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# Endoscopic treatment of rectal neuroendocrine tumors: a consecutive analysis of multi-institutional data

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**Purpose:** The incidence of rectal neuroendocrine tumors (NETs) is increasing owing to a rise in colonoscopy screening. For the endoscopic removal of NETs, complete resection including the submucosal layer is essential. Therefore, appropriate endoscopic resection techniques are of critical importance. This study aimed to analyze data on rectal NETs and help provide guidance for their endoscopic treatment.

**Methods:** A retrospective analysis was conducted on data from patients who underwent resection for rectal NETs at 6 institutions between 2010 and 2021.

**Results:** A total of 1,406 tumors were resected from 1,401 patients. During a mean follow-up period of 55.4 months, there were 8 cases (0.5%) of recurrence. Overall, a complete resection was achieved in 77.6% of the patients, with modified endoscopic mucosal resection (mEMR) and endoscopic submucosal dissection (ESD) showing the highest rate at 86.0% and 84.9%, respectively, followed by conventional EMR (cEMR; 68.7%) and snare polypectomy (59.0%). In the subgroup analysis, statistically significant differences were observed in complete resection rates based on tumor size. ESD and mEMR demonstrated significantly higher complete resection rates compared with cEMR. Univariate and multivariate analyses showed that tumor location of the lower rectum and advanced techniques (mEMR and ESD) were significant prognostic factors for complete resection rates.

**Conclusion:** When encountering rectal subepithelial lesions on endoscopic examination, endoscopists should consider the possibility of NETs and carefully decide on the endoscopic treatment method. Therefore, it is advisable to perform mEMR or ESD to achieve complete resection, especially for rectal NETs measuring ≤10 mm.

**Keywords:** Colonoscopy; Neuroendocrine tumor; Endoscopic mucosal resection; Endoscopic submucosal dissection

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## INTRODUCTION

Neuroendocrine tumors (NETs) are thought to arise from cells in the diffuse endocrine system. They comprise a broad family of tumors, the most common of which are carcinoid and pancreatic NETs [1]. Regarding their nomenclature, in 1980, the World Health Organization (WHO) proposed the use of the term "carcinoid tumor" for most NETs of the gastrointestinal tract, except for small cell carcinoma and pancreatic islet cell tumor. However, the term "carcinoid tumor" does not convey the malignant potential of these tumors and can be confused with "carcinoid syndrome." Therefore, the term "neuroendocrine tumors" has been accepted for use instead of "carcinoid tumor" [2, 3]. In 2022, the WHO Classification of Tumours continued to evolve, with recent updates further refining the tumor grading, integrating molecular and genetic features, and emphasizing the importance of tumor differentiation [4]. Rectal NETs represent 12% to 27% of all NETs and 20% of gastrointestinal NETs [5, 6]. Rectal NETs are usually asymptomatic, although they may be associated with rectal bleeding or changes in bowel habits and pain. Rectal NETs account for 2% of all rectal neoplasia [7–9]. Regarding prognosis, it is difficult to conclude that rectal NETs exhibit aggressive patterns. Accordingly, approximately 80% of rectal NETs are localized tumors measuring < 1 cm in size that are rarely accompanied by invasion or metastasis at the initial diagnosis. Consequently, during the last 35 years, the overall 5-year survival rate of patients with rectal NETs has increased by almost 20% in the United States [10]. The 5-year survival rate is estimated to be 93% in patients presenting with localized disease and 86% overall [11].

General consensus guidelines for the management of well-differentiated colorectal carcinoids suggest that a local resection is appropriate for tumors measuring < 20 mm confined to the submucosa [12]. The European Neuroendocrine Tumor Society (ENETS) guidelines suggest that rectal NETs measuring ≤ 10 mm are indolent, with a low risk of spread; however, published articles and reports indicate that lymph node metastasis can be observed even in small rectal NETs measuring ≤ 10 mm [13, 14]. The European guidelines for rectal NETs, published by Rinke et al. [15] in 2023, provide recommendations for endoscopic excision based on tumor size. For lesions ≤ 1 cm, endoscopic resection is recommended as the primary treatment. In cases where the tumor size ranges from 1 to 2 cm, both endoscopic resection and transanal microinvasive surgery (TAMIS) are suggested as viable options. Particularly for lesions ≤ 1 cm, the guidelines emphasize the preference for advanced techniques rather than conventional endoscopic mucosal resection (cEMR). Methods such as modified EMR (mEMR), endoscopic submucosal dissection (ESD), and endoscopic full-thickness resection are recommended due to their superior efficacy in achieving complete resection with negative margins, which is crucial in the management of rectal NETs. Kang et al. [16] reported that the overall prevalence of lymphovascular invasion (LVI) in small rectal NETs (≤ 20 mm) was 21.8%. Although the progression may be slow, complete resection is considered important even for small NETs in cases where lymph node metastasis is present, as there is currently no effective chemotherapy for rectal NETs. Additionally, when performing endoscopic removal for rectal NETs, the lesion is typically located within the submucosal layer. As a result, conventional techniques such as snare polypectomy or cEMR may leave residual tumor tissue. Therefore, recent guidelines have increasingly recommended more invasive endoscopic resection methods to ensure complete removal of the lesion [15].

With advancements in colonoscopic equipment and an increase in colonoscopy screening for colorectal cancer, the incidence of small rectal NETs is on the rise. Therefore, in this study, we aimed to collect data regarding rectal NETs removed at various institutions and analyze their characteristics and prognoses. We conducted this study to determine an appropriate management strategy for rectal NETs.

