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ORIGINAL ARTICLE

Clinicopathological characteristics and frequency of multiple rectal neuroendocrine tumors: a single-center retrospective study

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Abstract

Background Rectal multiple neuroendocrine tumors (M-NETs) are rare, with only few epidemiologic reports on the topic. Therefore, their clinicopathological features are not completely known, and the appropriate treatment strategy has not been established.

Purpose This study aimed to compare the clinicopathological malignant potential (lymphatic or venous invasion-positive and lymph node metastasis rates) of M-NETs with that of solitary NETs (S-NETs).

Methods We retrospectively investigated 369 patients with NETs of the rectum. Patients who underwent colonoscopy at the Cancer Institute Hospital between January 1979 and 2016 and diagnosed with S-NETs were included, and S-NETs were found in 348 patients. Patients with M-NETs were classified into two groups as follows: patients with < 8 tumors (several (S) group, $n = 21$) and those with ≥ 8 tumors (numerous (N) group, $n = 3$).

Results The overall frequency of M-NETs was 5.7% and that of the N group was 0.8%. The mean tumor diameter in the N group was 6.0 mm (range, 4–8 mm). The lymphatic invasion rates of the S-NETs, and S and N groups of the M-NETs were 8.9%, 5.6%, and 66.7%, respectively. Moreover, the lymph node metastasis rates were 9.2%, 11.1%, and 33.3, respectively.

Conclusions While M-NETs in the S and N groups had different characteristics, they were rarer in the N group. The N group may have higher rates of lymphatic invasion and lymph node metastasis regardless of tumor size.

Keywords Neuroendocrine tumor · Multiple rectal neuroendocrine tumor · Gastrointestinal neuroendocrine tumor · Lymph node metastasis · Epidemiology for neuroendocrine tumor

Introduction

Gastrointestinal neuroendocrine tumors (GI NETs) originate from the endocrine cells of the archenteron; in Japanese patients, they are found in the rectum, stomach, and duodenum, in decreasing order of frequencies [1]. In Japan, rectal NETs account for 55.7% of GI NETs [2]. The malignant potential of GI NETs is often assessed based on the risk factors of metastasis and prognostic factors; therefore, it is well-recognized that the malignant potential varies according to the organ. However, these tumors are non-functional, not accompanied by hormone-related symptoms, and treated predominantly by tumor resection.

Most duodenal NETs are highly differentiated (NET-G1 grade) [3]. Although there is no consensus on the treatment modality, lymph node metastasis occurs in ≥ 25% of tumors with size ≥ 10 mm [4]. The metastasis rate is low in cases with tumor size ≤ 10 mm or with tumors limited to the mucosa or submucosa, and endoscopic resection is preferred in such cases [5, 6].

Gastric NETs are grouped according to the Rindi classification [7]: type I, NETs caused by hypergastrinemia

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secondary to gastritis type A; type II, NETs due to multiple endocrine neoplasia type 1 (MEN1); and type III, sporadic cases without a clear etiology. Types I and II gastric NETs with sizes ≤ 10 mm and ≤ 5 lesions that are limited to the submucosa are indications for endoscopic treatment [8, 9]. However, gastric resection with lymph node dissection is considered for type III gastric NETs, depending on the level of malignancy [7].

Solitary cases account for most rectal NETs. However, studies with ≥ 200 cases have reported tumor size ≥ 11 mm and lymphatic or venous invasion positivity as independent risk factors of regional lymph node metastasis [10, 11]. In contrast, rectal multiple NETs (M-NETs) are rare with only few epidemiologic reports currently available. Therefore, the clinicopathological features have not been clearly identified, and treatment strategies have not been clearly established. Additionally, no study has focused on the fact that there are cases of M-NET where the number of lesions can be counted macroscopically and those where they are innumerable.

This study aimed to compare the clinicopathological features and the malignant potential (lymphatic or venous invasion-positive and lymph node metastasis rate) of M-NETs with those of solitary NETs (S-NETs).

Materials and methods

This retrospective study was conducted in accordance with ethical principles of the Declaration of Helsinki and approved by the institutional review board of the Japanese Foundation for Cancer Research. All patients provided signed informed consent before colonoscopy.

