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의학석사 학위논문

Clinical Outcomes of Endoscopic Mucosal Resection for Rectal Neuroendocrine Tumor

직장 신경내분비종양의 내시경적 점막절제술의
치료 성적

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내시경적 점막절제술의 치료 성적

Clinical Outcomes of Endoscopic Mucosal
Resection for Rectal Neuroendocrine Tumor

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Abstract

Introduction: The incidence of rectal neuroendocrine tumors (NETs) is rapidly increasing because of the frequent use of endoscopic screening for colorectal cancers. However, the clinical outcomes of endoscopic resection for rectal NETs are still unclear. The aim of this study was to assess the histologically complete resection (H-CR) rate and recurrence after the endoscopic resection for rectal NETs.

Methods: A retrospective analysis was performed in the patients who underwent endoscopic mucosal resection (EMR) of rectal NETs between January 2002 and March 2015 at Seoul National University Hospital. Primary outcomes were H-CR and recurrence rates after the endoscopic resection. H-CR was defined as free of tumor invasion in the lateral and deep margins of resected specimens.

Results: Among 277 patients, 243 (88%) were treated with conventional EMR, 23 (8%) with EMR using a dual-channel endoscope, and 11 (4%) with EMR after precutting. The median tumor size was 4.96 (range, 1–22) mm in diameter and 264 (95%) of the lesions were confined to mucosa and submucosal layer. The en-bloc resection rate was 99% and all patients achieved

endoscopically complete resection. The H-CR rates were 75%, 74% and 73% for conventional EMR, EMR using a dual-channel endoscope and EMR after precutting, respectively. Multivariate analysis showed that H-CR was associated with tumor size regardless of endoscopic treatment modalities ($p=0.001$). Of the 277 patients, 183 patients (66%) underwent at least one endoscopic follow-up. Four out of the 183 patients (2%) with endoscopic follow-up had tumor recurrence with a median of 45 months (range 2-98). There was 1 case of disease-related death occurred 167 months after the endoscopic treatment because of bone marrow failure as a result of tumor metastasis.

Conclusions: Although the en-bloc resection rate was 99% in rectal NETs, H-CR rates were 72-74% for various EMR procedures. H-CR may be associated with tumor size regardless of endoscopic treatment modalities.

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Key Words: Neuroendocrine Tumor; Rectum; Endoscopic Resection; Efficacy; Prognosis

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CONTENTS

Abstract	i
Contents	iii
List of tables.....	iv
List of figures	iv
List of abbreviations.....	v
Introduction	1
Material and Methods	3
Results	7
Discussion	16
References	23
Abstract in Korean.....	27

LIST OF TABLES

Table 1 The clinicopathologic characteristics.....	10
Table 2 Factors associated with histologically complete resection	12
Table 3 Multivariate analysis to determine factors associated with histologically complete resection.....	12
Table 4 Histologically complete resection rates according to endoscopic treatment modalities.....	13
Table 5 Cases with tumor recurrence after endoscopic complete resection.....	14

LIST OF FIGURES

Figure 1 Flow chart showing the inclusion of study patients.	8
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LIST OF ABBREVIATIONS

CIs, confidence intervals; CT, computed tomography; EMR, endoscopic mucosal resection; EMR-D, EMR using a dual-channel endoscope; EMR-P, endoscopic mucosal resection after precutting; Gr, grade; H-CR, histologically complete resection; H-IR, histologically incomplete resection; LVI, lymphovascular invasion; NET, Neuroendocrine tumor; ORs, odds ratios

INTRODUCTION

Rectal neuroendocrine tumors (NETs) are uncommon tumors which account for approximately 10% to 17% of NETs.¹ Rectum is the third most common site of occurrence of NETs. Recently, the incidence of rectal NETs has rapidly increased worldwide due to part to rapid advances in screening endoscopy for colorectal cancer.²

