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Endoscopic Submucosal Dissection for Rectal Neuroendocrine Tumor: A Case Series

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Our study was approved by the Ethics Committee of NHO Kanmon Medical Center (H2807-3). Written informed consent was obtained from all participants.

Abstract **Background:** Less aggressive rectal neuroendocrine tumors (NETs) are mainly located in the submucosal layer. We analyze our clinical experience of endoscopic submucosal dissection (ESD) for rectal NETs. **Methods:** We experienced 27 consecutive rectal neuroendocrine neoplasms (NENs). In these cases, we retrospectively analyzed our selections and the therapeutic results of endoscopic mucosal resection (EMR) and ESD. **Results:** We initially used EMR for rectal NETs. However, there was one case of local recurrence with adjacent lymph-node metastasis. This was initially treated by EMR at another hospital 12 years earlier. We changed the resection modality from EMR to ESD, which has been useful for *en bloc* resection. Thereafter, we performed ESD for 16 cases. *En bloc* resection was performed in 15 cases. The vertical margin was positive in one case but there was no local residue. In one ESD case, detailed examination of the ESD *en bloc* specimen clarified lymphovascular invasion and was useful for the decision of additional surgical operation. **Conclusions:** Based on our experience of this case series of rectal NETs, *en bloc* resection using ESD is a promising treatment modality.

Key words: endoscopic submucosal dissection , rectal neuroendocrine tumors

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Introduction

Neuroendocrine neoplasms (NENs) are epithelial neoplasms with neuroendocrine differentiation, including neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). NETs are classified from G1 to G3 by the WHO according to their proliferative ability.[1] Less aggressive NETs are also called carcinoids. Almost half of carcinoids occur in the rectum.[2] Endoscopic resection is often indicated for colonic NETs, but tumors of over 1 centimeter in size, histologically G2 or higher, with muscularis propria invasion, suspected lymph node involvement, vascular invasion or positive resection margins of endoscopic resection specimens are thought to be indicative of the need for additional treatment.[3]

Rectal NETs are mainly located in the submucosal layer and ordinary endoscopic mucosal resection (EMR) may be insufficient for *en bloc* resection. Different from adenomatous polyps, positive vertical resection margins may be achieved by EMR for rectal NETs.

Endoscopic submucosal dissection (ESD) is useful for *en bloc* resection of rectal tumors containing a submucosal layer with a negative vertical resection margin and is expected to be a suitable therapeutic modality for rectal NETs.[4] In this report, we analyze our clinical experience of ESD for rectal NETs.

Materials and Methods

We experienced 27 consecutive rectal NENs from April 2004 through March 2018 at the National Hospital Organization Kanmon Medical Center (Table 1). The patients consisted of 14 males and 13 females whose mean age was 62.9 years old (range: 35-87). EMR was employed for 8 mainly early cases and ESD for 16 late cases. Surgical operation was needed for three cases and one post-ESD case. ESD was performed using the HookKnife, the ITknife-nano and the ITknife-2 electrosurgical knife (Olympus Corporation, Tokyo, Japan). A typical ESD case of a rectal carcinoid tumor is presented in Fig. 1. (case number 10). In these cases, we retrospectively analyzed our selections and the therapeutic results of EMR and ESD.

Our study was approved by the Ethics Committee of National Hospital Organization Kanmon Medical Center (H2807-3). Written informed consent was obtained from all participants.

Results

As shown in Table 1, we performed EMR for 6 cases before August 2009. Five were *en bloc* resection and one was vertical margin positive but without local recurrence. However, there was one case of local recurrence with adjacent lymph-node metastasis. This was initially treated by EMR at another hospital 12 years earlier. We found local recurrence, and the patient underwent surgical operation (case number 7, Fig. 2). The patient was in good health at over seven years since surgical operation without disease recurrence. We performed EUS for all of ESD cases. EUS was useful for the selection of ESD or surgical operation.

We changed the resection modality from EMR to ESD, which has been useful for *en bloc* resection. Thereafter, we performed ESD for 16 cases. *En bloc* resection was performed in 15 cases. The vertical margin was positive in one case but there was no local residue. In the same period, two NET cases were misrecognized as adenomatous polyps and EMR was performed.

In one case of *en bloc* resection, there was lymphatic invasion in the ESD specimen. The patient underwent additional surgery, and there was no local residue but there was lymph-node metastasis (case number 25, Fig. 3). The patient was in good health at over eight years since surgical operation without disease recurrence. There were no complications such as bleeding or penetration in any case.

