Predicting the factors for metastasis and determining treatment strategy in patients with 10–20 mm sized rectal neuroendocrine tumor

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Research

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Abstract

Background: Rectal neuroendocrine tumor (NET) smaller than 10 mm is typically treated with endoscopic resection. Rectal NET larger than 20 mm should be treated with radical surgical resection. However, proper treatment for 10 - 20 mm sized rectal NET is controversial. The purpose of this study was to investigate the appropriate treatment strategy for 10-20 mm sized rectal NET by verifying factors that can predict metastasis.

Methods: A total of 23 patients with 10–20 mm sized NET who were treated at Pusan National University Yangsan Hospital from January 2009 to February 2020 were included. The patients were divided into metastasis group and non-metastasis group and their respective data were analyzed.

Results: Six patients had metastasis (26.1%) while 17 patients had no metastasis (73.9%). Tumor size in endorectal ultrasound (EUS) was significantly larger in the metastatic group than in the non-metastatic group ($p = 0.036$), however pathological tumor size did not show significant difference ($p = 0.087$). The rate of involvement of muscularis propria was 50% in the metastatic group, which was significantly higher than that in the non-metastatic group ($p = 0.040$). Lymph node enlargement was observed in a single patient (16.7%) in the metastatic group for each of EUS and computed tomography (CT) imaging. Ki-67 index in the metastatic group was higher than in the non-metastatic group. The two groups also showed a significant difference in the proportion of patients with tumor grade 2 (66.7% vs. 5.9%, $p = 0.008$). In multivariate analysis, tumor grade was the only independent metastasis-predicting factor ($p = 0.010$).

Conclusions: EUS should be performed to evaluate tumor size, and muscularis propria involvement along with CT imaging to check lymph node enlargement before the treatment of 10–20 mm sized rectal NET. If endoscopic resection was performed, tumor grade should be the most important factor to determine whether additional radical resection is necessary.

Introduction

Neuroendocrine tumor (NET), which originates from chromaffin-like cells, is a tumor with neuroendocrine function and malignant potential [1]. The incidence of these tumors continues to increase, and rectal NET showed the largest increase in recent years [2, 3]. Rectal NET is known to have a better prognosis than NET of the small bowel, colon, and other sites of the body [2, 4, 5]. In particular, a rectal NET of a size less than 10 mm is considered an indolent lesion and is typically treated with endoscopic resection [6]. However, rectal NET over the size of 20 mm have a 60–80% chance of lymph node metastasis, in which case radical resection such as low anterior resection (LAR) or abdominoperineal resection is recommended for treatment [7, 8].

On the other hand, a proper treatment strategy for 10–20 mm sized rectal NET remains controversial [1, 3, 4, 9]. Endoscopic resection can be prioritized as a treatment method [2]. However, 10–15% of metastasis was observed in patients with 10–20 mm sized rectal NET; therefore, the risk of metastasis always exists for local excision [7]. Radical resection can be considered as another treatment option; however, in this case, a sacrifice of a huge portion of the rectum is inevitable, which leads to sequelae such as LAR syndrome. Moreover, there are also chances of post-operational morbidity and mortality. Therefore, selecting the proper treatment method for 10–20 mm sized rectal NET is a fundamental issue that determines the prognosis and quality of life of the patient.

In order to select an appropriate treatment method, predicting factors for lymph node or other organ metastasis in patients with rectal NET need to be identified. Factors known to date include tumor size, tumor depth, atypical endoscopic features, lymphovascular invasion, venous invasion, mitotic count, Ki-67 index, tumor grade, and muscularis layer invasion [3, 8–11]. However, due to inconsistency among guidelines and studies, there is a confusion about the determination of appropriate treatment methods using those predicting factors [1, 2, 4–6]. Furthermore, only a limited number of studies on 10–20 mm sized rectal NET are available. Therefore, the current study aimed to examine the appropriate treatment strategy for 10–20 mm sized rectal NET by verifying factors that can predict metastasis of rectal NET.

