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CASE REPORT

# 다발성 직장 신경내분비종양 5예

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## Multiple Rectal Neuroendocrine Tumors: Report of Five Cases

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Carcinoids are slow growing neuroendocrine tumors (NET) originating in the enterochromaffin cells of the gastrointestinal tract. In previous studies, rectal NET comprised only about 1% of all anorectal neoplasms; however, the incidence of rectal NET has shown a recent increase. Typically, rectal NET presents as a single subepithelial nodule, and multicentricity of rectal NETs is rare, with reported incidence of 2-4.5%. Due to the rarity of multiple rectal NETs, there is no consensus or guidelines for treatment of multiple rectal NETs. However, NETs of the rectum that are less than 10 mm in diameter and do not infiltrate the muscularis propria, without distant metastasis, can be removed by endoscopy, as with solitary rectal NET. We encountered five cases of multiple rectal NETs which were treated successfully by endoscopy. **(Korean J Gastroenterol 2014;64:103-109)**

**Key Words:** Multicentricity; Rectum; Neuroendocrine tumors

## INTRODUCTION

Carcinoid tumors are a group of well-differentiated neuroendocrine tumors (NETs) of neuro- endocrine neoplasms, according to the World Health Organization (WHO) classification,[1] and approximately 64% of cases arise in the gastrointestinal tract. The appropriate modern term for carcinoid is neuroendocrine neoplasm, NET, or neuroendocrine Carcinoma (NEC).

The small intestine is the most common location (28.7%), followed by the appendix (18.9%), rectum (12.6%), and colon (6%). As reported by Teleky et al.[2] in 1992, only 1% of all anorectal neoplasms are rectal NETs. However, recently, due to an increase in the number of screening colonoscopies, the incidence of rectal NETs has been increasing in Korea.

In the past, NETs were detected unexpectedly during autopsy or surgery for other causes. Currently, most rectal NETs are found incidentally during colonoscopy. In general, rectal NETs occur as a single subepithelial lesion, and multicentricity is rare, occurring in 2% to 4% of all cases.[3]

Therapeutic options for rectal NETs depend on size, depth of invasion, or presence of distant metastasis.[4,5] Rectal NETs smaller than 10 mm in diameter without distant metastasis can be completely removed by endoscopic resection. However, due to the rarity of multicentricity, no therapeutic consensus for multiple rectal NETs has been established. Nevertheless, as in the following cases, if each NET is less than 10 mm and is a Tis or T1 lesion without distant metastasis, multiple rectal NETs might be treated by endoscopy as a solitary lesion.

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We encountered five cases of multiple rectal NETs; three cases were triple NETs and two cases were double NETs. All five cases were treated successfully by endoscopic resection without local recurrence during a median follow-up period of 441.0±95.1 days.

## CASE REPORT

### 1. Case 1

A 52-year-old male who visited our institute for health promotion underwent colonoscopy, which showed two yellowish subepithelial nodules in the rectum; therefore, biopsies were performed. Grossly, the subepithelial lesions were similar to rectal NETs; however, two lesions were diagnosed pathologically as hyperplastic polyp and chronic non-specific inflammation, respectively. In gross finding by endoscopy and in our experiences, those lesions were strongly suspected as NETs. He was admitted to our hospital and no symptoms or signs of carcinoid syndrome were observed.

The patient underwent colonoscopy again, which showed two subepithelial lesions measuring 4 mm in size and small nodular mucosa adjacent to the two subepithelial lesions (Fig. 1). The two subepithelial lesions were removed by endoscopic submucosal resection using a ligation device (ESMR-L) and the nodular mucosa was removed by forcep biopsy (Fig. 1). In the pathological report, all of them were confirmed as well differentiated NETs (grade I according to WHO 2010 classification) (Fig. 2).