Table 1 Twenty-seven cases of rectal neuroendocrine neoplasm

Number	Sex	Age	Therapeutic method	Resection margin
1	Female	74	EMR	negative
2	Female	70	EMR	negative
3	Female	72	EMR	negative
4	Male	72	EMR	**positive**
5	Female	50	EMR	negative
6	Male	50	EMR	negative
7	Female	76	Operation after EMR at another hospital, with lymph node metastasis	
8	Male	76	ESD	**positive**
9	Male	67	ESD	negative
10	Male	59	ESD	negative
11	Female	44	ESD	negative
12	Female	76	EMR, endoscopically not recognized as NET	**positive**
13	Female	50	ESD	negative
14	Female	87	ESD	negative
15	Male	72	ESD	negative
16	Male	54	ESD	negative
17	Male	68	ESD	negative
18	Male	60	ESD	negative
19	Female	54	Operation, NET G2 with vascular invasion	
20	Male	47	Operation+chemotherapy, NEC	
21	Male	60	ESD	negative
22	Male	83	EMR, endoscopically not recognized as NET	**positive**
23	Female	47	ESD	negative
24	Female	56	ESD	negative
25	Male	35	ESD, additional operation, with lymph node metastasis	negative
26	Female	75	ESD	negative
27	Male	64	ESD	negative

years old

EMR: endoscopic mucosal resection
ESD: endoscopic submucosal dissection
NET: neuroendocrine tumor
NEC: neuroendocrine carcinoma

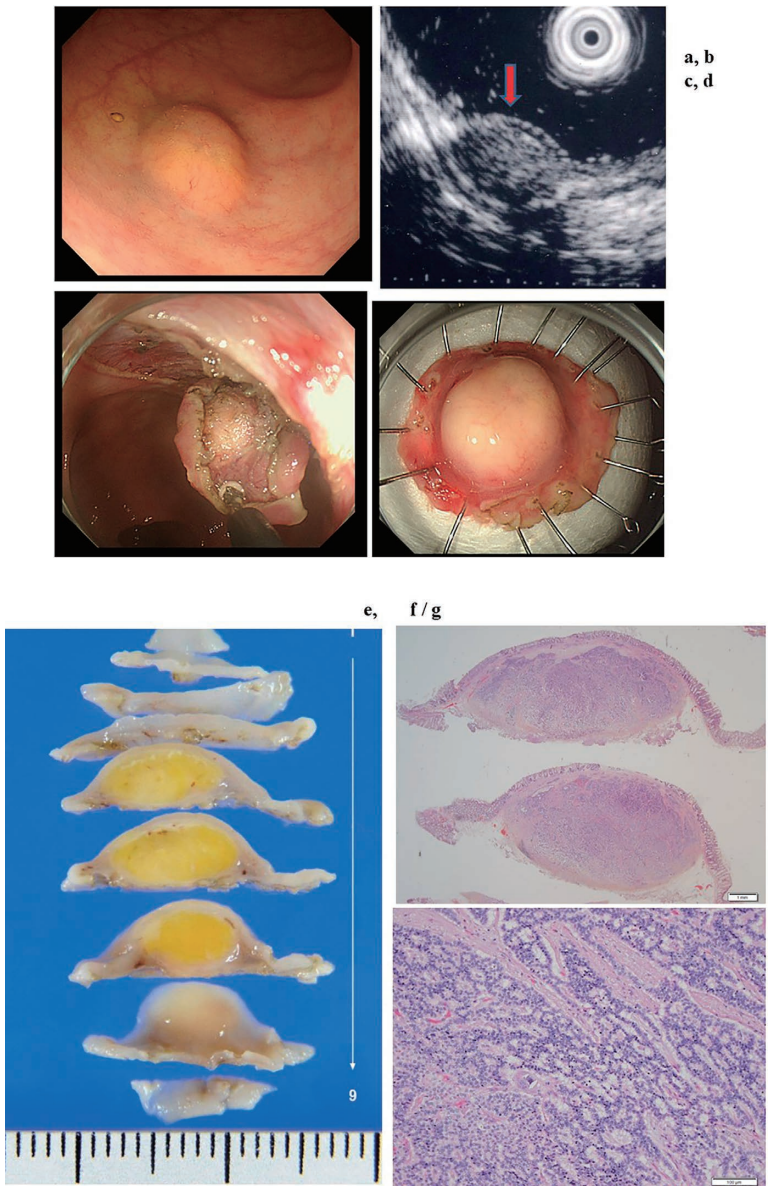

Fig. 1 Case number 10, a 59-year-old male.