Materials And Methods

Patient Population

Patients who underwent either endoscopic resection, transanal excision, or radical surgery for rectal NET (10–20 mm in size) at Pusan National University Yangsan Hospital from January 2009 to February 2020 were included. All data were taken from a prospectively maintained database. The exclusion criteria were as follows: pathologic tumor size less than 10 mm or larger than 20 mm; and follow-up period less than two years without radical surgery with lymph node dissection (Fig. 1.). The study design was approved by the Institutional review board (No. 05-2020-079) of the Pusan National University Yangsan Hospital.

Data selection and variables

Tumor size and surface patterns were evaluated by endoscopy. The smoothness of the tumor surface, central depression, and ulceration were checked. Endorectal ultrasound (EUS) was performed to examine tumor size, the involvement of muscularis propria, and lymph node enlargement. Lymph node enlargement and distant metastasis were checked using computed tomography (CT). Enlargement of the lymph node more than 5 mm was considered significant.

Tumor size, the involvement of muscularis propria, lymphovascular invasion, perineural invasion, and lymph node metastasis were checked pathologically. Immunohistochemical examination was performed to check the mitotic count and Ki-67 index, which were used to assess the tumor grade. In addition, expressions of synaptophysin, chromogranin A, and CD56 were tested.

Mitotic count, categories of Ki-67 index, and grading criteria were based on the 2019 WHO classification [12]. The definition of grading criteria of rectal NET was as described below. G1: mitotic count < 2 per 10 high-power fields (HPF) and Ki-67 index < 3%; G2: mitotic count 2–20 per 10 HPF and/or Ki-67 index 3–

20%, G3: mitotic count > 20 per 10 HPF or Ki-67 index > 20%.[12]

In the case of radical resection, the presence or absence of lymph node metastasis was examined pathologically. In the case of endoscopic resection or transanal local excision, if CT and colonoscopy detected no evidence of recurrence or lymph node metastasis after at least two years of a sufficient follow-up period, it was considered that there was no lymph node metastasis.

Standard Management Strategy

Every patient underwent endoscopic ultrasonography together with the abdomen and pelvis CT to assess the progress of the tumor and determine its stage. As the treatment method, endoscopic resection and surgical resection were performed. Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) was conducted as the endoscopic resection. The surgical resection included transanal excision and LAR. Metastasectomy was performed when metastasis was observed, and resection was possible.

Once it was deemed possible to apply endoscopic resection as judged based on the results of endoscopy and endoscopic ultrasonography, either EMR or ESD was performed by an experienced gastroenterologist. In cases of intrinsic muscle layer infiltration, tumors greater than 15 mm in size, and wide submucosal lesion where endoscopic resection would be challenging, a surgical treatment (transanal local resection or LAR) was performed in consideration of the patient's condition and intention. LAR, which is an radical resection, was performed either when lymph node metastasis was suspected on EUS, when lymph node or distant metastasis was suspected on CT, or when the tumor was confirmed to have infiltrated the margin after transanal local excision.

Statistical analyses

Statistical analysis was performed using IBM SPSS software (version 26; IBM Corp., Armonk, NY, USA). Mann-Whitney test was used for non-parametric continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. Multivariate analysis was performed with logistic regression analysis using a backward likelihood ratio approach. A p-value of less than 0.05 was considered statistically significant.

Results

Patient clinical characteristics

In total, 23 patients with 10–20 mm sized rectal NET from January 2009 to February 2020 were included in the present study (Fig. 1). Of these, six patients had metastasis (metastatic group, 26.1%), and 17 had no metastasis (non-metastatic group, 73.9%). Patient characteristics are summarized in Table 1. The mean age was 54.8 years in the metastatic group and 52.1 years in the non-metastatic group. Radical resection was performed in all six patients of the metastatic group, while 76.5% and 23.5% of the non-metastatic group underwent endoscopic resection and transanal local excision, respectively.