This study included 369 patients, who underwent colonoscopy at the Cancer Institute Hospital between 1979 and 2016, were diagnosed with rectal NETs, underwent initial treatment, and had a histopathological definitive diagnosis performed at this hospital, which included 449 lesions (348 S-NET lesions; 101 M-NET lesions). Patients who were treated at other hospitals and those with unclear initial endoscopic findings were excluded. Initial treatment techniques for the target cases include endoscopic local resection (endoscopic submucosal resection by cap aspiration–snare resection/endoscopic submucosal resection with a ligation device/endoscopic submucosal dissection) [12–14] and surgical radical resection. In addition, among the cases with endoscopic local resection, those with pathologically evaluated as non-curative resection have undergone additional surgery including lymph node dissection.

Tumor size—an important parameter for preoperative diagnosis—and invasion depth were measured using endoscopic ultrasonography (EUS) before treatment in all patients in whom lesions could be detected.

Clinicopathological, photographic, radiological, and pathological data were extracted from the medical records. In few cases that could be reassessed, grading was performed according to the 2010 World Health Organization (WHO) Classification [15]. Concurrent lymph node metastases were assessed in resected specimens in cases treated by surgical resection and by evaluating radiological images (computed tomography [CT], magnetic resonance imaging [MRI], or abdominal ultrasonography [AUS]) over a period of 1 year in cases treated by local excision. Multiple organ metastases were evaluated by sampling the tissues at sites identified by imaging using appropriate methods.

Classification of multiple NETs

There were 21 cases of M-NETs that included concurrent and metachronous multiple lesions, which were classified into two groups based on the total number of lesions.

Cases with < 8 lesions were classified as the several (S) group, while those with > 8 lesions or with clinical non-feasibility of counting were classified as the numerous (N) group. Figure 1 demonstrates the typical features of one case in the S group; two lesions were recognized as submucosal tumors in the lower rectum, and on EUS, both lesions were identified as independent low echoic tumors. Figure 2 demonstrates the typical features of a case in the N group; innumerable small submucosal tumor elevations from the lower rectum to the upper rectum can be seen without continuity on the mucosal surface. While indigo-carmine staining dispersion made the tumors clearer, the total number of tumors was still unclear.

Histological evaluation

The specimens were fixed in 20% formalin, cut into 2-mm sections, stained with hematoxylin and eosin, and examined histologically to determine the involvement of the excised margins, depth of invasion, and lymphovascular invasion. In all cases, we used Victoria Blue stain for investigating venous invasion and D2-40 immunohistochemical staining for lymphatic invasion.

Statistical analysis

Statistical analyses were performed using EZR [16]. Fisher's exact test was used to compare the rates of metastasis and venous and lymphatic invasion positivity between the groups. Similarly, the rates of metastasis and venous and lymphatic invasion positivity between tumors with diameter ≤ 5, 5–10, and > 10 mm were compared. A p value of < 0.05 was considered significant.