Several parameters have been suggested as predictive factors of the malignant potential including size, histological growth patterns, muscularis propria invasion, and lymphovascular invasion (LVI).³ Approximately 80% of rectal NETs are smaller than 10 mm in diameter, without invasion or metastasis at the time of diagnosis.⁴ As for the small rectal NET, the risk of metastasis is very low and local resection is thought to be curative.^{5, 6} According to previous study, metastasis occurs in less than 3% of tumors smaller than 10 mm in diameter, 5–15% of tumors 10–19 mm in diameter and 80% for those larger than 20 mm.⁷ Endoscopic resection is widely accepted because of its minimal invasiveness, low cost, better quality of life after treatment and patient tolerance. Rectal NETs smaller than 16 mm without lymphatic or distant metastasis can be treated by local excision such as endoscopic resection.⁸

Conventional endoscopic mucosal resection (EMR) has been the treatment of choice. However, conventional EMR often produces incomplete resection of rectal NETs because even small rectal

NETs can invade the submucosa. For this reason, various modified methods of endoscopic mucosal resection including endoscopic mucosal resection after precutting (EMR-P) and EMR using a dual-channel endoscope (EMR-D) have been developed for the treatment of small rectal NETs.⁹⁻¹¹ Previous studies that assessed the prognosis of rectal NETs included surgically resected cases.⁶⁻⁸ However, literature provided only limited information on the efficacy of various EMR modalities and prognosis of rectal NETs after endoscopic mucosal resection.

Therefore, we evaluated the clinical outcomes of endoscopic resection for rectal NETs in terms of the histologically complete resection (H-CR) rate and recurrence after the endoscopic resection. We further assessed the factors that were associated with a histologically complete resection.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of all patients who underwent EMR of rectal NET at Seoul National University Hospital from January 2002 to March 2015. Inclusion criteria were as follows: (1) patients who were of at least 18 years old at endoscopic treatment; (2) patients were identified by pathological diagnosis of rectal NETs. The following patients were excluded from the study: (1) patients who did not achieve endoscopically complete resection; (2) patients who had received endoscopic resection outside our center because we could not assess the clinicopathologic factors at initial treatment.

Endoscopically complete resection was defined as a resection of the lesion without grossly remnant tumor. Clinicopathologic and endoscopic data were retrospectively reviewed using electronic medical records of our institution. The Institutional Review Board of Seoul National University Hospital approved this study.

Endoscopic Procedures

Conventional EMR and EMR-P were carried out with a single channel colonoscope. EMR-D was carried out with single channel colonoscope. Saline solution mixed with a small amount of indigo-

carmine and diluted epinephrine (1:10,000) was injected into the submucosal layer beneath the tumor to reduce the risk of perforation and resection margin involvement. After then, in EMR, snare resection was performed with a electrosurgical current. With EMR-D, the lesion was grasped by alligator forcep; snaring was then performed below the grasping forcep. For EMR-P, marking dots were made on the circumference of the lesion by electrocautery using a hook knife. Mucosal incision in EMR-P enables effective snaring without slippage of the snare.

Evaluation of outcomes

Primary outcomes were H-CR and recurrence rates after endoscopic resection. H-CR was defined as when the lateral and deep margins of the specimens were free of tumor invasion. Secondary outcomes were additive treatment for histologically incomplete resection, procedure-related complications, and disease-related deaths.

All specimens were examined microscopically for histologic type, depth of invasion and resection margin. H-CR was defined as when the lateral and deep margins of the specimens were free of tumor invasion. Otherwise, they were considered histologically incomplete resection (H-IR). We also evaluated differentiation and LVI. Maximum diameter was used as the measure for tumor size.

Pathologic diagnosis was graded according to the 2010 World Health Organization classification of tumors of the digestive system.¹²

The procedure-related complications including bleeding and perforation were assessed. Procedure-related bleeding was classified as immediate when bleeding did not stop spontaneously and required intervention including argon plasma coagulation, electrocauterization or hemoclips, delayed when bleeding occurred later than 24 hours after endoscopic resection. Perforation was readily observed endoscopically or detected by the presence of free air on a plain radiograph taken after procedure.

Follow-up

Subsequent treatments including additional endoscopic resection or surgery were recommended if H-IR or LVI were detected by pathological results. The patient who refused surgery underwent close observation with short-term endoscopic examination. Patients continued to undergo periodic follow-up with colonoscopy or sigmoidoscopy, and/or abdominal computed tomography (CT) scanning.