Tumor markers were within normal limits, level of CEA was 1.7 ng/mL, and CA 19-9 was 7.76 U/mL. CT of the abdomen and pelvis did not show abnormality. PET scan showed no evidence of distant metastasis. After six months, he underwent sigmoidoscopy and no abnormality was found. In colonoscopic finding, there was no sign of recurrence after 12 months, and he underwent sigmoidoscopy again after 18 months. Due to the possibility of incomplete resection by forcep biopsy, he was examined by EUS, which showed no residual tumor.

### 2. Case 2

A 32-year-old male was transferred to our hospital for treatment of rectal NETs. He had undergone examination of his colon and rectum by colonoscopy for health screening at a local medical center. He had no history of specific disease, alcohol intake, or smoking, and no characteristic familial history. He also had no symptoms. Peripheral blood test performed at

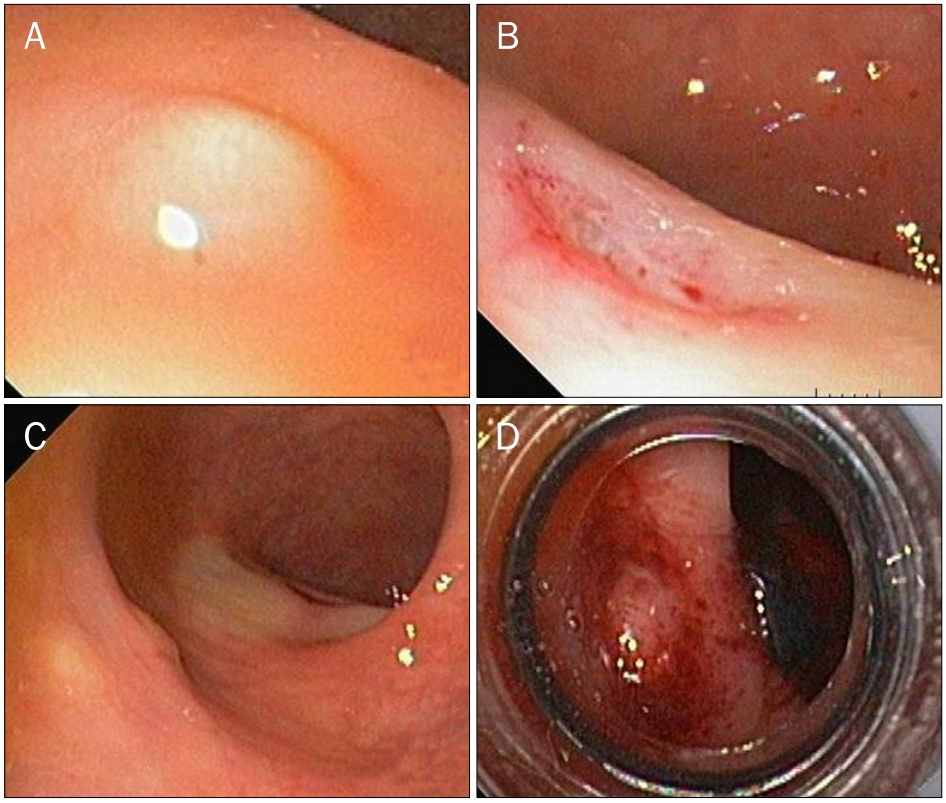


**Fig. 1.** Endoscopic views. (A) A small subepithelial nodule at the rectum was observed. (B) The small nodule was removed by biopsy. (C) Two other subepithelial nodules distal to the lesion (A) were observed. (D) Two subepithelial nodules were removed by endoscopic submucosal resection using a ligation device.