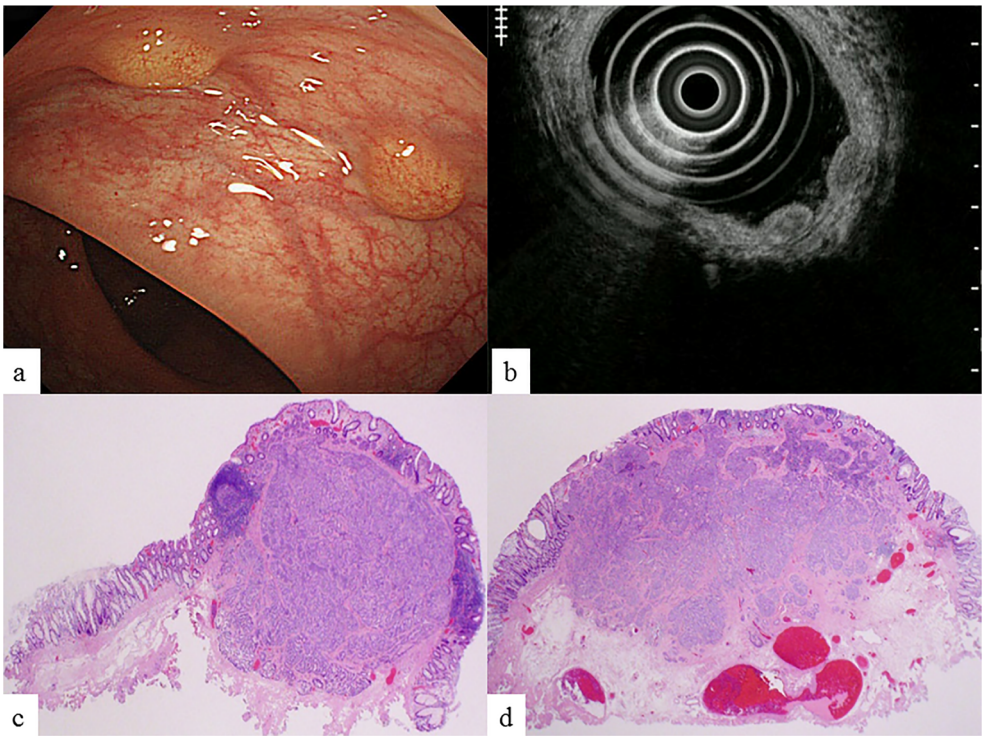

Fig. 1 A typical case of "several" neuroendocrine tumors (NETs). **a** Two submucosal tumors are seen in the lower rectum on endoscopy. **b** Two independent low echoic tumors are seen in the submucosal layer on endoscopic ultrasonography. **c**, **d** Histopathologic examination of each tumor showed NETs within the submucosal layer (hematoxylin and eosin, magnification × 2)

Results

Clinicopathological features

Table 1 summarizes the basic clinical features of the three groups. Of the 369 patients, S-NETs and M-NETs were diagnosed in 348 (94.3%) and 21 (5.7%) patients, respectively. In the M-NET group, 18 (4.9%) and 3 (0.8%) patients were classified in the S and N groups, respectively.

The mean tumor diameter in the S-NETs, S, and N groups was 7.0 mm (range, 1.5–30 mm), 5.8 mm (range, 3–10 mm), and 6.0 mm (range, 4–8 mm), respectively. The mean number