Statistical analysis

The χ^2 or Fisher's exact test was used for to assess relationships among categorical variables, and the t test or Mann-

Whitney test was used for noncategorical variables. Multivariate logistic regression analysis was used to identify the factors that were associated with H-CR. Variables with p -values less than 0.2 in the univariate analysis were considered for entry into final multivariate analysis. The analysis results are presented as odds ratios (ORs) with 95 % confidence intervals (CIs). Statistical analysis was performed using the software Statistical Package for the Social Sciences v. 15.0 for Windows (SPSS, Chicago, IL) and all the results were considered significant under two sided p -value of less than 0.05.

RESULTS

Patient Selection

A total of 350 patients who underwent EMR for rectal NETs were initially included in our study. Of the 350 patients, the following 73 patients were excluded from analysis: 3 patients who did not achieve endoscopically complete resection; 70 patients who had undergone endoscopic resection at outside hospital. The flow chart showing the inclusion of study patients is shown in Figure 1.

Thus, a total of 277 patients were included in the initial analysis for efficacy of H-CR and factors contributing to H-CR for rectal NETs. Of the 277 patients, 183 patients (66 %) underwent at least one endoscopic follow-up. Finally, these 183 patients were included in the assessment for long-term prognosis.

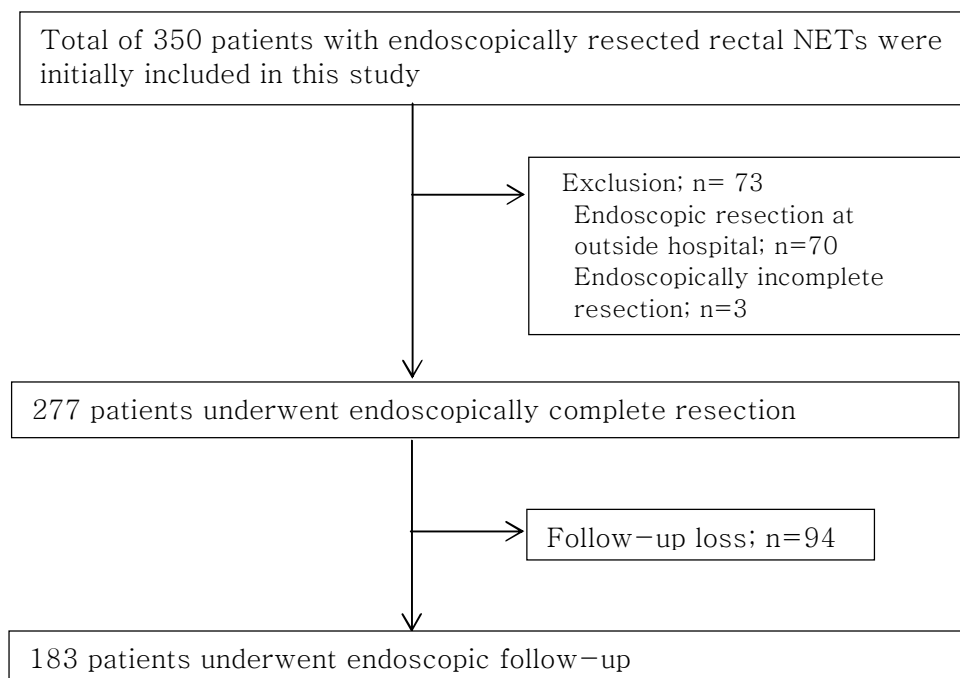
Clinicopathologic Characteristics

Of the 277 patients finally included, the median age at diagnosis was 50.9 years (range, 26 –79) and 170 (61.4%) were male patients. The median distance from the anal verge was 7.1 cm (range, 1–15). Among 277 patients, 243 (87.7%) were treated with conventional EMR, 23 (8.3%) with EMR-D, and 11 (4.0%) with EMR-P. Regarding the number of resection fragments, en-bloc resections were performed in 274 (98.8%) cases and piecemeal

resections in the remaining 3 cases (1.1%).

The histologically estimated median tumor size was 4.96 mm (range, 1–22) in diameter. Rectal NETs less than 10 mm were observed in 256 (92.4%) patients and tumors 10–19 mm and larger than 10 mm in diameter were observed in 20 (7.3%) and 1 (0.3%), respectively. The histological assessment of resection margin indicated H-CR in 206 (74.4%) patients. LVI was founded in 14 (5.1%) patients. **According to WHO classification**, grade (Gr) 1 was founded in 246 cases (88.8%) and Gr 2 in 3 cases (1.1%).