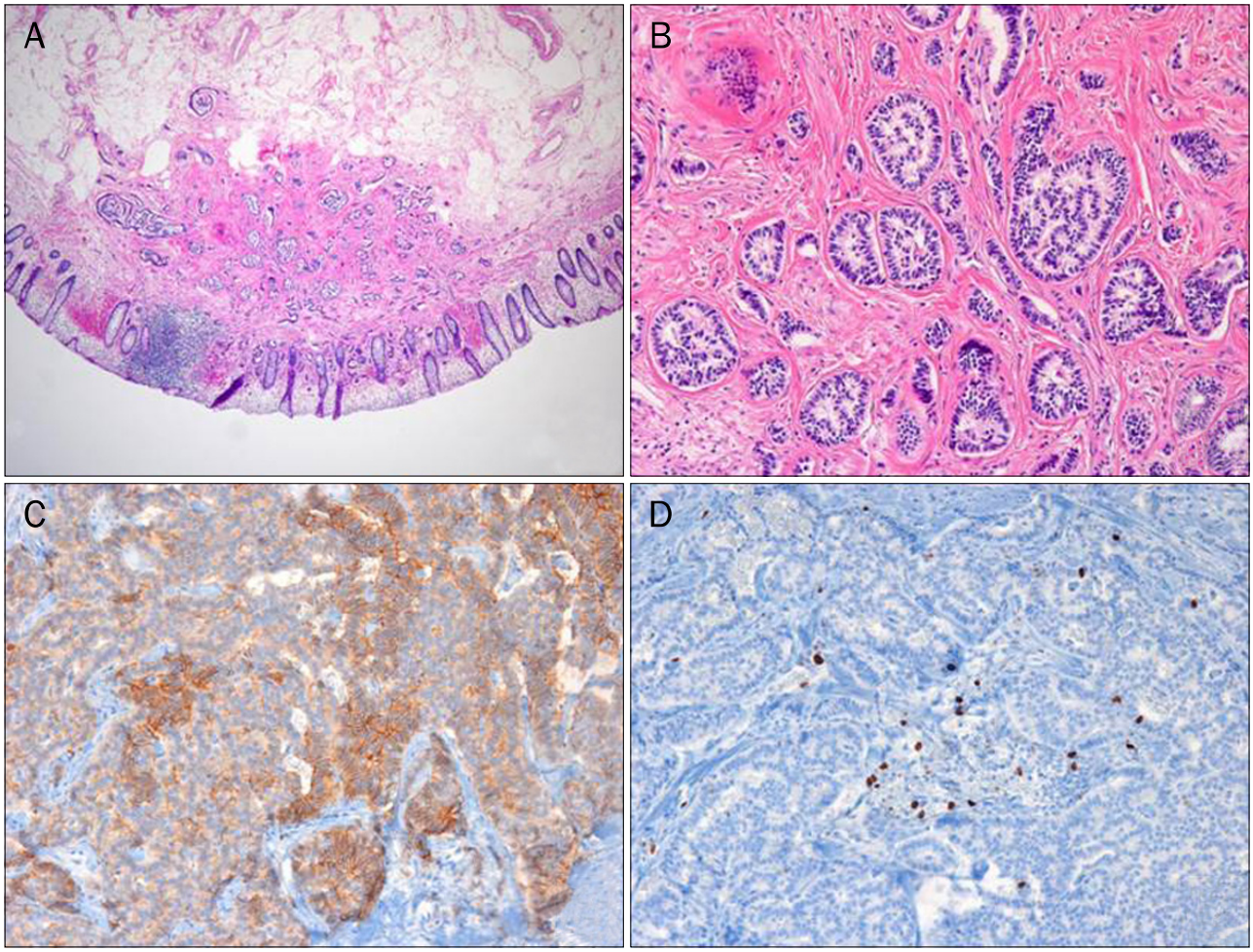


**Fig. 2.** Pathologic findings. (A) Carcinoid tumor is arising from lamina propria and infiltrating to the upper portion of submucosa (H&E, ×40). (B) Tumor cells forming a mostly glandular and trabecular pattern (H&E, ×100). (C) CD56 immunohistochemical staining is positive along the tumor cell membrane (×200). (D) Few Ki-67 nuclear stain positive cells are observed in the tumor (×200).

