detection rates by advanced

endoscopic devices, and increased clinical awareness by endoscopists [1-4]. The majority of NETs are asymptomatic and are detected accidentally at an early stage. Given the low risk of metastasis [5,6] and their benign behavior [7], it is recommended that small rectal NETs less than 10 mm in size can be treated by endoscopic resection if there is no lymphovascular invasion, muscularis invasion, or lymph node metastasis [8]. Several studies also suggest that selected tumors 10-15 mm in size can be removed endoscopically if there is no lymph node metastasis or muscularis invasion [5,9-11].

Various endoscopic treatments, such as conventional endoscopic mucosal resection (EMR), modified EMR, and endoscopic submucosal dissection (ESD), are used to remove rectal NETs. Several studies report that complete resection rates of conventional EMR are variable, ranging from 30-70% [12-16]. Modified EMR includes cap-assisted EMR (EMR-C), EMR with a ligating device (EMR-L), and EMR after circumferential precutting (EMR-P). Recent meta-analyses showed that modified EMR and ESD are preferable treatment methods to conventional EMR for the endoscopic resection of rectal NETs, because of their high rates of complete tumor resection [17,18]. The ESD method requires extensive endoscopic experience and the procedure takes more time.

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Conflict of Interest: None

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Received 8 October 2019; accepted 5 February 2020; published online 10 May 2020

DOI: <https://doi.org/10.20524/aog.2020.0485>

Modified EMR is widely used because of its short procedure time and low complication rate compared to ESD. Among the modified EMR techniques, EMR-C and EMR-L are commonly performed, with EMR-P being used more recently.

It is not well established which method of modified EMR provides a better outcome. In general, the choice is typically determined by the operator's preference, along with any cost and equipment considerations. Therefore, the aim of this study was to compare the clinical outcomes of EMR-C and EMR-L. We also evaluated the factors associated with histologic incomplete resection.

Patients and methods

Patients

We performed a retrospective medical chart review and collected data on patients with rectal NETs treated endoscopically at a single Korean tertiary hospital from March 2010 to November 2017. The characteristics of the patients and rectal NETs, as well as the clinical outcomes of endoscopic resection, were analyzed. Abdominal and pelvic computed tomography (CT) and chest radiography were performed in all patients to assess metastasis. Out of 177 patients, 19 were treated using conventional EMR, 40 using EMR-C, and 118 using EMR-L. After excluding the 19 patients who underwent conventional EMR, 158 patients with 162 rectal NETs were enrolled in this study. This study was approved by the Institutional Review Board of our hospital. Informed consent was not obtained because this was a retrospective study.

Endoscopic treatment methods

All endoscopic treatments were conducted by 3 highly experienced endoscopists, who have each performed over 6000 colonoscopies. We recommended EMR-C and EMR-L for rectal NETs <10 mm in diameter and surgery for NETs \geq 20 mm in diameter. For NETs of \geq 10 mm in diameter, endoscopic ultrasonography was recommended to assess the exact size and the depth of invasion before treatment. Endoscopic resection was considered when the tumor was confined to submucosa and was less than 15 mm in size. For NETs sized 16-20 mm, either endoscopic submucosal dissection or surgery was recommended, taking into account the patient's preference and the risk of metastasis. The resection methods for rectal NETs were determined according to the endoscopist's preference. All procedures were performed in the outpatient endoscopy clinic.

The EMR-C procedure was carried out as follows (Fig. 1). A single-channel endoscope (GIF-H260, Olympus, Japan) was used with a transparent cap (reusable oblique distal attachments with rim, MAJ-290, Olympus, Japan) and a crescent-type snare (SD-221L-25, Olympus, Japan). First, a 0.9% saline solution mixed with epinephrine and indigo carmine was injected beneath the tumor to lift the lesion. After a transparent cap had

been fitted to the scope, the crescent-type snare was looped along the inner ridge of the cap. Endoscopic suctioning of the tumor into the cap was performed, followed by closure of the snare.

For the EMR-L technique (Fig. 2), a 0.9% saline solution mixed with epinephrine and indigo carmine was injected into the submucosal layer of the tumor to elevate the lesion. The endoscopic scope was equipped with a ligating device (Stigmann-Goff Clearvu Endoscopic ligator, Conmed, Mexico). After aspiration into the ligating device and deployment of the elastic band, snare resection was performed below the band.