Figure 1. Flow chart showing the inclusion of study patients.



The mitotic index was assessed in 211 (76.2%) patients. Of these, a high mitotic index ($\geq 2/10$ high-power field) was noted only was noted in only 9 (4.3%) patients. Three (1.1%) patients had synchronous rectal NETs at initial diagnosis, and those lesions were removed at the initial endoscopic resection. Tumor invasion was confined in the submucosal layer in 269 (97.3%) patients.

Of the 277 patients, 183 (66.4%) patients continued to undergo follow-up colonoscopy or sigmoidoscopy. The median follow-up period was 32.1 months (range, 2.3–146.0).

Table 1 summarizes the clinicopathologic characteristics of the patients underwent endoscopically complete resection for rectal NET.

Clinical Outcomes

The overall rate of H-CR was 74.4%. A total of 3 patients underwent additive surgery at 1.1 months (range, 0.4–2.3) after initial endoscopic resection because the pathologic examination showed presence of NET cells at the resection margin (n=2) and LVI (n=1). Only one of whom underwent surgery after initial endoscopic resection had residual tumor on the surgical specimen. This patient had not been suspected by endoscopy as having residual disease before surgery. No residual tumor was found in other 3 patients.

Table 1. The clinicopathologic characteristics

Variables	No.
Age, median (range), years	50.9 (26–79)
Gender, male	170 (61.4%)
Endoscopic appearance	
Polyp	22 (7.9%)
Submucosal tumor	255 (92.1%)
Distance from anal verge, median (range), cm	7.1 (1–16)
Treatment modalities	
Conventional EMR	243 (87.7%)
EMR–D	23 (8.3%)
EMR–P	11 (4.0%)
En–bloc resection	274 (98.9%)
Tumor size, median (range), mm	4.96 (1–22)
Group according to tumor size (%)	
<10 mm	256 (92.4%)
10–19 mm	20 (7.3%)
≥20 mm	1 (0.3%)
Histologically complete resection	206 (74.4%)
Negative lateral margin	240 (86.6%)
Negative deep margin	201 (72.6%)
Lymphovascular invasion	
Yes	14 (5.1%)
No	235 (85.1%)
Indeterminate	28 (9.8%)
Grade	
Gr1	246 (88.8%)
Gr2	3 (1.1%)
Not described	30 (10.8%)
Mitotic count	
< 1/10	202 (95.7%)
≥ 2/10	9 (4.3%)
Presence of synchronous rectal NETs	3 (1.1%)
Tumor depth	
Limited to mucosa	5 (1.8%)
Submucosa	264 (95.3%)
Muscularis propria or deeper	0 (0%)
Indeterminate	8 (2.9%)
Follow–up	183 (66.4%)
Follow–up duration, median (range), months	32.1 (2.3–146.0)

Values are presented as median (range) or as numbers (%)

Abbreviations: EMR, endoscopic mucosal resection; EMR–D, EMR using a dual–channel endoscope; EMR–P, endoscopic mucosal resection after precutting; Gr, grade; NET, neuroendocrine tumor

The complications after endoscopic resection occurred in 11 patients (4.0%). All complications were procedure-related bleeding, and 1 patient was delayed bleeding. All bleeding events were successfully managed by endoscopic clipping or coagulation therapy. There was no perforation after treatment.

Factors associated with histologically complete resection

In the analysis of pathologic results, 206 (74.4%) patients were included in the H-CR group and 71 (25.6%) patients were included in the H-IR resection group. Table 2 shows factors associated with H-CR. There were no significant differences between two the groups in age, gender, gross type of tumor and distance from AV. The median size of tumor was significantly smaller in H-CR group than in H-IR group ($p=0.001$).