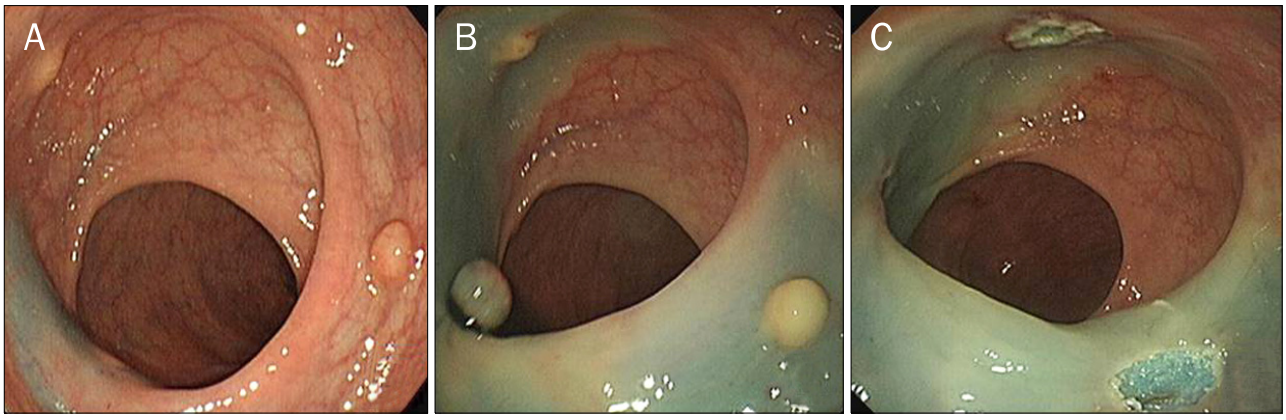


**Fig. 3.** Endoscopic submucosal resection using a ligation device (ESMR-L) technique. (A) Yellowish triple subepithelial lesions at the rectum were noted. (B) Lifting of lesions by hypertonic saline injection and band ligation are noted. (C) Triple rectal carcinoids were removed by ESMR-L.

the time of the visit showed the following; hemoglobin 16.7 mg/dL, white blood cell count 5,650/$mm^3$, and platelet 246,000/$mm^3$ and other laboratory tests, including tumor markers, showed no abnormality.

His colonoscopic finding showed triple yellowish subepithelial lesions in the rectum; lesions measured 5 mm, 5

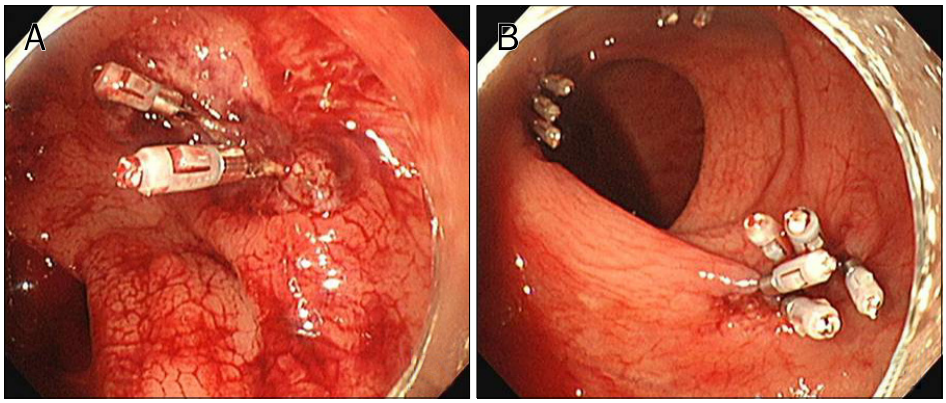


**Fig. 4.** Endoscopic views. (A) Bleeding related to the endoscopic submucosal resection using a ligation device was noted. (B) Bleeding was controlled by endoscopic hemoclipping.