## METHODS

### Ethics statement

This study was approved by the institutional review boards of Daehang Hospital (No. DH24-0001), Hanyang University Seoul Hospital (No. HYUH2024-09-025), and Gibbeum Hospital (No. 001-240724 001). Informed consent was not required as this study was a retrospective analysis using anonymized data.

### Data collection

Six institutions agreed to contribute data to this study. Data from patients who underwent resection for rectal NETs between January 2010 and December 2021 were collected, including patient demographics (including age and sex), clinical data (including symptoms, site and size of tumor, distance from the anal verge [AV], treatment, duration of follow-up, presence of recurrence or metastatic disease), and pathological data (including depth of invasion, LVI, margin status, and nodal involvement). Enrolled patients aged > 18 years were identified from prospective databases maintained at each institution. Patients with rectal neuroendocrine carcinoma were excluded. Data were analyzed retrospectively, and each contributing institution was responsible for obtaining approval from its institutional review board.


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### Diagnosis of rectal NETs

Most rectal NETs are incidentally diagnosed during colonoscopy. If there was a yellowish, hard lesion and rolling sign on endoscopic forceps or instruments, the colonoscopist suspected rectal NETs. If a rectal NET was strongly suspected or confirmed by biopsy prior to resection, a computed tomography (CT) scan was performed before endoscopic polypectomy to confirm lymph node metastasis. If lymph node metastasis was not suspected, endoscopic resection was performed. If lymph node metastasis was suspected, surgery was recommended first. In cases which the colonoscopists may have omitted the consideration of a rectal NET before excision, CT was performed after resection. Radical surgery was recommended if lymph node metastasis was suspected.

### Resection method

Each institution performed endoscopic examinations and selected the resection method based on the examiner's judgment. When the lesions were small or not identified as rectal NETs, cold forceps polypectomy was performed for the removal. Some patients underwent snare polypectomy with or without electrocautery, while others underwent endoscopic mucosal resection (EMR) using various methods, including cEMR, precut EMR (EMR-P), lifting the lesion with a rubber band ligation before EMR (EMR-L), and underwater EMR. The term mEMR includes EMR-P, EMR-L, and underwater EMR. Resection was performed using ESD, transanal excision (TAE), and transanal endoscopic microsurgery (TEM) using laparoscopic instruments. When lymph node dissection was necessary, radical surgery, such as low anterior resection (LAR), was performed. Additional resections such as additional EMR, ESD, or TAE/TEM were carried out based on the presence of positive resection margins if the patients consented.

### Follow-up of rectal NETs

In the follow-up period, an abdominopelvic CT scan and colonoscopy were performed 1 year after the initial endoscopic procedure or surgery. Subsequent follow-up assessments were conducted every 1 to 2 years within the first 5 years post-procedure. If the resection margin was found to be indeterminate or positive after polypectomy, additional endoscopic procedure or surgery was recommended to the patient. In cases where the patient consented, further resection was performed either endoscopically or surgically. However, if the patient declined additional procedures, the follow-up interval was shortened to monitor the resection site via sigmoidoscopy within 3 to 6 months. During this interval, additional biopsies were performed as necessary. If there were no signs of recurrence, colonoscopy or sigmoidoscopy was conducted annually for up to 5 years to confirm the absence of recurrence.

### Statistical analysis

For the primary outcomes, we assessed the complete resection rate of rectal NETs according to different resection methods. Complete resection was determined by microscopic examination of the resected tissue, where a margin without tumor cells was classified as "negative," indicating a complete resection. When the margin status could not be determined accurately due to fragmentation or cauterization of the tissue, it was classified as "indeterminate." Margins that contained NETs were classified as "positive." The secondary outcome was the recurrence rate after resection, which was analyzed accordingly. Parametric variables were given as mean ± standard deviation and were analyzed with Student t-test. Frequencies were analyzed with the chi-square test. Multivariate analysis was conducted using logistic regression analysis. All the analyses were performed using IBM SPSS ver. 20.0 (IBM Corp).

## RESULT

This study analyzed 1,406 rectal NETs from 1,401 patients. The patient and tumor characteristics are presented in Table 1. The median age of the patients at diagnosis was 46 years (range, 19–89 years), and mean age was 53.6 ± 12.7 years. In total, 874 male patients (62.4%) and 527 female patients (37.6%) underwent treatment for rectal NETs. Among the 1,406 rectal NETs, 505 (35.9%) were located in the upper rectum (≥ 8 cm from the AV) and 901 (64.1%) in the lower rectum (< 8 cm from the AV), with the majority in the lower rectum. In 132 cases (9.4%), tissue biopsies (cold forceps biopsy) were performed for confirmation before resection.

Among the resected lesions, 689 (49.0%) were removed using ESD, making it the most common method. This was followed by 403 lesions (28.7%) removed by cEMR. Snare polypectomy was performed in 139 cases (9.9%), mEMR in 57 (4.1%), and cold forceps polypectomy in 16 (1.1%). Surgeries using a transanal approach (TAE/TEM) were performed in 77 cases (5.5%), while 25 (1.8%) were removed by LAR (Fig. 1).