The variables with p -value less than 0.2 in univariate analysis were tumor size, en-bloc resection, LVI status, and presence of synchronous rectal NETs. However, in the multivariate analysis, only tumor size was significantly associated with H-CR. (Table 3)

The H-CR rate according to endoscopic treatment modalities is shown in Table 4. The H-CR for rectal NETs in conventional EMR group was 74.5%, which was similar to that in EMR-D group (73.9%) and EMR-P group (72.7%). There was no significantly difference in H-CR among the conventional EMR, EMR-D and EMR-P groups (conventional EMR vs EMR-D, $p=0.114$,

conventional EMR vs EMR-P, $p=1.000$, EMR-D vs EMR-P, $p=1.000$).

There was no significant difference between the groups in procedure-related complications (7 (3.4%) in H-CR, 4 (5.6%) in H-IR, $p=0.481$) and in recurrence (2 (1.0%) in H-CR, 2(2.8%) in H-IR, $p=0.272$).

Table 2. Factors associated with histologically complete resection.

Variables	H-CR (n=206) (n, %)	H-IR (n=71) (n, %)	<i>p</i> value
Age, median(range), years	50.0 (26-79)	52.7 (26-73)	0.330
Gender, male	123 (59.7%)	47 (66.2%)	0.333
Endoscopic appearance			0.489
Polyp	15 (7.3%)	7 (9.9%)	
Submucosal tumor	191 (92.7%)	64 (90.1%)	
Distance from anal verge, median, cm	6.34 (1-16)	6.0 (1-15)	0.852
Tumor size, median, mm	4.70 (1-22)	5.70(2-12)	0.001
En-bloc resection	205 (99.5%)	69 (97.2%)	0.162
Lymphovascular invasion			0.158
Yes	10 (4.9%)	4 (5.6%)	
No	179 (87.3%)	56 (78.9%)	
Indeterminate	16 (7.8%)	12 (15.5%)	
Grade			0.668
Gr1	185 (89.8%)	61 (85.9%)	
Gr2	2 (1.0%)	1 (1.4%)	
Not described	19 (9.2%)	9 (12.7%)	
Mitotic count			0.429
< 1/10	148 (94.3%	54 (100.0%)	n/a
≥ 1/10	9 (5.7%)	0 (0.0%)	
Presence of synchronous rectal NETs	1 (0.5%)	2 (2.8%)	0.162

Values are presented as median (range) or as numbers (%)

Abbreviations: H-CR, histologically complete resection; H-IR, histologically incomplete resection; n/a, not applicable; NET, neuroendocrine tumor

Table 3. Multivariate analysis to determine factors associated with histologically complete

	OR (95% CI)	P value
Tumor size	0.90 (0.819–0.99)	0.029
En-bloc resection	5.03 (0.44–58.2)	0.196
Lymphovascular invasion		0.159
No	2.25 (0.97–5.21)	
Yes	1.62 (0.40–0.66)	
Indeterminate	1 (ref)	
Presence of synchronous rectal NETs	5.79 (0.51–66.1)	0.158

Abbreviations: NET, neuroendocrine tumor

Table 4. Histologically complete resection rates according to endoscopic treatment modality.

	H-CR rate, n (rate , %)	P value
Treatment modalities		0.99
Conventional EMR	181/243 (74.5%)	
EMR-D	17/23 (73.9%)	
EMR-P	8/11 (72.7%)	

Abbreviations: H-CR, histologically complete resection; EMR, endoscopic mucosal resection; EMR-D, EMR using a dual-channel endoscope; EMR-P, endoscopic mucosal resection after precutting

Clinical outcomes during follow-up

During a median follow-up period of 32.1 (range, 2.3–146.0) months, the 183 (66.1%) patients were followed by endoscopic evaluation. There were 4 (2.2%) patients of tumor recurrence during follow-up period of median of 104.0 (range 59.3–167.3) months. The clinicopathologic characteristics of these patients are shown in Table 5. Of these, 3 patients were local recurrence and other 1 patient were distant metastasis to liver, bone. In all of these patients had tumor less than 10 mm in diameter.

All patients treated with en-bloc resection; 2 patients underwent conventional EMR and 2 patients underwent EMR-D. In pathologic examination, no patient had a high mitotic index. Two of these patients had been regarded as achieving H-CR at initial endoscopic resection, however, they had indeterminate LVI status. These 4 patients received additive treatments; 3 endoscopic treatment (1 electrocauterization, 2 EMR) and 1 liver metastasectomy.