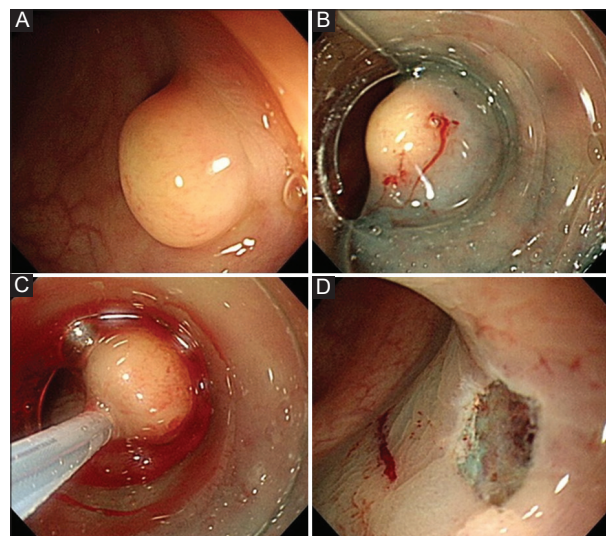


Figure 1 Cap-assisted endoscopic mucosal resection. (A) A yellowish tumor was detected; (B) adequate lift after submucosal injection; (C) endoscopic suctioning of the tumor into the cap followed by closure of the snare; (D) complete resection with no signs of perforation or residual tissue

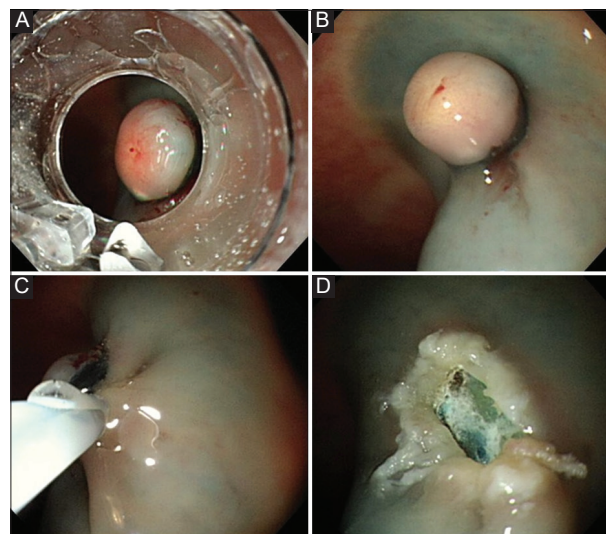


Figure 2 Endoscopic mucosal resection with a ligating device. (A) Aspiration of a tumor into the ligating device; (B) deployed elastic band; (C) snare resection performed below the band; (D) complete resection with no signs of perforation or residual tissue

Outcomes analysis

The histopathologic findings, such as tumor size, depth of invasion, presence of lymphovascular invasion, and status of deep and lateral resection margins, were evaluated by an experienced pathologist. Immunohistochemical staining for neuron-specific enolase and synaptophysin was done to support the diagnosis. Each specimen was graded based on mitotic count and Ki-67 index, according to the World Health Organization's classification.

Endoscopic *en bloc* resection was defined as a resection in one piece during a procedure, and histologic complete resection (H-CR) was defined as a status of no involvement of the tumor in vertical and lateral margins. The procedure time was defined as the period from submucosal injection of the saline mixture to endoscopic resection of the tumor.

Statistical analysis

Data were expressed as mean±standard deviations (SD) for continuous variables and as frequencies and percentages for categorical variables. Differences in patient and tumor characteristics were compared using independent *t*-tests for numerical variables and the chi-square test for categorical variables. Factors related to incomplete histologic resection were assessed using logistic regression analysis. All statistical analyses were performed using MedCalc Statistical Software v.16.2.1 (MedCalc Software, Mariakerke, Belgium). A P-value <0.05 was considered to be statistically significant.