Histological analysis revealed a mean tumor size of 5.6 mm. Among rectal NETs, 550 (39.1%) were measured < 5 mm, 735 (52.3%) were measured 5–9 mm, 111 (7.9%) were measured 10–19 mm, and 10 (0.7%) were measured ≥ 20 mm (Fig. 1). Regarding depth, 1,097 lesions (96.5%) extended into the submucosa. In the analysis of LVI in NETs, data from 1,099 cases were reviewed, of which 988 cases (89.9%) were found to be free of LVI. For perineural invasion (PNI), 249 cases among the enrolled patients were investigated, and 240 cases (96.4%) were free of PNI. Regarding the Ki-67 index, a total of 608 NETs were included in the analysis,

**Table 1.** Characteristics of 1,406 rectal neuroendocrine tumors from 1,401 patients

| Characteristic | Value |
|---|---|
| Age (yr) | 53.6 ± 12.7 (19–89) |
| Sex (n = 1,401) | |
| Male | 874 (62.4) |
| Female | 527 (37.6) |
| Previous management (cold forceps biopsy) | 132 (9.4) |
| Histologic size (mm) | 5.7 ± 3.2 |
| Tumor location (n = 1,406) | |
| ≥ 8 cm from the AV | 505 (35.9) |
| < 8 cm from the AV | 901 (64.1) |
| Depth (n = 1,136) | |
| Mucosa | 28 (2.5) |
| Submucosa | 1,097 (96.5) |
| Muscle | 11 (1.0) |
| Lymphovascular invasion (n = 1,099) | |
| Positive | 111 (10.1) |
| Negative | 988 (89.9) |
| Perineural invasion (n = 249) | |
| Positive | 9 (3.6) |
| Negative | 240 (96.4) |
| Ki-67 index (n = 608) | |
| Low grade (≤ 2%) | 583 (95.9) |
| Intermediate grade (3%–20%) | 24 (3.9) |
| High grade (> 20%) | 1 (0.2) |
| Follow-up (mo) | 55.4 ± 41.6 |
| Recurrence according to tumor size (n = 1,406) | |
| No recurrence | 1,398 (99.4) |
| < 5 mm | 548 |
| 5–9 mm | 732 |
| 10–19 mm | 110 |
| ≥ 20 mm | 8 |
| Local recurrence | 3 (0.2) |
| < 5 mm | 2 |
| 5–9 mm | 0 |
| 10–19 mm | 1 |
| ≥ 20 mm | 0 |
| Distant (systemic) recurrence | 5 (0.4) |
| < 5 mm | 0 |
| 5–9 mm | 3 |
| 10–19 mm | 0 |
| ≥ 20 mm | 2 |

Values are presented as mean ± standard deviation (range), number (%), mean ± standard deviation, or number only.
AV, anal verge.

and 583 cases (95.9%) were classified as low grade with a Ki-67 index below 2% (Table 1). There was a statistically significant increase in the likelihood of LVI with increasing size of the NETs (4.6% for < 5 mm, 10.6% for 5–9 mm, 24.7% for 10–19 mm, and 71.4% for ≥ 20 mm; P < 0.001). However, there was no significant difference in PNI based on size (Table 2).

**Table 2.** Association between LVI/PNI and tumor size

| Neuroendocrine tumor | No. of patients (%) | P-value |
|---|---|---|
| LVI positive (n = 111) | | < 0.001 |
| < 5 mm | 18 (16.2) | |
| 5–9 mm | 64 (57.7) | |
| 10–19 mm | 24 (21.6) | |
| ≥ 20 mm | 5 (4.5) | |
| PNI positive (n = 9) | | 0.870 |
| < 5 mm | 3 (33.3) | |
| 5–9 mm | 5 (55.6) | |
| 10–19 mm | 1 (11.1) | |

LVI, lymphovascular invasion; PNI, perineural invasion.

Among the 1,406 cases analyzed for resection margins, 1,091 (77.6%) were margin-negative, 66 (4.7%) were margin-indeterminate, and 249 (17.7%) were margin-positive (Fig. 1). The complete resection rates according to the resection methods were as follows: cold forceps polypectomy, 31.2%; snare polypectomy, 59.0%; cEMR, 68.7%; mEMR, 86.0%; ESD, 84.9%; and TAE/TEM, 88.3% (Fig. 2A). The size-based complete resection rates were as follows: < 5 mm, 76.4%; 5–9 mm, 78.6%; 10–19 mm, 77.5%; and ≥ 20 mm, 70.0% (Fig. 2B). No significant differences were observed based on size. For patients with margin-indeterminate or margin-positive results, additional resection was performed for those who consented to further intervention. Specifically, mEMR was performed in 12 cases, ESD in 33 cases, LAR in 59 cases, and transanal surgery in 31 cases. During a mean follow-up period of 55.4 months (median, 52.9 months), among the 1,406 cases, local recurrence occurred in 3 cases (0.2%), and systemic recurrence occurred in 5 cases (0.4%) (Table 1). In this study involving rectal NETs < 5 mm, local recurrence occurred in 1 out of 550 treated with EMR, and in 1 case treated with ESD. For NETs measuring 5–9 mm, systemic recurrence was observed in 2 cases out of 735 treated with EMR and in 1 case treated with ESD. Among tumors measuring 10–19 mm, local recurrence was noted in 1 case out of 111 treated with snare polypectomy. For tumors measuring ≥ 20 mm, systemic recurrence was found in 2 cases out of 10, with 1 case occurring after snare polypectomy and 1 case after LAR. Owing to the small number of recurrences, further analyses based on tumor size or resection methods were not conducted.