There was 1 patient with disease-related death who died 156 months after the endoscopic treatment because of bone marrow failure as a result of tumor metastasis. The NET of this patient measured 5 mm in diameter without depression, ulcer, or a high mitotic index and was assessed as endoscopically complete resection but not H-CR. Because the patient refused surgical resection, he underwent annually follow-up with sigmoidoscopy and abdominal ultrasonography. After 70 months of initial endoscopic treatment, the metastasis in liver was founded at abdominal CT, while there was no evidence of local recurrence at sigmoidoscopy. This patient underwent liver metastasectomy. However, the patients died after 8 years of surgery because of disease progression in liver and bone marrow.

Table 5. Cases with tumor recurrence after endoscopic complete resection.

Age (years) /Gender	Initial treatment for rectal carcinoma tumor										Recurred tumor			Treatment	Final outcome
	Size (mm)	En-bloc	H-CR	Depth of invasion	Mitotic count	Grade	LVI	Initial Tx.	Diagnosis after initial resection (months)	Site	Final f/u period (months)				
62/M	5	yes	No*	Submucosa	<1/10	1	indefinite	EMR-D	70.8	Distant meta**	167.3	Liver metastasectomy	Death		
43/M	4	yes	Yes	Submucosa	<1/10	1	indefinite	Conventional EMR	98	Local recurrence	129.3	EMR	NED		
51/F	4	yes	No*	Submucosa	<1/10	1	indefinite	Conventional EMR	2	Local recurrence	59.3	Electrocauterization	NED		
49/F	4	yes	Yes	Submucosa	<1/10	1	indefinite	EMR-D	18.5	Local recurrence	60	EMR	NED		

* Deep margin involved by NETs in two cases.

** Distant metastasis site: liver, bone

Abbreviations: F, female; H-CR, histologically complete resection; EMR, endoscopic mucosal resection; EMR-D, EMR using a dual-channel endoscope; EMR-P, endoscopic mucosal resection after precutting; f/u, follow-up; M, male; NED, no evidence of disease; Tx., treatment

DISCUSSION

In this study, we evaluated the clinical outcomes in 277 patients with endoscopically resected rectal NETs from single center in Korea.

It is well-known that rectal NETs have the smallest in size among gastrointestinal NETs.¹³ Moreover, rectal NETs was found to have the best prognosis among all NETs with 5-year survival rate of 88.2%.² Thus, local excision is considered to be sufficient to treatment for the lesions less than 10 mm in diameter because of extremely low risk of lymph node metastasis.⁵ However, there was no guideline about the management for rectal NETs 10–20mm in diameter.

Conventional EMRs cannot remove the tumors with free vertical margin because of the presence of submucosal layer involvement and increase the need for further treatment.^{14, 15} The ESD applied for deep resection of rectal NETs requires a long learning period, specific devices and longer procedure time than conventional EMR. Therefore, variable new endoscopic modalities including EMR-D, EMR-P or endoscopic submucosal resection with a ligation device (ESMR-L) have been developed and reported to be effective for complete resection compared with ESD.^{16–18}

To date, several studies have reported on factors for H-CR or prognosis in rectal NET after endoscopic resection according to

treatment modalities.¹⁶⁻²⁰ However, those studies were limited by small study populations.

Son *et al.* found that treatment modality was the only factor independently affected the H-CR rate of small rectal NETs.¹⁹ He L *et al.* According to previously reported meta-analysis, ESD or modified EMRs including EMR-D, EMR-L, EMR using a transparent cap (EMR-C), and ESMR-L are superior to EMR, and the efficacy of modified EMR nearly equals to that of ESD in terms of H-CR rate.²⁰ However, our result showed that H-CR rates were 72-74% for various EMR procedures and the only tumor size was significantly associated with the H-CR rate. There was no significant difference among the conventional EMR, EMR-D and EMR-P groups in terms of H-CR rate. According to previous studies, the resection time was significantly longer in modified methods of endoscopic resection including EMR-P, EMR-D, ESMR-L and ESD than in the conventional EMR group.^{18, 21} Thus, considering efficacy of modality including time and resources, conventional EMR would be an efficient modality for treatment of rectal NETs.