Table 1
Clinical patient characteristics

Parameters	Metastasis (n = 6)	Non-metastasis (n = 17)	p-value
Age (years)	54.8 ± 12.5	52.1 ± 13.0	0.562
Sex	4 (66.7)	12 (70.6)	> 0.999
Male	2 (33.3)	5 (29.4)	
Female			
Treatment methods	0 (0)	13 (76.5)	< 0.001
Endoscopic resection	(0)	4 (23.5)	
Transanal excision	6 (100)	0 (0)	
Radical resection			
Follow-up periods (months)	18.2 ± 21.0	46.8 ± 19.8	0.010

Endoscopic and imaging results

A smooth surface of tumors and ulceration was observed in 50% and 33.3% of the metastatic group, respectively (Table 2). In the non-metastatic group, 70.6% of the patients had tumors with a smooth surface, and no cases of ulceration were observed (p = 0.080). While the two groups showed no difference in endoscopic tumor size, EUS tumor size was statistically larger in the metastatic group than in the non-metastatic group (14.6 mm vs. 10.2 mm, p = 0.036). Furthermore, the proportion of patients with EUS tumor size larger than 15 mm was higher in the metastatic group (66.7% vs. 17.6, p = 0.045). The rate of muscularis propria involvement was 50% in the metastatic group, which was significantly higher than that in the non-metastatic group (p = 0.040). Lymph node enlargement was observed in a single patient (16.7%) from the metastatic group in each of the EUS and CT imaging. Liver metastasis from CT results was observed in two patients (33.3%) of the metastatic group.

Table 2
Endoscopic, EUS, and CT imaging results

Parameters	Metastasis (n = 6)	Non-metastasis (n = 17)	p-value
Surface	3 (50.0)	12 (70.6)	0.080
Smooth	1 (16.7)	5 (29.4)	
Central depression	2 (33.3)	0 (0)	
Ulcer			
Tumor size on endoscopy (mm)	14.2 ± 2.0	12.1 ± 5.6	0.235
Tumor size on EUS (mm)	14.6 ± 3.7	10.2 ± 3.9	0.036
Tumor size on EUS	2 (33.3)	14 (82.4)	0.045
< 15 mm	4 (66.7)	3 (17.6)	
≥ 15 mm			
MP involvement	3 (50.0)	1 (5.9)	0.040
LN enlargement on EUS	1 (16.7)	0 (0)	0.273
LN enlargement on CT	1 (16.7)	0 (0)	0.261
Liver metastasis on CT	2 (33.3)	0 (0)	0.059
MP, muscularis propria; LN, lymph node; EUS, endorectal ultrasound; CT, computed tomography			

Pathologic features

There was no significant difference in pathological tumor size between the two groups (13.3 mm vs. 11.8 mm, p = 0.087) (Table 3). Lymphovascular invasion and perineural invasion was observed in 33.3% and 5.9% of the patients in the metastatic and non-metastatic group, respectively, but this difference was not statistically significant (p = 0.155). In the metastatic group, 33.3% of the patients showed the mitotic count two or more, while this was not observed in the non-metastatic group (p = 0.059). Ki-67 index was higher than 2 in 50% and 5.9% of the metastatic and non-metastatic groups, respectively. This difference between the groups was statistically significant (p = 0.040). The two groups also showed a statistically significant difference in the proportion of patients with tumor grade 2 (66.7% vs. 5.9%, in metastatic and non-metastatic groups, respectively, p = 0.008). The numbers of positive cases of chromogranin A, synaptophysin, and CD56 expression were not significantly different between the two groups.