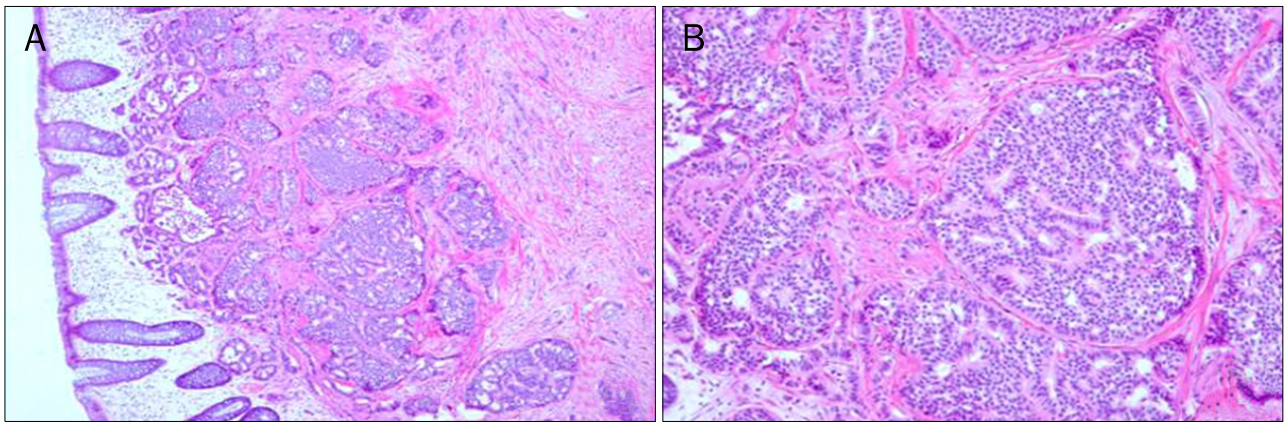


**Fig. 5.** Pathologic findings. (A) Carcinoid tumor is arising from lamina propria and infiltrating to submucosa (H&E, ×40). (B) Tumor cells forming the nesting pattern of growth (H&E, ×100).

mm, and 7 mm in diameter (Fig. 3). All lesions were removed by ESMR-L (Fig. 3). Although bleeding related to the endoscopic procedure occurred, it was managed successfully with endoscopic hemoclipping (Fig. 4). The triple subepithelial lesions were confirmed as WHO grade I NETs by a pathologist and resection margins were all negative (Fig. 5). CT of the abdomen and PET scan showed no evidence of distant metastasis. Sigmoidoscopy after six months and 12 months and colonoscopy after 18 months showed no local recurrence.

### 3. Case 3

A 65-year-old female was transferred to our institute for an elevated level of serum CEA . She had no specific symptoms or signs. Colonoscopy showed multiple rectal polyps and three yellow-colored elevated mucosa measuring approximately 5 mm, 6 mm, and 7 mm in size, located at 8 cm, 10 cm, and 11 cm from the anal verge. Biopsies were performed for each of the three lesions. The pathologic report showed chronic non-specific inflammation in all specimens. Gross colonoscopic findings were highly suggestive of NETs, therefore, she was admitted, and each lesion was removed by endoscopic mucosal resection. The final pathological report showed that all three lesions were NETs with positive immuno-histochemical staining of chromogranin and synaptophysin and resection margins were all clear.

Serum serotonin and 5-hydroxyindoleacetic acid level were within normal limits and no symptoms or signs of carcinoid syndrome were observed. CT of the abdomen and pelvis did not show any abnormality. She did not visit our institute afterwards and follow-up was lost.

### 4. Case 4

A 62-year-old male was examined by colonoscopy for health promotion. Two subepithelial nodules measuring 5 mm in size were detected at the rectum. Regarding past medical history, he had undergone subtotal gastrectomy due to stomach cancer two years ago and he took a medication for