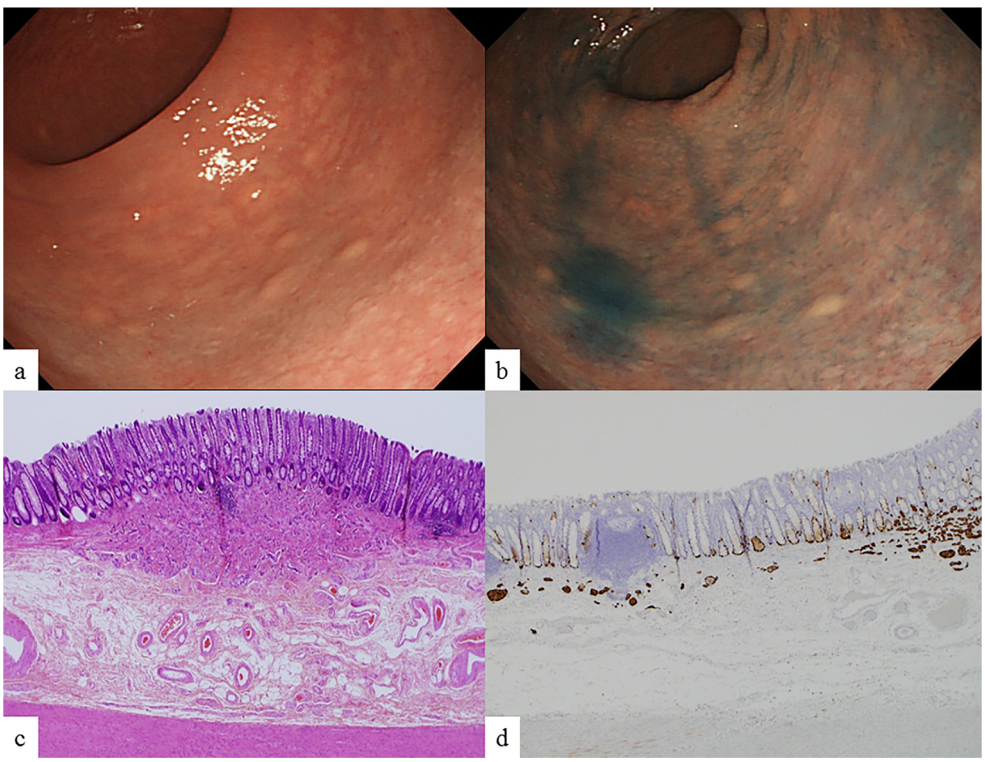

Fig. 2 A typical case of "numerous" neuroendocrine tumors (NETs). **a** Numerous submucosal tumor elevations are seen in the lower and upper rectum without continuity on the mucosal surface with adjacent tumors. **b** Indigo-carmine pigment dispersion increased the visibility of each tumor, but the total number of tumors could not be counted. **c** Histopathologic examination of the tumor showed aggregate neuroendocrine tumor cells within the submucosal layer (hematoxylin and eosin, magnification × 4). **d** Endocrine cell micronests are seen in several parts without the main tumor (immunohistochemical staining for chromogranin A, magnification × 2)

Table 1 Clinicopathological features of 369 patients with rectal neuroendocrine tumors (NETs)

	Solitary NETs		Multiple NETs			
			Several group		Numerous group	
	N	(%)	*N*	(%)	*N*	(%)
Number of cases	348	(94.3)	18	(4.9)	3	(0.8)
Sex				(50)		
Male	199	(57.2)	9	(50)	3	(100)
Female	149	(42.8)	9	(50)		
Age, median (years) [range]	56 [27–88]		59 [42–81]		58 [53–61]	
Size, median (mm) [range]	7.0 [1.5–30]		5.8 [3–10]		6.0 [4–8]	
Number of tumors [range]	1		2.7 [2–7]		17.7 [10–27]	
Tumor depth						
Limited to the mucosa or submucosa	335	(96.3)	18	(100)	3	(100)
Into or through the muscularis propria	13	(3.7)				
Grading						
G1	181	(52.0)	11	(61.1)	2	(66.7)
G2	9	(2.6)			1	(33.3)
NEC	3	(0.9)				
Lymphatic invasion						
Positive	31	(8.9)	1	(5.6)	2	(66.7)
Negative	317	(91.1)	17	(94.4)	1	(33.3)
Venous invasion						
Positive	49	(14.1)	2	(11.1)	1	(33.3)
Negative	299	(85.9)	16	(88.9)	2	(66.7)
Lymph node metastasis						
Positive	32	(9.2)	2	(11.1)	1	(33.3)
Negative	316	(90.8)	16	(88.9)	2	(66.7)
Distant metastasis						
Positive	7	(2.0)	0	(0)	0	(0)
Negative	341	(98.0)	18	(100)	3	(100)

of tumors in the S and N groups was 2.7 (range, 2–7) and 17.7 (range, 10–27), respectively. The lymphatic invasion rates of the S-NETs, and S and N groups of the M-NETs were 8.9%, 5.6%, and 66.7%, respectively. The venous invasion rate of the S-NETs, and S and N groups of the M-NETs were 14.1%, 11.1%, and 33.3, respectively. Moreover, the lymph node metastasis rates of the S-NETs, and S and N groups of the M-NETs were 9.2%, 11.1%, and 33.3%, respectively.

Table 2 summarizes the lymph node metastasis rate according to the tumor diameter in S-NETs with lymphatic or venous invasion. Lymph node metastasis was seen in 28.1% of patients with S-NETs who underwent lymph node dissection for lymphatic or venous invasion. Lymph node metastasis was seen in 41.9% of patients with S-NETs who underwent lymph node dissection for only lymphatic invasion and in 28.6% of patients with S-NETs who underwent lymph node dissection for only venous invasion. In cases with tumor diameter ≤ 5 mm, lymph node metastasis was not observed in cases that were lymphatic invasion-positive only. In venous invasion-positive cases with lymph node metastasis, 15.4% of the cases had tumor diameter ≤ 5 mm. In lymphatic or venous invasion-positive cases with lymph node metastasis, 11.8% of cases with tumor diameter ≤ 5 mm, 19.4% of cases with a tumor diameter of 5–10 mm, and 62.5% of cases with tumor diameter > 10 mm were positive for metastasis.