Results

Baseline characteristics

A total of 158 patients with 162 rectal NETs were treated endoscopically. Among 162 rectal NETs, 42 lesions were resected by the EMR-C method and 120 lesions using EMR-L. Four patients had multiple synchronous rectal NETs, 2 NETs in each case. The mean age of enrolled patients was 51.0 (range: 27-80) years, with 91 male (57.6%) and 67 female patients (42.4%). The mean size of tumors was 4.8±2.0 (range: 1.0-12.0) mm, with mean distance from the anal verge 7.8±3.0 (range: 1.0-15.0) cm. Before referral to our hospital, endoscopic biopsy was done in 23 (54.8%) lesions in the EMR-C group and 51 lesions (42.5%) in the EMR-L group. The characteristics of patients and tumors are summarized in Table 1.

Clinical outcomes

The outcomes of EMR-C and EMR-L are summarized in Table 2. Overall, the endoscopic *en bloc* resection rate for both groups (EMR-C and EMR-L) was 98.1% and the H-CR rate was 90.1%. The endoscopic *en bloc* resection rate was higher in

the EMR-L group than in the EMR-C group (100% vs. 92.9%, P=0.003). A trend was observed towards a superior H-CR rate in the EMR-L group, but it was not statistically significant (92.5% vs. 83.3%, P=0.087). Among a total of 16 patients with histologic incomplete resection, the vertical margin was positive in all patients. In 2 patients, both vertical and lateral margins were positive. In most cases, resected tumors were located in the center of the submucosa in the histopathologic image, so all specimens with histologic incomplete resection were positive for the vertical margin, while only 2 cases were positive for both vertical and lateral margins (Fig. 3). There was no difference in procedure time between the 2 groups. Complications occurred in 7 patients (4.4%): 5 patients had

Table 1 Baseline characteristics of patients and tumors

Characteristics	EMR-C (n=42)	EMR-L (n=120)	P-value
Age (years)	49.2±12.2	51.7±10.7	0.208
Male sex	23 (54.8)	68 (56.7)	0.831
Tumor size (mm)	4.6±2.3	4.8±1.9	0.590
Distance from anal verge (cm)	7.2±3.4	7.9±2.8	0.179
Presence of previous biopsy	23 (54.8)	51 (42.5)	0.171
Grade of NETs			0.078
Grade 1	39 (92.9)	118 (98.3)	
Grade 2	3 (7.1)	2 (1.7)	
Grade 3	0 (0)	0 (0)	
Lymphovascular invasion			0.152
Yes	1 (2.4)	1 (0.8)	
No	6 (14.3)	31 (25.8)	
Not identified	35 (83.3)	88 (73.3)	
Depth of tumor			0.599
Mucosa	1 (2.4)	5 (4.2)	
Submucosa	41 (97.6)	115 (95.8)	
Muscularis propria or deeper	0 (0)	0 (0)	

Values are mean±standard deviation or number (%)

EMR-C, cap-assisted endoscopic mucosal resection; EMR-L, endoscopic mucosal resection with ligating device

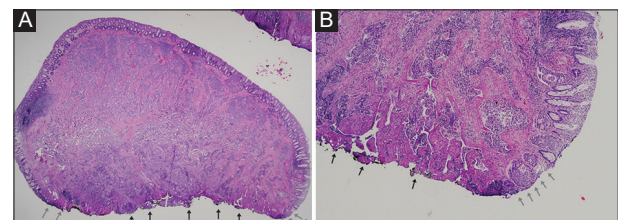


Figure 3 Histopathologic images of a rectal neuroendocrine tumor with both vertical and lateral margin involvements. Vertical (black arrow) and lateral (gray arrow) margin involvements are noted. (A) H&E stain, ×1.5; (B) ×100

Table 2 Clinical outcomes of EMR-C and EMR-L

Outcomes	Overall (n=162)	EMR-C (n=42)	EMR-L (n=120)	P-value
Endoscopic complete resection	159 (98.1)	39 (92.9)	120 (100)	0.003
Histologic complete resection	146 (90.1)	35 (83.3)	111 (92.5)	0.087
Vertical margin positive	14 (8.6)	6 (14.3)	8 (6.7)	0.131
Vertical and lateral margin positive	2 (1.2)	1 (2.4)	1 (0.8)	0.435
Procedure time (min)	5.5±5.2	5.5±2.5	5.5±5.9	0.983
Complication	7 (4.3)	2 (4.8)	5 (4.2)	0.870
Intraprocedural bleeding	5 (3.1)	1 (2.4)	4 (3.3)	0.759
Delayed bleeding	1 (0.6)	0 (0)	1 (0.8)	0.554
Perforation	1 (0.6)	1 (2.4)	0 (0)	0.091

Values are mean±standard deviation or number (%)

EMR-C, cap-assisted endoscopic mucosal resection; EMR-L, endoscopic mucosal resection with ligating device

intra-procedural bleeding, 1 had delayed bleeding, and 1 had a perforation. Complications were treated with endoscopic procedures such as clipping or coagulation therapy. There were no significant differences in the margin status between the 3 operators ($P>0.05$).