For rectal NETs measuring ≤ 10 mm, with minimal risk of lymph node metastasis, it is deemed important to determine the complete resection rate according to different endoscopic resection methods. Therefore, subgroup analysis was conducted to as-



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sess complete resection rates. For rectal NETs measuring <5 mm, the complete resection rates were as follows: cold forceps polypectomy, 23.1%; snare polypectomy, 60.7%; cEMR, 72.4%; mEMR, 78.3%; ESD, 87.7%; and TAE/TEM, 93.3% (Fig. 3A). For rectal NETs measuring 5–9 mm, the complete resection rates were as follows: snare polypectomy, 61.2%; cEMR, 64.2%; mEMR, 90.0%; ESD, 85.3%; and TAE/TEM, 88.1% (Fig. 3B). Among the resection methods, including ESD and mEMR, the complete resection rates were significantly higher than those of cEMR (Table 3).

Univariate analysis revealed that surgical resection and advanced endoscopic techniques such as mEMR or ESD achieved a complete resection rate exceeding 80%, indicating superior efficacy. Lesions located in the lower rectum demonstrated a significantly higher complete resection rate compared to those in the upper rectum ($P<0.001$). Although recurrence rates across groups were generally very low and may not carry strong statistical implications, complete resection was significantly associated with a lower recurrence rate (Table 4).

Multivariate analysis confirmed this finding, showing a statistically significant increase in complete resection rates in the lower rectum compared to the upper rectum. When conducting a multivariate analysis, specifically for cEMR, mEMR, and ESD, the same trend was observed, with the lower rectum, mEMR, and ESD emerging as significant factors for complete resection. This finding was consistent on analyzing rectal NETs <10 mm and even when univariate and multivariate analyses were performed using 3 different resection methods: cEMR, mEMR, and ESD. Compared with cEMR, mEMR and ESD were identified as prognostic factors for complete resection (Tables 5–7).

## DISCUSSION

The choice of resection for rectal NETs depends on their features, especially size, grade of differentiation, depth, LVI, increased tu-

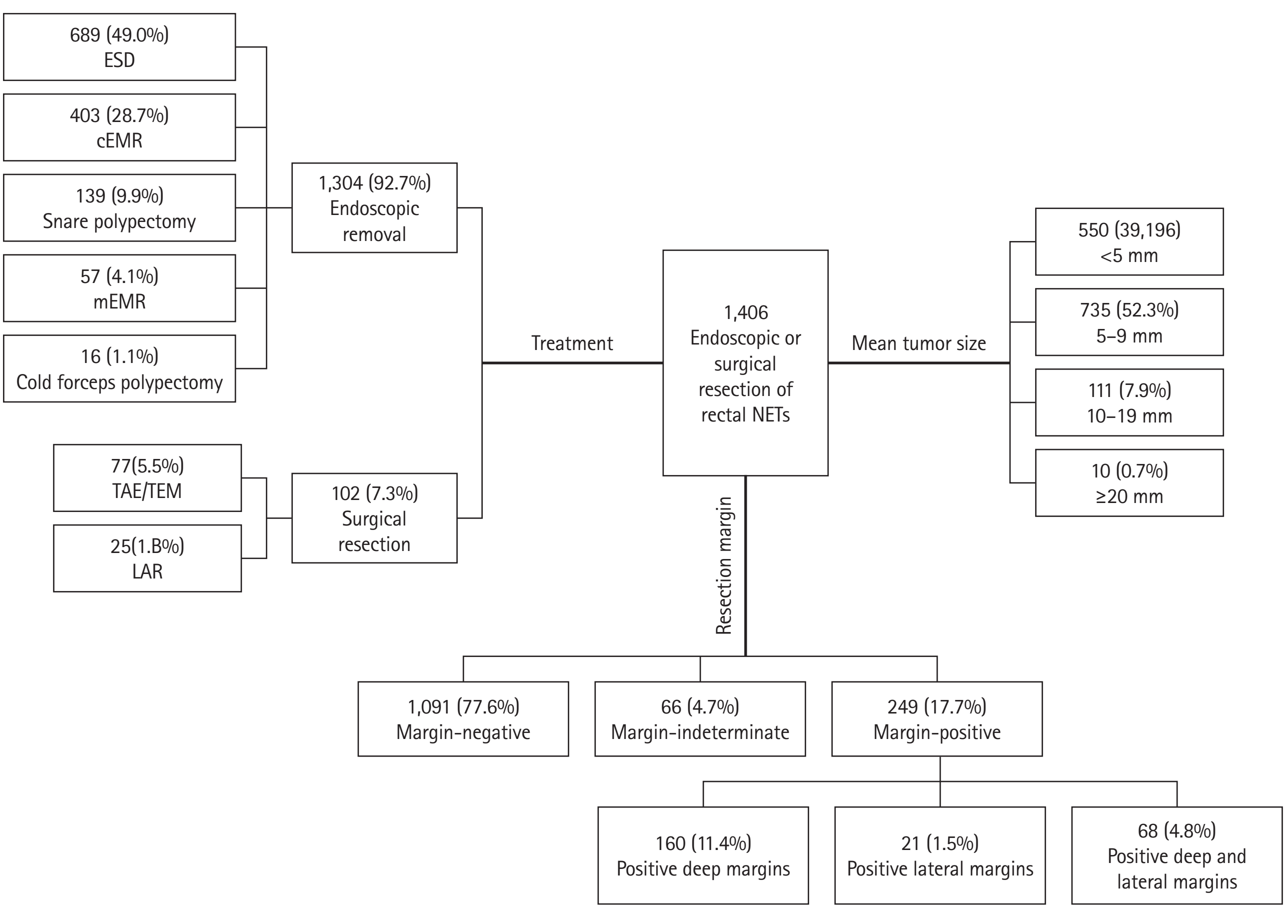


**Fig. 1.** Flow diagram of tumor characteristics. Complete resection was determined by microscopic examination: negative (tumor-free margins), positive (margins with neuroendocrine tumors [NETs]), and indeterminate (unclear margin status due to fragmentation or cauterization). Low anterior resection (LAR) is not performed for rectal NETs less than 5 mm. Cold forceps polypectomy is not performed for rectal NETs larger than 10 mm. Transanal excision (TAE) and transanal endoscopic microsurgery (TEM) have no positive deep margins. NETs removed by LAR were completely tumor-free at the resection margins (negative). cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