Table 3 summarizes the lymphatic or venous invasion-positive rates according to the tumor diameter and lymph node metastasis rate in the S-NET group. Compared with the cases with tumor diameter ≤ 5 mm, those with tumor diameter > 5 mm did not show significant differences in the rates of lymph node metastasis, venous invasion positivity, and lymphatic invasion positivity. Furthermore, a comparison between tumors of sizes ≤ 10 and > 10 mm revealed that lymph node metastasis, venous invasion-positive, and lymphatic invasion-positive rates were significantly higher in the subgroup with tumor size > 10 mm.

Table 2 Rate of lymph node metastasis in cases with lymphatic or venous invasion by tumor diameter in solitary neuroendocrine tumor

	Number of cases	Lymph node metastasis	
		Positive	Negative
Lymphatic invasion positive	31	13 (41.9%)	18 (58.1%)
≤ 5 mm	5	0 (0)	5 (100%)
5–10 mm	13	4 (30.8%)	9 (69.2%)
> 10 mm	13	9 (69.2%)	4 (30.8%)
Venous invasion positive	49	14 (28.6%)	35 (71.4%)
≤ 5 mm	13	2 (15.4%)	11 (84.6%)
5–10 mm	23	5 (21.7%)	18 (78.3%)
> 10 mm	13	7 (53.8%)	6 (46.2%)
Lymphatic or venous invasion positive	64	18 (28.1%)	46 (71.9%)
≤ 5 mm	17	2 (11.8%)	15 (88.2%)
5–10 mm	31	6 (19.4%)	25 (80.6%)
> 10 mm	16	10 (62.5%)	6 (37.5%)

Comparisons between 5–10 mm and > 10 mm denote the same tendency of that in between tumors of sizes ≤ 10 and > 10 mm.

Pathological factors and lymph node metastasis

Table 4 compares the positive rates of pathological factors and lymph node metastasis between the following groups: S-NETs vs. M-NETs (S + N); S-NETs vs. S; S-NETs vs. N; S-NETs + S vs. N; and S vs. N. No significant differences were found in lymph node metastasis, venous invasion-positive rate, and lymphatic invasion-positive rates between the S-NETs and M-NETs (S + N groups) and S-NETs and S groups. Comparisons between S-NETs and N groups demonstrated no significant differences between lymph node metastasis and venous invasion-positive rates, but the lymphatic invasion-positive rate was significantly higher in the N group ($p = 0.03$). Similarly, comparison between the S and N groups revealed no significant differences between lymph node metastasis and venous invasion-positive rate; however, the lymphatic invasion-positive rate was significantly higher in the N group ($p = 0.04$). The S-NETs + S groups and N group were compared to investigate whether only the N subgroup of the M-NET group had a high lymphatic invasion-positive rate. No significant differences were noted in lymph node metastasis or venous invasion-positive rates, but the lymphatic invasion-positive rate was significantly higher in the N group ($p = 0.02$). Lymphatic invasion- or venous invasion-positive rates were only marginally higher in the N group than in S-NETs vs. N group, S-NETs + S group vs. N group, and S vs. N group.

Clinicopathological features of numerous NETs

Table 5 summarizes the follow-up results of the clinicopathological features of the three cases in the N group. The invasion was limited to the submucosa in all three cases, and there was no invasion of the muscularis propria. Radical surgical resection had been performed in all three cases; it was performed after endoscopic resection in one case.

In case 2 (Fig. 2), on preoperative endoscopy, 13 identifiable tumors were counted. Two of the multiple lesions that were the closest to the anus (1.5 cm from the dentate line, measuring 4 and 3 mm in diameter) were treated by endoscopic mucosal resection, and radical dissection (D3 dissection) was performed because the venous invasion was found in the 3-mm lesion. The range of the located area was 10 cm, from the lower to the upper rectum. The resected rectum was

Table 3 Rate of lymphatic or venous invasion and rate of lymph node metastasis according to the diameter of the solitary neuroendocrine tumor

	≤ 5 mm/5–10 mm	*p* value	≤ 10 mm/> 10 mm	*p* value	5–10 mm/> 10 mm	*p* value
Number of cases	152/151		303/45		151/45	
Lymphatic invasion positive	5/13	0.06	18/13	0.00002	13/13	0.002
Venous invasion positive	13/23	0.08	36/13	0.005	23/13	0.048
Lymphatic or venous invasion positive	17/31	0.03	48/16	0.003	31/16	0.047
Lymph node metastasis positive	2/8	0.06	10/22	0.4×10^{-14}	8/22	0.1×10^{-9}