Follow up and recurrence

During a 26.2-month (range: 2.6-96.0) median follow-up period, surveillance endoscopic evaluations were performed in 105 (66.5%) patients and abdominopelvic CT (APCT) was performed to assess metastatic recurrence in 80 (50.6%) patients. Among 16 patients histologically incompletely resected, 13 underwent follow-up evaluation with APCT and colonoscopy. No evidence of recurrence was seen on CT and endoscopy.

Risk factors for histologic incomplete resection of rectal NETs

In univariate and multivariate analyses, a tumor located ≥ 10 cm from the anal verge was related to histologic incomplete resection (Table 3). Odds ratios were 2.9 (95% confidence interval [CI] 1.00-8.49; $P=0.048$) in univariate analysis and 3.1 (95%CI 1.05-9.26; $P=0.039$) in multivariate analysis. The tumor size, presence of previous biopsy, and method of EMR were not associated with incomplete histologic resection in multivariate analysis.

Discussion

Various endoscopic treatments, such as conventional EMR, modified EMR and ESD, are used to remove rectal NETs. Modified EMR is widely used because of its high complete resection rates, short procedure times and low complication rates. Among modified EMR methods, EMR-C and EMR-L are commonly used, with EMR-P also used more recently.

EMR-L is the one of the most commonly used methods for modified EMR. EMR-L differs from EMR as the lesion is suctioned into the ligating device and an elastic band is deployed before snare resection. In a study by Mashimo *et al* [19], H-CR using EMR-L was 95.2% ($n=63$), similar to the rate reported for ESD. In another relatively large-scale study comparing EMR-L ($n=45$) and EMR ($n=55$), the overall H-CR was significantly higher for EMR-L than for EMR (93.3% vs. 65.5%) [16]. Other studies showed similar results, such as an H-CR of EMR-L at 93.9% ($n=33$) and 100% ($n=40$) [20,21]. An analysis of 17 studies reported that the complete resection rate of rectal NETs using EMR-L was 94.8% ($n=248$) compared with 72.4% for EMR-C ($n=152$) [5]. Most previous studies have shown a high rate of complete resection in their EMR-L groups.

EMR-C is a widely used treatment method for rectal NETs. Previous studies [13,22-25] reported that EMR-C is an effective method for the endoscopic resection of rectal NETs. However, its H-CR rate varies from 71.7-100%, while the studies included relatively small sample sizes. Some studies have also reported low rates of complete resection [22,23], while others have shown relatively high rates [24,25]. Kim *et al* found a relatively low H-CR, at 83.3%, but their sample size was very small ($n=6$) [22]. Son *et al* [23] also reported tumor-free margins in 71.7% of 53 patients treated with EMR-C. However, Zhao *et al* ($n=10$) reported that the H-CR of EMR-C was 100% [24], while Park *et al* ($n=65$) compared the outcomes of EMR-C with those of ESD and reported high rates of endoscopic *en bloc* resection and H-CR (100% and 92.3%, respectively) in the EMR-C group [25]. Yang *et al* ($n=34$) found similar results, with an H-CR of 94.1% [13]. As mentioned above, the complete resection rate of EMR-C was not consistently high compared with that of EMR-L. These different results among studies, which each assessed the clinical outcomes of EMR-C in a single hospital, may be attributable to the relatively small sample sizes; hence, further large-scale studies are needed to clarify this issue.