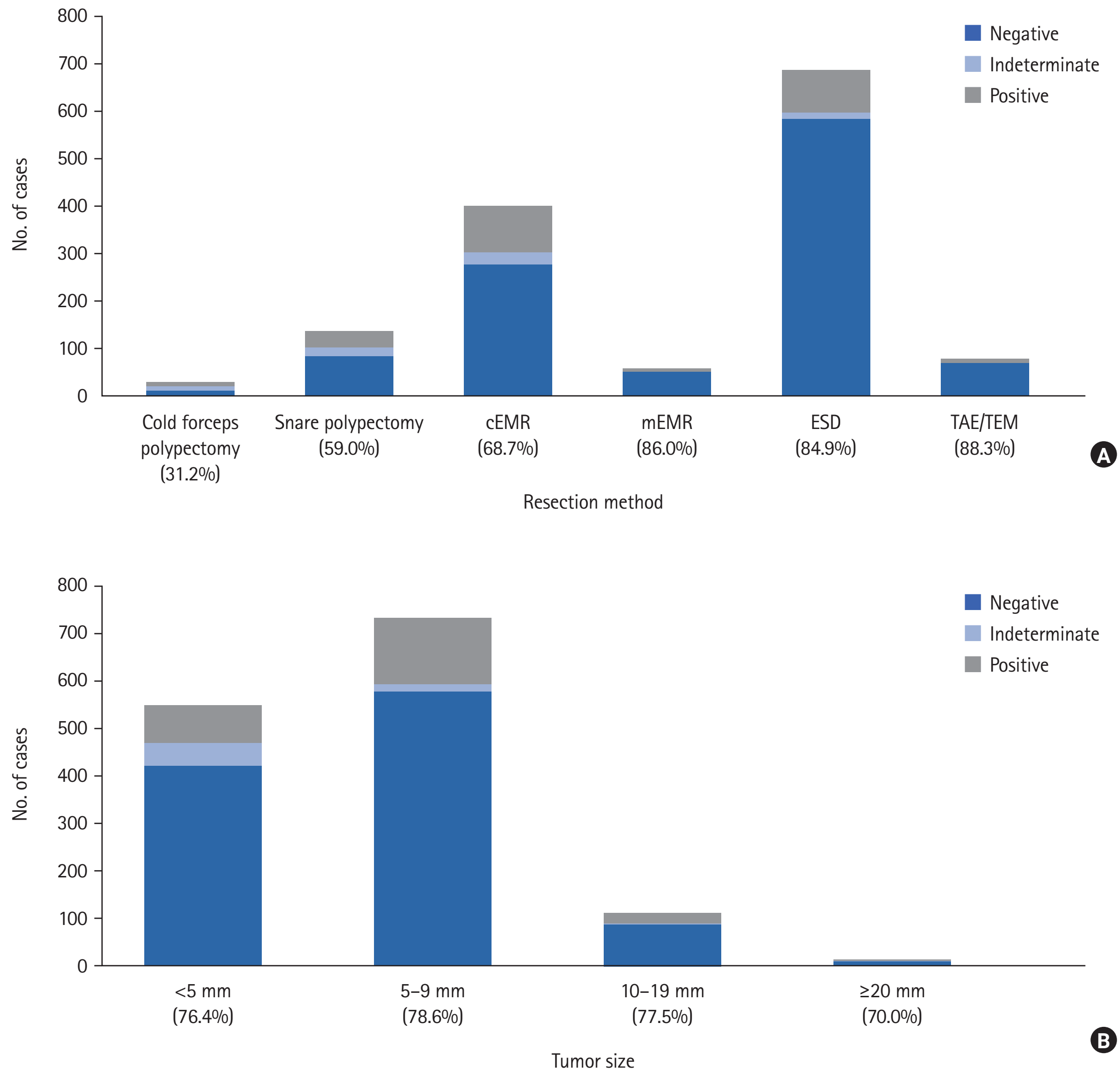


**Fig. 2.** Complete resection rate in excised neuroendocrine tumors (NETs). Complete resection was determined by microscopic examination: negative (tumor-free margins), positive (margins with NETs), and indeterminate (unclear margin status due to fragmentation or cauterization). (A) Complete resection according to resection methods. (B) Complete resection according to tumor size. The percentages within parentheses indicate the complete resection rate. cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TAE, transanal excision; TEM, transanal endoscopic microsurgery.

mor proliferative index, and risk of metastasis. Although rectal NETs are slow-growing tumors, lymph node metastasis has been reported even in cases of small NETs [14, 17]. Therefore, complete oncological resection with clear margins is considered a crucial element of treatment. In an article presented by the Korean Society of Coloproctology in 2011 regarding rectal NETs, the lymph node metastasis rate was found to be 1.95% in lesions measuring < 10 mm, but increased to approximately 23.5% in lesions measuring 10–20 mm. Therefore, for lesions > 10 mm, a more aggressive treatment approach rather than local excision is recommended [18]. Maione et al. [19] suggested that radical surgery, including lymph node resection, should be considered for the tumors graded as 2 to 3.