A case of curative ESD *en bloc* resection for rectal NET.

a), Endoscopic features. There was a light-yellowish protruded lesion in the rectum 10 millimeter in size. Biopsy finding was NET G1.

b), Features using endoscopic ultrasonography (EUS). EUS revealed a moderately high-echoic tumor located at the mucosal layer to submucosal layer almost 10 millimeter in diameter (red arrow). There was no change of the hypoechoic proper muscle layer.

c), *En bloc* resection using ESD for rectal NET. The vertical margin is observable during the procedure.

d), Surface macroscopic view of ESD *en bloc* resection specimen of rectal NET. The yellowish tumor was resected with the surrounding non-tumorous horizontal margin.

e), Serial macroscopic view of ESD *en bloc* resection specimen of rectal NET. The yellowish tumor was resected in an *en bloc* manner.

f), Low power histologic view of H&E stain (x 12.5). *En bloc* resection was achieved.

g), Moderate power view of H&E stain (x 100). Pathologically, the tumor was NET G1 within 10 millimeter in diameter invading the submucosal layer without lymphovascular or venous invasion. Curative ESD for rectal NET was completed.

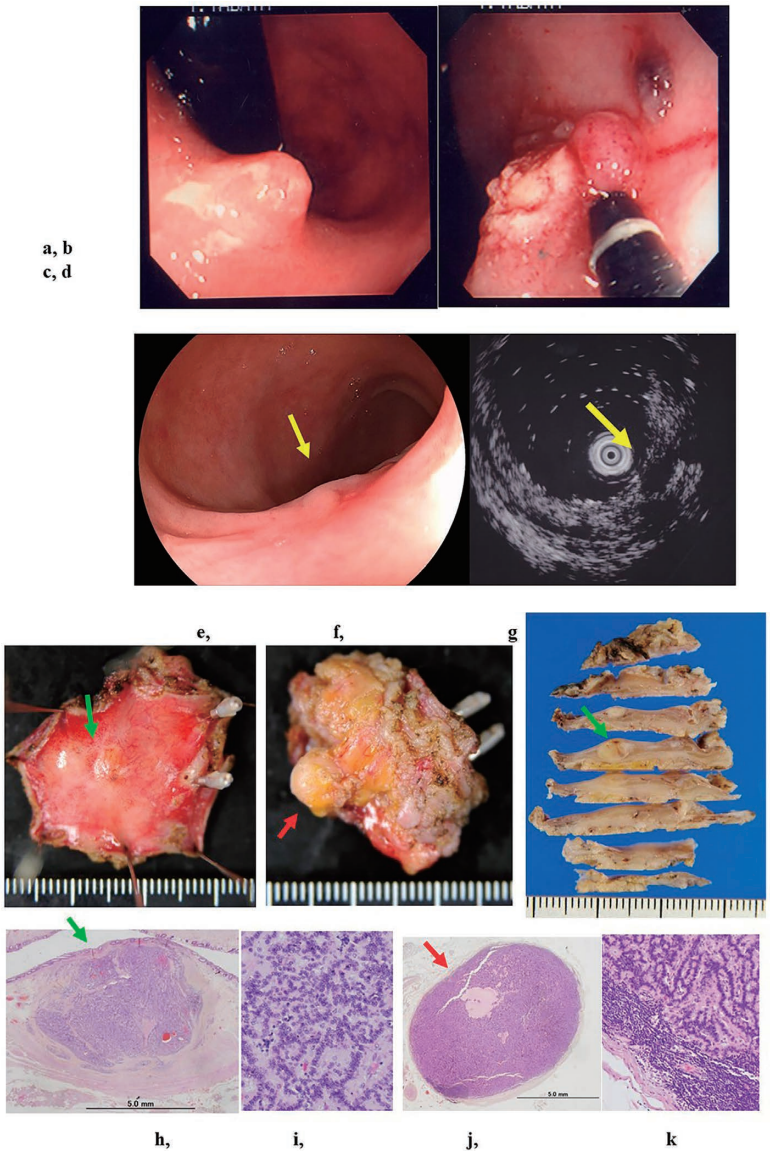

Fig. 2 Case number 7, a 76-year-old female.