**Table 1.** Summary of Our Five Cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Sex | Male | Male | Female | Male | Female |
| Age (yr) | 52 | 32 | 65 | 62 | 48 |
| Shape | SEL | SEL | Sessile polyp | SEL | SEL |
| Location | Rectum | Rectum | Rectum | Rectum | Rectosigmoid |
| Multicentricity | Triple | Triple | Triple | Double | Double |
| Therapy | ESMR-L and biopsy | ESMR-L | EMR | ESMR-L | ESMR-L |
| Complication | No | Bleeding | No | No | Bleeding |
| WHO grade | NET G1 | NET G1 | Unknown | NET G1 | NET G1 |
| Follow-up (mo) | 6, 12 and 18 | 6, 12 and 18 | No | 12 | 12 and 24 |
| Modality of follow-up | SFS, CFS and EUS | SFS and CFS | No | SFS | CFS |
| Recurrence | No | No | Unknown | No | No |

SEL, subepithelial lesion; ESMR-L, endoscopic submucosal resection with ligation; EMR, endoscopic mucosal resection; WHO, World Health Organization; G, grade; SFS, sigmoidoscopy; CFS, colonoscopy.

diabetes mellitus. Two subepithelial nodules were removed by ESMR-L. In the pathological report, the lesions were diagnosed as WHO grade 1 NETs; resection margins were negative and perilymphatic-vascular or perineural invasion was not observed. Abdominal CT and PET scan showed no evidence of distant metastasis.

### 5. Case 5

A 48-year-old female with a family history of colon cancer underwent colonoscopy, which showed two yellowish subepithelial lesions in the rectum and sigmoid colon. Each of the two lesions was removed by ESMR-L and post-ESMR-L bleeding of the rectum was treated with endoscopic hemoclipping. Pathologically, the two lesions were NETs grade 1 of the WHO 2010 classification, and were completely removed. After 12 months and 24 months, follow-up colonoscopy showed no evidence of local recurrence. We provide a schematic summary of the five cases in Table 1.

## DISCUSSION

Carcinoid tumors were first named as “karzinoide” by Oberndorfer in 1907. The first clinical feature of a carcinoid tumor of the rectum was described by Saltykow in 1912. The appropriate modern term for carcinoid is neuroendocrine neoplasm. Nowadays, the concept of carcinoid can be divided into two parts, NET and neuroendocrine carcinoma (NEC).

Most NETs are asymptomatic, thus, prediction of an accurate prevalence rate is difficult; however, annual incidence has generally been reported as 1 to 2/100,000/year.[6] In Korea, 64% of NETs arise in the gastrointestinal tract, and rectum and stomach are the most frequently involved sites.[6,7]

Based on past studies, rectal NET comprises only 1% of all anorectal tumors, 80-90% of rectal NETs are diagnosed incidentally by sigmoidoscopy for examination of anal diseases, such as hemorrhoid, anal fissure, and anal fistula, or for health screening, and incidence rate by sigmoidoscopy is 1/2,500 person.[2] However, in the USA, frequency of rectal NETs has increased by 800-1,000% in the past 35 years.[8] This increase is probably related to the introduction of colonoscopic screening, which has also resulted in “incidentally” detected neuroendocrine rectal tumors. As in the USA, in the era of screening colonoscopy, rectal NETs are becoming more common in Korea.

Nevertheless, multicentricity of rectal NET is rare, and has been reported as only 2 to 4%.[3] Saha et al.[9] reported that up to 10% of rectal NETs show multicentricity and three to 10 lesions can occur in the same area. In Japan, two cases of multiple NETs of the colon and rectum, containing numerous carcinoid micronests with lymph node metastasis have been reported.[10] Although Japanese cases are extremely rare, they are not NET, but NEC. Several cases of multiple NETs in patients with neurofibromatosis or ganglioneuromatosis have also been reported.[11] Two cases of double rectal NET in a patient without underlying disease have been reported in the Korean literature.[12,13] Multicentricity is a poor prognostic factor in small intestinal carcinoids, however, its prognostic effect in rectal NET is not known.[14]

In the case of a single rectal NET, metastasis is found in 0-3% when the size of the rectal NET is less than 10 mm, 10%

when 10-19 mm, and 80-100% when greater than 20 mm.[5] Naunheim et al.[5] reported that if size is less than 20 mm, invasion to muscularis propria occurs in 20%, if greater than 20 mm, 94% and if it invades the muscular layer, and the possibility of malignancy and distant metastasis increases.