In 2016, Ramage et al. [20] reported consensus guidelines for rectal NETs, stating that endoscopic resection of rectal tumors can be performed using various techniques, including simple polypectomy, EMR, EMR-L, ESD, and TEM. A meta-analysis showed that ESD was successful for rectal NETs, with an 89% complete resection rate, 4% adverse events, and < 1% local recurrence. The complete resection rate was higher in ESD than in cEMR. However, mEMR (with band ligation, double channel, cap-assisted, circumferential precutting) showed complete resection in 91% of patients [15]. Zhang et al. [21] reported that both ESD and mEMR have great advantages over cEMR in terms of complete resection


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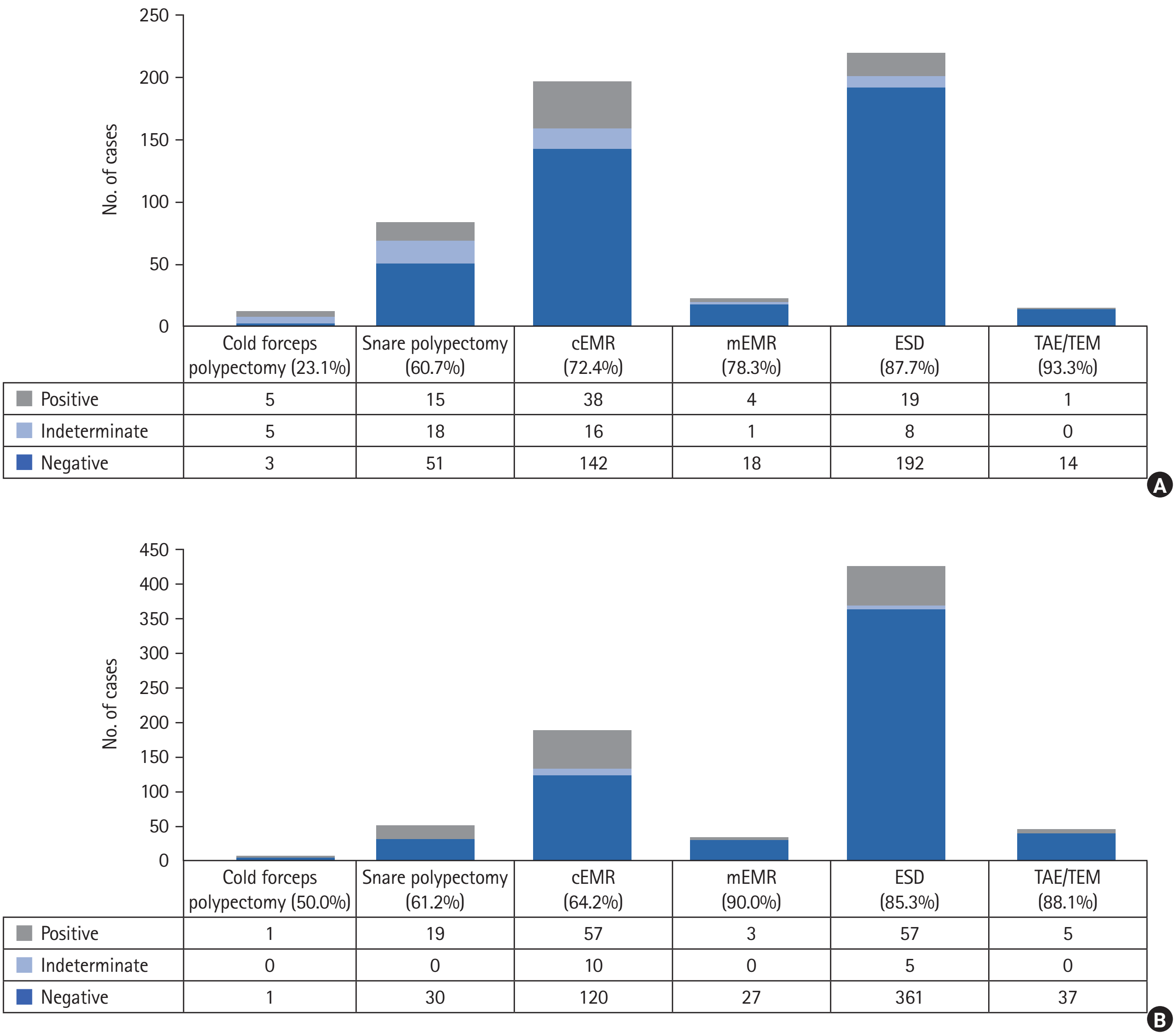


**Fig. 3.** Subgroup analysis of complete resection rates according to tumor size. Complete resection was determined by microscopic examination: negative (tumor-free margins), positive (margins with neuroendocrine tumors [NETs]), and indeterminate (unclear margin status due to fragmentation or cauterization). Rectal NETs sized (A) < 5 mm and (B) 5–9 mm. The percentages within parentheses indicate the rate of complete resection. cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TAE, transanal excision; TEM, transanal endoscopic microsurgery.