Table 3
Pathologic features

Parameters	Metastasis (n = 6)	Non-metastasis (n = 17)	p-value
Tumor size (mm)	13.3 ± 1.4	11.8 ± 2.4	0.087
Tumor size	4 (66.7)	14 (82.4)	0.576
<15 mm	2 (33.3)	3 (17.6)	
≥ 15 mm			
MP involvement	1 (16.7)	0 (0)	0.261
Lymphovascular invasio	2 (33.3)	1 (5.9)	0.155
Perineural invsion	2 (33.3)	1 (5.9)	0.155
Mitotic count[a]	4 (66.7)	17 (100)	0.059
<2	2 (33.3)	0 (0)	
2–20			
Ki-67 index	3 (50.0)	16 (94.1)	0.040
<3%	3 (50.0)	1 (5.9)	
3–20%			
Tumor grade			
1	2 (33.3)	16 (94.1)	0.008
2	4 (66.7)	1 (5.9)	
ChromograninA (+)	2 (33.3)	4 (23.5)	0.632
Synaptophysin (+)	6 (100)	17 (100)	> 0.999
CD 56 (+)	6 (100)	17 (100)	> 0.999
MP, muscularis propria; LN, lymph node; EUS, endorectal ultrasound			
[a]Mitotic count is per 10 high-power fields.			

Table 3
Multivariate analysis of predicting factor for metastasis

Predictor	Odds ratio	95% CI	p-value
Tumor size ≥ 15 mm on EUS	7.61	0.53–109.84	0.136
MP involvement	6.86	0.15–308.48	0.322
Tumor grade 2	32.00	2.29–447.83	0.010
CI, confidence interval; EUS, endorectal ultrasound; MP, muscularis propria			

Multivariate analysis of predicting factor for metastasis

In multivariate analysis, tumor grade 2 was identified as a significant independent factor for predicting metastasis (OR = 32.00, 95% CI = 2.29–447.83, p = 0.010) (Table 4).

Table 4
Patient characteristics in the metastatic group

Case	Age (years)	Sex	Surface	Size on EUS (mm)	MP involvement on EUS	LN enlargement on EUS	LN enlargement on CT	Pathologic Size (mm)	LVI	PI	Mitotic count	Ki-67 index (%)	Tumor Grade	Meta
1	35	M	Ulcerated	15	O	X	X	13	X	X	3	2	2	LN
2	61	M	Ulcerated	15	O	X	X	15	X	O	10	11	2	Liver LN
3	61	M	Smooth	17.2	X	X	X	13	O	O	0	< 1	1	LN
4	69	F	Smooth	18.7	X	X	O	15	O	X	5–7	5	2	Liver
5	58	F	Smooth	8	O	X	X	12	X	X	0	3	2	LN
6	45	M	Central depression	13.9	X	O	X	12	X	X	1	< 1	1	LN

EUS, endorectal ultrasound; MP, muscularis propria; LN, lymph node; CT, computed tomography; LVI, Lymphovascular invasion; PI, perineural invsion

Clinicopathologic patient characteristics in the metastatic group

Clinicopathologic characteristics of the patients in the metastatic group are summarized in Table 5. Metastasis was observed in a total of six patients with five cases of lymph node metastasis and two cases of liver metastasis. Of these, four cases were tumor grade 2, and the remaining two cases were tumor grade 1. In one of the patients with tumor grade 1 (Case 3), lymphovascular invasion and perineural invasion were identified. In Case 6, in which tumor grade 1 was assigned, lymph node metastasis was suspected from the results obtained with EUS. In Cases 1 and 2, haematoxylin and eosin (H&E) and immunohistochemical staining for Ki-67 are shown in Figs. 2 and 3, respectively.

Discussion

In this study, the tumor grade defined using immunopathological tests was the most significant predictor for metastasis in patients with 10–20 mm sized rectal NET. Ki-67 index itself was also meaningful; however, it was less significant than the tumor grade. Tumor size and muscularis propria involvement were significant based on the EUS results in univariate analysis. Pathological tumor size, lymphovascular invasion, and perineural invasion showed no statistically significant differences.

It is surprising that tumor size, as determined by EUS, was a more significant factor than the pathological tumor size in predicting metastasis. There is a possibility that the biopsy results may not accurately reflect the original tumor properties since tissue deformation may occur during and after resections. On the other hand, it can be thought that EUS retains the original shape before the manipulation and better reflects the original size of the tumor. This reasoning seems to be more conspicuous as the accuracy of the measurements obtained with the EUS machine has been improved according to technological advancement [1]. Moreover, the risk of metastasis can be assessed before treatments such as endoscopic resection. Thus, the tumor size defined by EUS could be considered more significant to determine radical resection than pathological tumor size.