In the present study, among the patients with rectal NETs completely removed through endoscopy and underwent at least 1 follow-up endoscopy, total 4 recurrence including 3 local recurrences and 1 development of distant metastasis were occurred after a median of 44.6 months. According to previous literatures, recurrence rate after endoscopic resection for rectal

NET is almost 0–4.2%.^{8, 20, 22, 23} Park *et al.* reported 2 cases of recurrence after endoscopic resection for rectal NETs in 304 patients with a median 48 months follow-up periods.²⁴ Son *et al.* reported neither local recurrence nor metastasis to regional lymph node or distal organs in any of the 153 lesions with the median 31.0 month follow-up period.¹⁹ In previous meta-analysis report, 6 patients had tumor recurrence within follow-up period among the 687 patients with rectal NET removed by endoscopic treatment.²⁰ The recurrence rate after endoscopically complete resection in our study was 2.5% similar to that of reported elsewhere.^{8, 19, 20, 24}

Of note, all recurrence cases had small size less than 10mm in diameter and low mitotic index and were confined in the submucosal layer. Our results showed differences from those recommended in the recent guidelines in terms of the development of tumor recurrence.²⁵ Follow-up is not recommended for rectal NETs less than 10 mm in diameter according to the National Comprehensive Cancer Network guidelines.²⁵ However, in this study, 3 local recurrence and 1 distant metastasis leading to death were observed in small rectal NETs less than 10mm after endoscopic resection during follow-up and occurred even after 6 years in 1 case.

A close relationship has been noted between tumor size and risk of metastasis.^{3, 7, 26} Jetmore *et al.* noted none of the 56 patients with tumors less than 10 mm in size developed metastatic disease during a 32-years follow-up period.²⁷ However, Naunheim *et al.* raised

concerns on the issue of size of the NET. They founded that 13 of 388 patients (3.4 %) patients with rectal NETs smaller than 10 mm in diameter had either metastatic disease on presentation or developed to metastatic disease.²⁸ Although the risk of metastasis from small rectal NETs is generally low, some patients, even those with NETs smaller than 10 mm in diameter, may show metastasis.⁸ Although small tumors have a benign course, our finding of recurrence from 4 of the 152 tumors smaller than 10 mm (2.6%) after excision reminds us that the behavior of these tumors is not easily predicted.

Previous studies suggest that residual macroscopic disease is a poor prognostic factor.²⁹ However, in our study, 97.2% patients with H-IR were free of local recurrence and distant metastasis on follow-up, raising the question of whether H-CR is required to prevent disease progression. However, given the small number of cases with recurrence, further studies about recurrence of rectal NETs after endoscopic resection are warranted to confirm this finding.

In recently published study, CM Moon *et al.* revealed that synchronous rectal NET at the initial diagnosis was associated with the development of development of matachronous rectal NETs.³⁰ Similar results were found in studies of colorectal adenoma. According to previous studied about metachronous colorectal adenoma after resection for colorectal cancer, synchrononous

colorectal adenoma was a risk of the development metachronous lesion.^{31, 32} However, in our study, presence of synchronous rectal NETs showed no significant association with recurrence of NETs after endoscopic resection.

Present study has several limitations. First, this is a single-center study and the number of rectal NETs in modified EMR groups and recurred group are relatively small. Because of this reason, the risk factors of recurrence after endoscopic resection were not analyzed.

Second, because it was a retrospective study, strategies for staging work up and surveillance were not standardized. Thus, the follow-up schedules may differ across the clinicians, because there is no consensus on the treatment strategy and surveillance of rectal NETs in general yet. So, we included the patients who were underwent at least 1 follow-up endoscopic evaluation for analysis for clinical outcome during follow-up. However, there was wide variation in the follow-up periods and some patients might have relatively insufficient follow-up period considering indolent course of NETs. Thus, further study with longer follow-up duration after endoscopic resection for rectal NETs should be required, considering the slow growth rate of NETs.

Third, this study did not include the endoscopic submucosal dissection cases. Because inter-endoscopist variation may be affect clinical outcomes, especially in ESD modality which requires a high level of technical expertise, as discussed before.³³ Moreover,

inclusion period of this study was relatively long period. These may lead to include the early experience with ESD. To minimize inter-endoscopist variation in the various EMR procedures, we excluded the patients with endoscopically incomplete resection in the outcome analysis.