Table 4 Clinicopathological factors and lymph node metastasis (A, solitary neuroendocrine tumor (NET); B, multiple NETs (several group); C, multiple NETs (numerous group))

	A:B	*p* value	A:B+C	*p* value	A:C	*p* value	A+B:C	*p* value	B:C	*p* value
Number of cases	348:18		348:21		348:3		366:3		18:3	
Lymphatic invasion										
Positive	31:1	1.0	31:3	0.43	31:2	0.03	32:2	0.02	1:2	0.04
Negative	317:17		317:18		317:1		334:1		17:1	
Venous invasion										
Positive	49:2	1.0	49:3	0.99	49:1	0.38	51:1	0.38	2:1	0.39
Negative	299:16		299:18		299:2		315:2		16:2	
Lymphatic or venous invasion										
Positive	64:2	0.55	64:4	1.0	64:2	0.10	66:2	0.09	2:2	0.08
Negative	284:16		284:17		284:1		300:1		16:1	
Lymph node metastasis										
Positive	32:2	0.69	32:3	0.44	32:1	0.26	34:1	0.27	2:1	0.39
Negative	316:16		316:18		316:2		332:2		16:2	

postoperatively incised to check for tumor formations and count the number of tumors; there were 27 tumors of 1.5–4-mm diameter with venous and lymphatic invasion. Three metastases were found in the pararectal lymph nodes, and one was found in the inferior mesenteric lymph nodes. The patient was diagnosed with NET-G2, with Ki-67 positivity of 5%.

In all cases, the submucosal tissues between the tumors were normal. None of the tumors were connected with the adjacent tumors in the submucosal layer. The total number of tumors was counted by the total cleavage of the surgically resected specimen.

Discussion

Most rectal NETs are solitary, and M-NETs are rare. A previous study reported that M-NETs occur in 2.0–4.5% of conventional NETs including solitary NETs [17]. In this study, M-NETs were observed in 5.7% (21/369) of patients with rectal NETs. Of them, only three patients belonged to the N group, accounting for 0.8% of all rectal NETs. In this study, patients with ≥ 8 tumors were classified in the N group and those with < 8 tumors were classified in the S group because the N group included those patients in whom the tumors could not be macroscopically counted by endoscopy and because the maximum number of countable tumors was 7.

The prognosis in rectal NET with metastasis is reported to be the same as that in colon cancer, and the 5-year survival rate is 54–73% [10, 18–21]. In recurrent NETs or those with metastasis, the efficacy of chemotherapy is not sufficient; however, surgical resection of the metastatic lesions has been reported to increase the survival rate [22–25].

Initial diagnosis and evaluation of the risk factors of metastasis are important in rectal NETs, as early detection and prediction of metastasis can help prolong patient's survival with certainty. Some factors that can indicate the malignant potential of rectal NETs include not only the tumor size but also the number of cell divisions and Ki-67 positivity used for grading [15]. These tumors are carcinoid tumors that originate from the deepest mucosal layer and infiltrate the submucosal layer; therefore, the degree of invasion in the submucosal layer is not focused

Table 5 Clinicopathological features of the numerous group

	Sex	Age (years)	Size (mm)	Number	Depth	Lymphatic invasion	Venous invasion	Grading	Lymph node metastasis	Treatment methods	Follow-up (months)
Case 1	Male	53	6.0	10	SM	−	−	G1	−	Surgical resection	108
Case 2	Male	61	4.0	27	SM	+	+	G2	+	Endoscopic resection and surgical resection	65
Case 3	Male	58	8.0	16	SM	+	−	G1	−	Surgical resection	61

SM submucosa

upon, but it is a serious factor in terms of tumor volume or invasion of the muscularis propria, which is rich in lymph and blood vessels. However, with regard to evaluating the lymphatic or venous invasions, substantial inter-observer variability was noted among institutions that evaluate them and those that do not anymore.