Among immunochemical examinations, the tumor grade was the most significant to predict metastasis in the present study. Several previous studies and guidelines stated that each of these factors mitotic count and Ki-67 index were significant in predicting metastasis risk and prognosis [10, 13]. On the other hand, different studies also reported that the tumor grade assessed by combining these two factors was a significant predictor [6, 11]. In the present study on 10–20 mm sized rectal NET, the grade defined based on the two factors combined was independent predictive factor for metastasis in multivariate analysis. In particular, 67% of the patients with the metastasis had a tumor grade 2. The remaining two patients with tumor grade 1 were suspected of lymph node metastasis based on lymphovascular and perineural invasion, or lymph node enlargement on EUS. Therefore, it seems that the proper treatment would be determined if the tumor grade had been used as the main factor to predict metastasis in post-operative biopsy while referring to the results of imaging and other pathological tests.

Lymphovascular invasion and perineural invasion had no statistical significance; however, they were observed in 33.3% of the patients with the metastasis (vs. 6% in non-metastatic group), therefore, an increase in sample size may demonstrate a statistical significance for these factors. As mentioned above, one case with metastasis was determined as tumor grade 1, in which lymphovascular invasion and perineural invasion were identified. The significance may be lower than that of the tumor grade, but it may certainly be considered as a clinically meaningful test.

Immunochemical methods for diagnosis of rectal NET include chromogranin A, B, synaptophysin, CD56, CD57, p53, and neuron-specific enolase [4]. There is no consensus regarding the need for immunochemical examinations in all cases of NET. However, immunochemical testing is encouraged when the tumor presents with histologically unclear characteristics. Tests for chromogranin A and synaptophysin are considered as a standard [4]. Other tests are not recommended for routine staining. p53 may be used as a marker for hypodifferentiated tumors, but it is not recommended as part of the routine [14]. In the present study, tests for chromogranin A, synaptophysin, and CD56 were performed. In addition, this study also investigated whether immunochemical tests can be used not only for diagnosis but also for determining the treatment method. However, none of the above immunochemical tests for NET diagnosis could

be identified to have an association with lymph node metastasis. Synaptophysin and CD56 were expressed in all of the patients in metastatic and non-metastatic groups. Chromogranin A was expressed in only a few cases, and no statistically significant difference was observed between the groups.

This study focused on the controversy in the appropriate treatment choice for 10–20 mm sized rectal NET. Since previous studies have focused on various sizes of rectal NET, the predictors of metastasis of 10–20 mm sized rectal NET could not be directly identified. The current study suggests that tumor grade is the most important factor in determining the radical treatment of 10–20 mm sized rectal NET. In addition, it is considered essential to examine the tumor size, lymph node enlargement, and muscularis propria involvement using EUS, and lymph node enlargement using CT. Thereafter, if the tumor size defined with EUS is 15 mm or larger, muscularis propria has been infiltrated, and lymph node enlargement has been identified in EUS and CT results, radical resection should be considered for the first option. In other cases, endoscopic resection may be considered at first; afterward, radical resection is suggested for tumor grade 2 or higher in pathologic examination.

This study has a few limitations. First, small numbers of patients were included in the study. The incidence of 10–20 mm sized rectal NET was low, and that of metastasis was even lower, which led to the limitation of the small sample size. To compensate for this limitation, we extended the study period to 11 years. Another limitation was a retrospective of this study; therefore, the possibility for selection bias existed. In the future, prospective studies could obtain more significant results. The other limitation is that lymph node metastasis was not pathologically confirmed in all patients. To exclude potential errors that could not be identified with imaging, even though there was lymph node metastasis, only those patients who were followed-up for at least two years after receiving endoscopic resection with no pathologically identified lymph node metastasis, were included in the study. Patients who underwent only endoscopic resection with a follow-up duration of fewer than two years were excluded.