In addition, there were some patients with indeterminate pathology. Especially, all the patients with tumor recurrence had indeterminate LVI state. Two previous studies reported a 7% to 13% risk of regional lymph node metastasis or distant metastasis, and LVI of the submucosal layer by NETs was a risk factor for metastasis.^{6, 8} Even though LVI was not associated with H-CR rate, the influence of LVI on recurrence could not be ruled out in our study. Thus, physicians should consider regular follow-up, especially in cases with indeterminate pathologic result in real practice.

In spite of these limitations, our study is meaningful as it is the largest single-center experience of rectal NETs resected endoscopically and included relatively long follow-up period with endoscopic examination. To our best knowledge, this is the first study about rectal NETs after endoscopic resection with analysis in various aspects including efficacy as the H-CR rate, factors associated with H-CR and long-term prognosis after endoscopic resection.

In conclusion, although the en-bloc resection rate was 99% in rectal NETs, H-CR rates were 72-74% for various EMR procedures. H-CR may be associated with tumor size regardless of endoscopic treatment modalities. Thus, considering efficacy of modality, conventional EMR would be an efficient modality for treatment rectal NETs. There might still have significant recurrence risk in small rectal NETs less than 10mm resected endoscopically, even though with achieving H-CR. Further large-scaled studies are needed to find out the risk factors for recurrence after endoscopic resection, which will help to establish a guideline for treatment small rectal NETs.

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국문 초록

서론: 직장 신경내분비종양의 발생률은 대장암을 위한 내시경적 선별 검사의 증가로 인하여 최근 급격하게 증가하는 추세이다. 그러나 직장신경내분비종양에 대한 내시경 절제술의 치료 성적은 아직 불분명하다. 본 연구의 목적은 직장신경내분비종양에 대한 내시경 절제술의 조직학적 완전절제율과 재발률에 대하여 알아보는 것이다.

방법: 서울대학교병원에서 2002년 1월부터 2015년 3월까지 직장신경내분비종양에 대한 내시경 점막절제술을 받은 환자들을 대상으로 후향적 분석을 시행하였다. 1차 연구목표 변수는 조직학적 완전절제율과 치료 후 종양의 재발이었다. 조직학적 완전 절제는 수직 및 수평 절제연이 모두 음성인 경우로 정의하였다.

결과: 총 277명의 환자 중에서 243 명 (88%)은 고식적인 내시경 점막절제술, 23 명 (8%)은 이중 채널을 사용한 내시경 점막절제술, 그리고 11 명 (4%)은 점막절개 후 내시경 점막절제술로 치료받았다. 종양 크기의 중앙값은 직경 4.96 mm (범위 1-22)였고 264 (95%)의 병변은 점막하층에 국한되었다. 일괄절제술의 비율은 99% 였으며 모든 환자들에게서 내시경적인 완전절제를 달성하였다. 조직학적 완전 절제율은 고식적인 내시경 점막절제술, 이중 채널을 사용한 내시경 점막절제술 그리고 점막절개 후 내시경 점막절제술에서 각각 75%, 74%, 그리고 73% 이었다. 다변량 분석에서 오직 종양의 크기만이 조직학적 완전 절제와 연관성을 나타냈다. 277명의 환자들 중에서 183 명 (66%)이 최소 1번 이상의 내시경적인 추적 관찰을 받았다. 183 명 중 4 명 (2%) 에서 중앙값 45 개월 (범위 2-98) 후 종양의 재발이

관찰되었다. 종양 전이의 결과로 발생한 골수 부전에 의한 1 레 (0.5%)의 질병 관련 사망이 내시경 치료 167개월 후 발생하였다.

결론: 직장 신경내분비종양에서 비록 일괄절제술의 비율이 99% 이더라도, 다양한 내시경 점막절제술의 조직학적 완전절제율은 72-75 % 이었다. 종양의 크기만이 내시경 치료의 종류와 무관하게 직장 신경내분비종양에 대한 내시경 절제술의 조직학적 완전절제와 연관이 있는 것으로 나타났다.

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주요어: 유암종, 직장, 내시경 절제술, 효능, 예후

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