Therefore, the method used for treatment of rectal NET differs according to size and depth of invasion, and, typically, if the tumor size is less than 10 mm and does not infiltrate the muscularis propria, endoscopic resection is recommended first. Even small rectal NETs can primarily invade the submucosa, therefore, a special technique for reliable resection of deep regions of the submucosal layer is needed, and ESMR-L is a good method for complete resection of rectal NET. This procedure is known to be technically simple, minimally invasive, and relatively safe. In addition, the treatment efficacy of ESMR-L was far better in margin negativity and local recurrence than that of conventional polypectomy.[15,16]

However, a few cases of small rectal NET less than 10 mm in diameter with liver metastasis or distant lymph node metastasis have been reported.[17-19] Thus, evaluation of the CT, PET, or EUS before performance of endoscopic resection is essential.

In contrast with consensual treatment options for single rectal NET, due to the rarity of multiple NETs, there are no standard guidelines for treatment. In addition, the long-term prognosis of endoscopic resection for multiple rectal NETs is still uncertain. However, treatment can be administered based on size and depth of invasion of each rectal NET. All of our multiple NETs were removed successfully by endoscope and the short-term prognosis was good, without local recurrence. However, because rectal NET is very slow growing, assessment of the long-term efficacy of endoscopic resection or long-term prognosis is difficult.

In all four cases, multiple NET lesions were located at the rectum, and in the fifth case, the lesion was located at the sigmoid colon and rectum. Particularly in the first case, two rectal NET lesions were too adjacently located and removal of the second lesion with ESMR-L was difficult due to adhesion made by ESMR-L of the first lesion. Although risk of perforation in removal of sigmoid colon NET is higher than that of rectal lesions, the NET lesion at the sigmoid colon was removed without complication.

All of our five cases were confined to the mucosa and submucosa layer and were less than 10 mm in size, with no vascular or neural invasion and clear resection margins; mitotic count was under 2 and Ki-67 count was below 2% at 10 high power field (HPF), indicating a grade 1 NET. In the first case, follow up rectal EUS was also performed in order to rule out the possibility of residual tumor as resection margin of the biopsy lesion was positive. In the second case, although the resection margin was negative, with a benign, low grade tumor, follow up endoscopy was performed three times with intervals of six months, as in the first case. In the fifth case, follow-up colonoscopy was performed two times with an interval of 12 months due to tumor lesion of the sigmoid colon. However, due to a small number of NET cases, there are no established principles concerning follow-up periods and modalities for multiple NETs. Merely, in the case of multiple NETs, relatively short term follow-up endoscopy might be needed in order not to miss other residual NET lesions.

Rectal EUS, which can determine size, invasion depth, and metastasis status to adjacent lymph node, and detect separation of a submucosal tumor from muscularis propria, is essential in testing when deciding on a treatment plan or for evaluation of the stability of endoscopic resection.[20] However, as distant lymph node or liver metastasis is not identifiable through EUS, abdominal CT or PET should be performed in order to confirm distant metastasis status. As in the first case, EUS can also be a good modality in follow-up testing for verification of completeness of resection or local recurrence of NET removed by forcep biopsy.

In recent years, the incidence rate of rectal NET in Korea has increased beyond our expectation. In addition, as in our cases, the endoscopist might encounter multiple rectal NETs. Thus, when incidental rectal NET is found, the possibility of multicentricity should be considered. There is no established gold standard treatment for multiple rectal NETs, and the efficacy or long-term prognosis of endoscopic resection in patients with multiple rectal NETs is uncertain. However, according to our results, in cases of multiple rectal NETs, tumors that are 10 mm or less, which do not infiltrate the muscularis propria, can also be successfully treated endoscopically. The treatment policy, long-term prognosis, and methods of follow-up for multiple rectal NETs should also be discussed in the future by accumulating cases like those described in our report.

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