A case of local recurrence with adjacent lymph-node metastasis after EMR.

a), Endoscopic features 12 years earlier at another hospital. There was a polypoid lesion 8 mm in diameter at Rb of the rectum. Initially, it was misdiagnosed as an ordinary adenomatous polyp.

b), This lesion was resected using EMR at another hospital. The result of EMR was a carcinoid (NET G1) with a positive vertical margin.

c), d), Endoscopic and endoscopic ultrasonographic features of the recurrent lesion. After 12 years, we observed a carcinoid lesion within the rectal wall, and a NET G1 biopsy result. The recurrent lesion was buried under an EMR scar, and second endoscopic resection seemed difficult (endoscopic feature and EUS, yellow arrow). Therefore, the patient underwent additional surgical resection.

e), f), g), Macroscopic features of surgical resection. The local recurrent lesion (green arrow) with one metastatic lymph node (red arrow) was surgically resected.

h), i), Pathologic features of the surgically resected specimen of the locally recurrent rectal NET 8.6 mm in diameter (green arrow). Low-power (x 12.5) and moderate power (x 100) microscopic views of H&E staining.

j), k), Pathologic features of the surgically resected specimen of the metastatic lymph node of the rectal NET (red arrow). Low-power (x 12.5) and moderate-power (x 40) microscopic views of H&E staining.

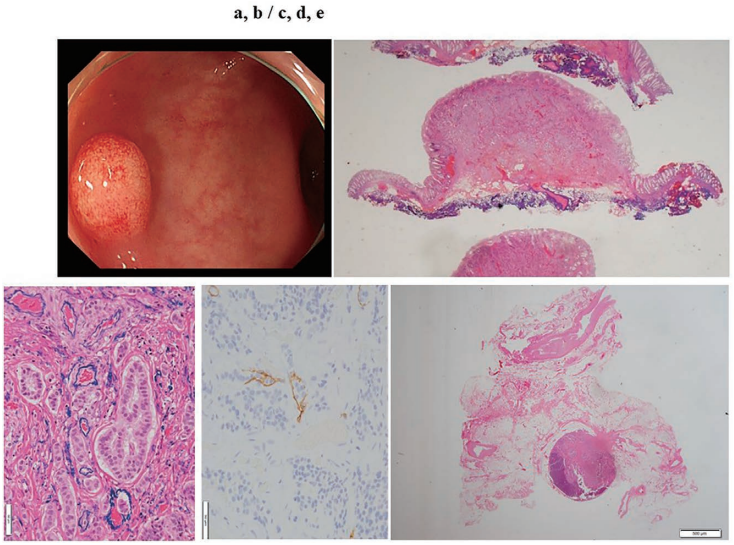

Fig. 3 Case number 25, a 35-year-old male.

A case of *en bloc* ESD for rectal NET with lymphovascular invasion.

a), Endoscopic features. There was a yellowish polypoid lesion at Rb of the rectum 10 mm in diameter. The biopsy result was NET G1.

b). Low-power microscopic view of ESD specimen with H&E staining (x 12.5). The pathological results for the *en bloc* resection specimen of the rectal NET were WHO; NET G1 with positive markers such as synaptophysin, CD56, and chromogranin. Additionally, there was unexpected lymphovascular invasion.

c), Microscopic feature of negative venous invasion of rectal NET with Victoria Blue/H &E double staining (x 200).

d), Microscopic features of lymphovascular invasion of rectal NET with D2-40 staining (x 200).

e), Low-power microscopic view of metastatic lymph node with H&E staining (x 20). The patient underwent additional surgical resection. There was no local recurrence but one metastatic lymph node.

Discussion

Soga et al. reported a rate of late metastasis of 13.2% even for small rectal carcinoids 5.1 to 10 millimeters in size.[2] Furthermore, Sekiguchi et al. reported 26.4% lymphovascular involvement in colorectal NET less than 5 mm in size.[5] Thus, detailed examination of *en bloc* resection specimens is needed for the choice of clinical management of rectal NETs. There are various endoscopic resection methods for rectal NETs such as EMR, its variation with a cap, pre-cutting or ligation and ESD. In these modalities, ESD is reported to be highly effective, but EMR variations are also reported to have short procedure times and sufficient efficacy.[6-10]

We initially used EMR for rectal NETs. However, our case of local recurrence with lymph-node metastasis case indicated the importance of *en bloc* resection. We changed the resection modality from EMR to ESD, which has been useful for *en bloc* resection. Actually, in one ESD case, detailed examination of the ESD *en bloc* specimen clarified lymphovascular invasion and was useful for the decision of additional surgical operation.

On the other hand, endoscopic differential diagnosis between adenomatous polyps and NETs is important for the selection of EMR or ESD. Carcinoids are yellowish protrusions with a smooth surface.[11] Image-enhanced endoscopy or future artificial intelligence-assisted endoscopy may be useful for the endoscopic diagnosis of rectal NETs. When we endoscopically find a protruded lesion in the

rectum, we should keep in mind the possibility of rectal NETs.

Conclusion

Based on our experience of this case series of rectal NETs, *en bloc* resection using ESD is a promising treatment modality.

Conflict of Interest

The authors declare no conflict of interest.

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