**Table 3.** Subgroup analysis for complete resection among patients with tumor size < 10 mm

| | cEMR (n = 383) | mEMR[a] (n = 53) | ESD (n = 642) | P-value | | | |
|---|---|---|---|---|---|---|---|
| | | | | cEMR vs. mEMR vs. ESD | cEMR vs. mEMR | cEMR vs. ESD | mEMR vs. ESD |
| Margin-negative | 262 (68.4) | 45 (84.9) | 553 (86.1) | < 0.001 | 0.008 | < 0.001 | 0.836 |
| Margin-indeterminate and margin-positive | 121 (31.6) | 8 (15.1) | 89 (13.9) | | | | |

Values are presented as number (%). Complete resection was determined by microscopic examination: negative (tumor-free margins), positive (margins with neuroendocrine tumors), and indeterminate (unclear margin status due to fragmentation or cauterization).
cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection.
[a]Includes 3 techniques: precut, band ligation, and underwater endoscopic mucosal resections.

**Table 4.** Univariate analysis of clinicopathologic parameters between complete and incomplete resection for tumors

| Variable | Complete resection | | P-value |
|---|---|---|---|
| | Margin-negative | Margin-indeterminate and margin-positive | |
| Sex (n = 1,406) | | | 0.531 |
| Male (n = 876) | 675 (77.1) | 201 (22.9) | |
| Female (n = 530) | 416 (78.5) | 114 (21.5) | |
| Age (yr) | 53.9 ± 12.7 | 52.2 ± 12.6 | 0.791 |
| ASA physical status (n = 130) | | | 0.439 |
| I (n = 87) | 54 (62.1) | 33 (37.9) | |
| II (n = 43) | 30 (69.8) | 13 (30.2) | |
| Resection method | | | < 0.001 |
| Cold forceps polypectomy (n = 16) | 5 (31.2) | 11 (68.8) | |
| Snare polypectomy (n = 139) | 82 (59.0) | 57 (41.0) | |
| cEMR (n = 403) | 277 (68.7) | 126 (31.3) | |
| mEMR (n = 57) | 49 (86.0) | 8 (14.0) | |
| ESD (n = 689) | 585 (84.9) | 104 (15.1) | |
| TAE/TEM (n = 77) | 68 (88.3) | 9 (11.7) | |
| LAR (n = 25) | 25 (100) | 0 (0) | |
| Tumor location (n = 1,406) | | | < 0.001 |
| ≥ 8 cm from the AV (n = 505) | 363 (71.9) | 142 (28.1) | |
| < 8 cm from the AV (n = 901) | 728 (80.8) | 173 (19.2) | |
| Tumor size (mm) | | | 0.735 |
| < 5 (n = 550) | 420 (76.4) | 130 (23.6) | |
| 5–9 (n = 735) | 578 (78.6) | 157 (21.4) | |
| 10–19 (n = 111) | 86 (77.5) | 25 (22.5) | |
| ≥ 20 (n = 10) | 7 (70.0) | 3 (30.0) | |
| Perineural invasion (n = 249) | | | > 0.999 |
| No (n = 240) | 213 (88.7) | 27 (11.3) | |
| Yes (n = 9) | 8 (88.9) | 1 (11.1) | |
| Lymphovascular invasion (n = 1,099) | | | 0.479 |
| No (n = 988) | 785 (79.5) | 203 (20.5) | |
| Yes (n = 111) | 85 (76.6) | 26 (23.4) | |
| Ki-67 index (%) (n = 608) | | | 0.240 |
| Low grade (≤ 2%) (n = 583) | 500 (85.8) | 83 (14.2) | |
| Intermediate and high grade (≥ 3%) (n = 25) | 19 (76.0) | 6 (24.0) | |
| Recurrence (n = 1,406) | | | 0.021 |
| No (n = 1,398) | 1,088 (77.8) | 310 (22.2) | |
| Yes (n = 8) | 3 (37.5) | 5 (62.5) | |

Values are presented as number (%) or mean ± standard deviation. Complete resection was determined by microscopic examination: negative (tumor-free margins), positive (margins with neuroendocrine tumors), and indeterminate (unclear margin status due to fragmentation or cauterization).
ASA, American Society of Anesthesiologists; cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TAE, transanal excision; TEM, transanal endoscopic microsurgery; LAR, low anterior resection; AV, anal verge.

rate without increasing safety concerns, while mEMR shares similar outcomes with ESD for rectal NETs measuring < 16 mm. Although a meta-analysis by Zhou et al. [22] found that EMR and ESD had similar efficacies and safety profiles in resecting rectal NETs measuring ≤ 10 mm, most studies suggest that for small rectal NETs, ESD or mEMR is more suitable for achieving complete resection [15]. The full-thickness resection device may be an effective endoscopic resection method for achieving complete resection of rectal NETs [23]. However, due to its high cost and lack of national insurance coverage, this technique is currently unavailable in Korea.

In this study, univariate and multivariate analyses were per-



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**Table 5.** Multivariate analysis for complete resection (logistic regression analysis)

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| Resection method | | | < 0.001 |
| Cold forceps polypectomy | Reference | Reference | - |
| Snare polypectomy | 0.316 | 0.104–0.959 | 0.042 |
| cEMR | 0.207 | 0.070–0.608 | 0.004 |
| mEMR | 0.074 | 0.020–0.271 | 0.001 |
| ESD | 0.081 | 0.028–0.237 | < 0.001 |
| TAE/TEM | 0.060 | 0.017–0.213 | < 0.001 |
| Upper rectum | 0.602 | 0.466–0.779 | < 0.001 |
| Recurrence | 3.568 | 0.745–17.100 | 0.112 |
| Lymphovascular invasion | 1.265 | 0.770–2.080 | 0.353 |
| Perineural invasion | 0.961 | 0.787–2.211 | 0.962 |

OR, odds ratio; CI, confidence interval; cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TAE, transanal excision; TEM, transanal endoscopic microsurgery.