Among the reports that focused on the lymphatic or venous invasion of rectal NETs, many have identified lymph node metastasis as an independent risk factor along with tumor size ≥ 11 mm as a risk factor of lymph node metastasis [10, 11]. Both reports recommend considering surgical resection with lymph node dissection in rectal NETs if either of these criteria are met. In this study, lymphatic or venous invasion in S-NETs often occurred with tumors of size ≥ 6 mm. Lymph node metastasis occurred in 28.1% of patients who underwent additional lymph node dissection for lymphatic or venous invasion. Our previous study of 229 patients showed that tumor size and venous invasion were independent risk factors of lymph node metastasis [26]. However, while lymph node metastatic lesions were histopathologically confirmed to be NETs, it is unclear whether all types of NETs have the same proliferation potency as adenocarcinoma. Therefore, the outcomes should be considered according to the initial malignancy.

Although the mean tumor size in patients in the N group was small (6.0 mm; range, 4–8 mm), the rate of lymphatic invasion was significantly higher. Furthermore, the total number of tumors could not be counted macroscopically on endoscopy, and it would have been difficult to identify small lesions in the submucosa had it not been a surgically resected specimen of the affected area. Although there were cases in this group that were confirmed using endocrine cell micronest (ECM), such pathological findings cannot be ascertained without the surgically resected specimens. Therefore, surgical resection with lymph node dissection is recommended as radical therapy for this group of patients regardless of the tumor size because lymphatic or venous invasion is a risk factor of lymph node metastasis.

In patients with M-NETs, those of the S group were not found to be significantly different from those of the S-NET group in terms of the rates of lymph node metastasis, venous invasion, or lymphatic invasion. Therefore, as per the treatment plans for S-NETs, histopathological diagnosis by local resection would be the first line of initial treatment for cases limited to the submucosa with tumor size ≤ 10 mm without metastasis found on imaging.

Although the etiopathogenesis of rectal M-NET is unknown, its incidence is approximately 10-fold of that of sporadic cases in patients with ulcerative colitis (UC), in whom the reported rate is 3–5% [27]. Some reports have suggested that mucosal damage due to the persistent inflammation associated with UC is involved in the development of M-NETs [28, 29]. However, no reports have focused on the influence of rectal inflammation on the development of M-NETs or the relationship between ECM and the proliferating ability of these cells. Furthermore, M-NETs are reported to be a common complication of MEN1 syndrome [30]. However, none of the three patients in the N group in this study had UC, primary hyperparathyroidism, hypophyseal adenoma, insulinoma or gastrinoma, or family history of MEN1 syndrome. Primary hyperparathyroidism was assessed by measuring serum calcium levels alone. Serum parathyroid hormone levels were not measured; therefore, normocalcemic primary hyperparathyroidism could not be excluded. Histologically, extensive extra-glandular endocrine cell proliferation along neurofibers has been reported to be the mechanism of multiple lesions [17]; however, information regarding the mechanism of the onset of M-NETs remains unknown and warrants further investigations.

This study has some limitations. First, three patients in the N group of M-NETs had taken the radical surgical resection; however, lymph node dissection was not performed in some patients of the S-NETs and S groups, who had curative to local resection, to avoid excessive surgeries. Lymph node metastasis in these cases was assessed preoperatively by CT or MRI. Second, the number of cases in the N group was small.

Factors associated with malignancy are different in rectal NETs when compared with those in conventional colorectal cancers. Tumor size and volume, including invasion depth, which can be determined clinically, grading by a histopathological diagnosis of resected tissues, presence of lymphatic or venous invasion, and number of lesions (solitary or multiple), are risk factors of malignancy in rectal NETs. These lesions are often underestimated and considered less malignant than those of conventional colorectal cancers, but there are many unknown phenomena related to NETs. Since metachronous lesions have been previously reported, an accurate initial diagnosis is essential for elucidating the pathology of this disease.

In conclusion, the frequency of M-NETs in the N group in high-volume parameter was 0.8%, which was rare. Although the tumor size of the N group tends to be small, the lymphatic invasion was high, suggesting potential malignancy. Treatment should be selected according to the number of NET lesions (solitary, countable, or innumerable), which are accompanied by higher rates of lymph node metastasis and require cautious selection of management.

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Compliance with ethical standards The study protocol was reviewed and approved by the institutional review boards of the participating institutions.

Conflict of interest The authors declare that they have no conflict of interest.

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