According to many previous studies, EMR-L is thought to be superior, or similar, to EMR-C in terms of complete

Table 3 Risk factors for positive resection margin of rectal neuroendocrine tumor

Risk factors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Tumor size ≥ 5 mm (vs. < 5 mm)	1.3 (0.49-3.94)	0.529	1.4 (0.47-4.15)	0.532
EMR-C (vs. EMR-L)	2.4 (0.85-7.10)	0.094	2.6 (0.87-7.80)	0.086
Presence of previous biopsy	0.9 (0.32-2.59)	0.870	0.7 (0.26-2.37)	0.679
Distance from anal verge (≥ 10 cm)	2.9 (1.00-8.49)	0.048	3.1 (1.05-9.26)	0.039

EMR-C, cap-assisted endoscopic mucosal resection; EMR-L, endoscopic mucosal resection with ligating device; OR, odds ratio; CI, confidence interval

resection rates of rectal NETs. In this study, we evaluated the clinical outcomes of EMR-C and EMR-L and found that the H-CR rate did not differ significantly between the 2 groups (92.5% vs. 83.3%, $P=0.087$). However, a numerical trend was observed towards a superior H-CR rate in the EMR-L group, while the endoscopic *en bloc* resection rate was significantly higher in the EMR-L group than in the EMR-C group (100% vs. 92.9%, $P=0.003$). These results could be due to several reasons. For example, since the band thickness used in EMR-L is larger than the thickness of the snare in EMR-C, lateral and deep margins are more easily secured in EMR-L. Additionally, EMR-L uses a technique that resects the tumor by snaring below the band ligation. Although procedural time did not differ significantly between the 2 treatments, until sufficient skill had been acquired through experience it was slightly more difficult to position a snare along the inner ridge of the cap in EMR-C, rather than simply ligating a tumor as in EMR-L. The economic factor may be another factor to consider; that is, the cost-benefit should be considered in the selection of endoscopic treatment method. In the case of EMR-L, the cost of the ligating device is about 20,000 KRW (17 USD). In EMR-C the oblique cap can be reused, making the cost the same as that of conventional EMR. There may be differences in the coverage of cost in medical care, depending on the insurance system in each country, which might influence the selection of treatment methods from the socioeconomic point of view.

Several previous studies [25-28] have reported factors relating to incomplete resection of rectal NETs. However, there are conflicting data regarding which factors, including tumor size and tumor location, are predictors of incomplete resection. Park *et al* [25] demonstrated that treatment method was the only significant factor related to incomplete resection. Lee *et al* [26] showed that both male sex and the treatment methods used were significantly associated with incomplete resection. Kim *et al* [27] found that H-CR was related to the tumor size, regardless of treatment method. Conflicting findings have also been reported regarding the association between tumor location and incomplete resection. The H-CR for lesions was significantly higher in the lower rectum than in the upper rectum (98.3% vs. 50%) [19]. However, another study reported that the location of tumors was not significantly associated with complete resection rates when EMR-L was conducted, in contrast to the results of other EMR methods [16]. In this study, the H-CR was higher in the tumors located < 10 cm from

the anal verge than in those located ≥ 10 cm from the anal verge (93.9% vs. 84.1%), consistent with the results of a previous study [19].

This study had several limitations which need to be addressed. First, it was performed at a single tertiary hospital; thus, the sample size was relatively small and may be insufficient for the generalization of results. Second, there was no randomization of treatment group, as this study was retrospective. Therefore, the number of patients in the EMR-L group was relatively high compared with that in the EMR-C group. Third, the follow-up period was relatively short, and therefore insufficient to assess the recurrence or prognosis of rectal NETs.

In conclusion, although both EMR-C and EMR-L are acceptable treatment methods in the endoscopic resection of rectal NETs, EMR-L may be the preferable method, considering both endoscopic *en bloc* resection rate and histologic complete resection rate. It would be better to select an appropriate treatment method taking the endoscopist's preference into account.

Summary Box

What is already known:

- Modified endoscopic mucosal resection (EMR) is considered a treatment option for rectal neuroendocrine tumors (NETs)
- Recent studies showed that modified EMR and endoscopic submucosal dissection are preferable to conventional EMR for the endoscopic resection of rectal NETs
- It has not been well established which method of modified EMR provides a better outcome

What the new findings are:

- Both EMR-C and EMR-L are acceptable treatments in the endoscopic resection of rectal NETs
- EMR-L may be the preferable treatment method, considering both endoscopic *en bloc* resection rate and histologic complete resection rate

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