**Table 6.** Multivariate analysis for complete resection in cases treated with cEMR, mEMR, or ESD

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| Resection method | | | < 0.001 |
| cEMR | Reference | Reference | - |
| mEMR | 0.366 | 0.168–0.799 | 0.012 |
| ESD | 0.395 | 0.292–0.533 | < 0.001 |
| Upper rectum | 0.620 | 0.461–0.835 | 0.002 |
| Recurrence | 5.128 | 0.811–32.403 | 0.082 |

cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection; OR, odds ratio; CI, confidence interval.

**Table 7.** Multivariate analysis for complete resection in cases with tumor size < 10 mm treated with cEMR, mEMR, or ESD

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| Resection method | | | < 0.001 |
| cEMR | Reference | Reference | - |
| mEMR | 0.390 | 0.178–0.855 | 0.019 |
| ESD | 0.351 | 0.256–0.480 | < 0.001 |
| Upper rectum | 0.667 | 0.488–0.911 | 0.011 |
| Recurrence | 3.573 | 0.464–27.542 | 0.222 |

cEMR, conventional endoscopic mucosal resection; mEMR, modified endoscopic mucosal resection; ESD, endoscopic submucosal dissection; OR, odds ratio; CI, confidence interval.

formed based on the criterion of complete resection. A significant correlation between recurrence and complete resection was observed in the univariate analysis, but not in the multivariate analysis. This discrepancy is likely due to the very low number of recurrence cases. While the association between complete resection and prognosis in rectal NETs ≤ 10 mm has not been definitively established, considering the limited efficacy of adjuvant therapies in rectal NETs, radical resection is deemed crucial. Therefore, we conducted an analysis to evaluate the importance of complete resection. This study also confirmed that for rectal NETs measuring < 10 mm, mEMR and ESD, rather than cEMR, were prognostic factors for complete resection. Although a clear rationale could not be found through a literature search for lower rectal tumors that were analyzed as prognostic factors for complete resection, it seems that the attempt for a more radical resection during endoscopic treatment might have influenced these results. This arises from the fact that the lower rectum is located below the peritoneal reflection, and even if there is damage to the muscle layer during resection, it does not result in intraperitoneal perforation.

Although this study is based on multi-institutional retrospective data, it has some limitations. It should be noted that there were slight variations in treatment policies and resection methods among 6 institutions due to the inclusion of data from multiple hospitals. Even when the same nomenclature is used to describe endoscopic resection methods, procedural differences may arise, potentially influencing the outcomes. To minimize these variations, data collection was restricted to cases managed by experienced specialists in NET resection. This approach ensured that the data represented a high level of expertise and consistency in resection techniques, thereby reducing the variability in procedural methods as much as possible. By standardizing the expertise of practitioners, we aimed to mitigate the potential impact of technique-related variability on the study's results, ensuring a more reliable comparison across institutions. Another limitation is the lack or exclusion of data on mitosis and the Ki-67 index. The Ki-67 index and mitotic count are closely associated with the prognosis of rectal NETs [24, 25]. Although efforts were made to collect these data during the study, incomplete documentation in hospital records limited the availability of these parameters. This prevented tumor grading analysis, which is essential for the selection of an additional treatment. More comprehensive data collection is needed in future studies. Another limitation is the absence of preprocedural endoscopic ultrasonography, which helps the diagnosis of depth of invasion. Consequently, the appropriate resection methods were not always selected. In this study, recurrence data were collected, but we did not analyze cancer-specific survival rates or overall survival rates. Although the correlation between cancer-specific survival and complete resection rates might be insignificant due to the low recurrence rate after resection of the rectal NETs, the lack of survival data remains an additional limitation of this study.

In this study, even in cases where complete resection was not achieved and the resection margins were positive or uncertain, the local recurrence rate was found to be low. This may be due to the potential removal of residual NET tissue by thermal damage during polypectomy. Although the follow-up period of this study was 55.4 months, given the slow-growing nature of NETs, the follow-up period may have been relatively short, potentially influencing our results. Generally, grade 1 low-risk rectal NETs exhibit a slow-growing pattern, leading to an excellent prognosis with very low recurrence rates, as observed in previous studies and confirmed in our study. However, occasional case reports and other studies have indicated instances of lymphatic spread or systemic metastasis, even in rectal NETs ≤10 mm. Therefore, when dealing with a lesion diagnosed as rectal NET, it cannot be simply regarded as a benign polyp. Considering these aspects, complete resection should be the goal when removing NETs. Based on the findings of our study, it may be reasonable to consider mEMR or ESD for removal, aiming for complete resection.

In conclusion, endoscopists should consider the possibility of NETs when encountering small rectal subepithelial lesions during endoscopic examinations. Endoscopic resection is currently recommended for the treatment of small rectal NETs. Advanced endoscopic techniques such as mEMR or ESD showed higher complete resection rates compared with simple snare polypectomy or EMR. Advanced endoscopic techniques should be considered to ensure complete resection of rectal NETs measuring ≤10 mm.

## ARTICLE INFORMATION

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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### Author contributions

Conceptualization: all authors; Data curation: JWS, SSP; Formal analysis: JWS, SSP; Investigation: CGK, HCC, WYK, ECJ; Methodology: KSH, HCC; Project administration: EJL, KSH; Resources: JWS, SSP; Supervision: EJL, KSH; Validation: DHC, KSH; Visualization: JWS, EJL; Writing–original draft: JWS, EJL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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