Conclusions

EUS should be performed to evaluate tumor size, and muscularis propria involvement in addition to CT imaging results to check lymph node enlargement before the treatment of 10–20 mm sized rectal NET. If endoscopic resection was performed, tumor grade should be the most important factor to determine whether additional radical resection is necessary.

Abbreviations

NET: Neuroendocrine tumor; LAR: Low anterior resection; EUS: Endorectal ultrasound; CT: Computed tomography; HPF: High-power fields; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; OR: Odds ratio; CI: Confidence interval; H&E: Haematoxylin and eosin

Declarations

Ethics approval and consent to participate

The study design was approved by the Institutional review board (No. 05-2020-079) of the Pusan National University Yangsan Hospital.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing of interests.

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Authors' contributions

Park BS, Son GM, Kim HS, and Kim HW designed the research; Park BS, Cho SH, Kim SJ, Park SB, Choi CW, and Shin DH collected the patients' clinical data; Park BS, Cho SH, Son GM, Kim SJ, Park SB, and Shin DH analyzed the data; Park BS, Cho SH, Son GM, Kim HS, and Kim SJ wrote the paper; Son GM, Kim HS, Choi CW, and Kim HW provided critical revision.

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References

1. Li P, Wu F, Zhao H, Dou L, Wang Y, Guo C, et al. Analysis of the factors affecting lymph node metastasis and the prognosis of rectal neuroendocrine tumors. Int J Clin Exp Pathol. 2015;8:13331-8.

2. Fields AC, Saadat LV, Scully RE, Davids JS, Goldberg JE, Bleday R, et al. Local Excision Versus Radical Resection for 1- to 2-cm Neuroendocrine Tumors of the Rectum: A National Cancer Database Analysis. Dis Colon Rectum. 2019;62:417-21.
3. McDermott FD, Heeney A, Courtney D, Mohan H, Winter D. Rectal carcinoids: a systematic review. Surg Endosc. 2014;28:2020-6.
4. Caplin M, Sundin A, Nillson O, Baum RP, Klose KJ, Kelestimur F, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. Neuroendocrinology. 2012;95:88-97.
5. Ford MM. Neuroendocrine Tumors of the Colon and Rectum. Dis Colon Rectum. 2017;60:1018-20.
6. Folkert IW, Sinnamon AJ, Concors SJ, Bennett BJ, Fraker DL, Mahmoud NN, et al. Grade is a Dominant Risk Factor for Metastasis in Patients with Rectal Neuroendocrine Tumors. Ann Surg Oncol. 2020;27:855-63.
7. Mani S, Modlin IM, Ballantyne G, Ahlman H, West B. Carcinoids of the rectum. J Am Coll Surg. 1994;179:231-48.
8. Starzynska T, Londzin-Olesik M, Baldys-Waligorska A, Bednarczuk T, Blicharz-Dorniak J, Bolanowski M, et al. Colorectal neuroendocrine neoplasms - management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2017;68:250-60.
9. Hyun JH, Lee SD, Youk EG, Lee JB, Lee EJ, Chang HJ, et al. Clinical impact of atypical endoscopic features in rectal neuroendocrine tumors. World J Gastroenterol. 2015;21:13302-8.
10. Sugimoto S, Hotta K, Shimoda T, Imai K, Yamaguchi Y, Nakajima T, et al. The Ki-67 labeling index and lymphatic/venous permeation predict the metastatic potential of rectal neuroendocrine tumors. Surg Endosc. 2016;30:4239-48.
11. Bertani E, Ravizza D, Milione M, Massironi S, Grana CM, Zerini D, et al. Neuroendocrine neoplasms of rectum: A management update. Cancer Treat Rev. 2018;66:45-55.
12. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76:182-8.
13. Hotta K, Shimoda T, Nakanishi Y, Saito D. Usefulness of Ki-67 for predicting the metastatic potential of rectal carcinoids. Pathol Int. 2006;56:591-6.
14. Klimstra DS, Modlin IR, Adsay NV, Chetty R, Deshpande V, Gonen M, et al. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. Am J Surg Pathol. 2010;34:300-13.

Figures

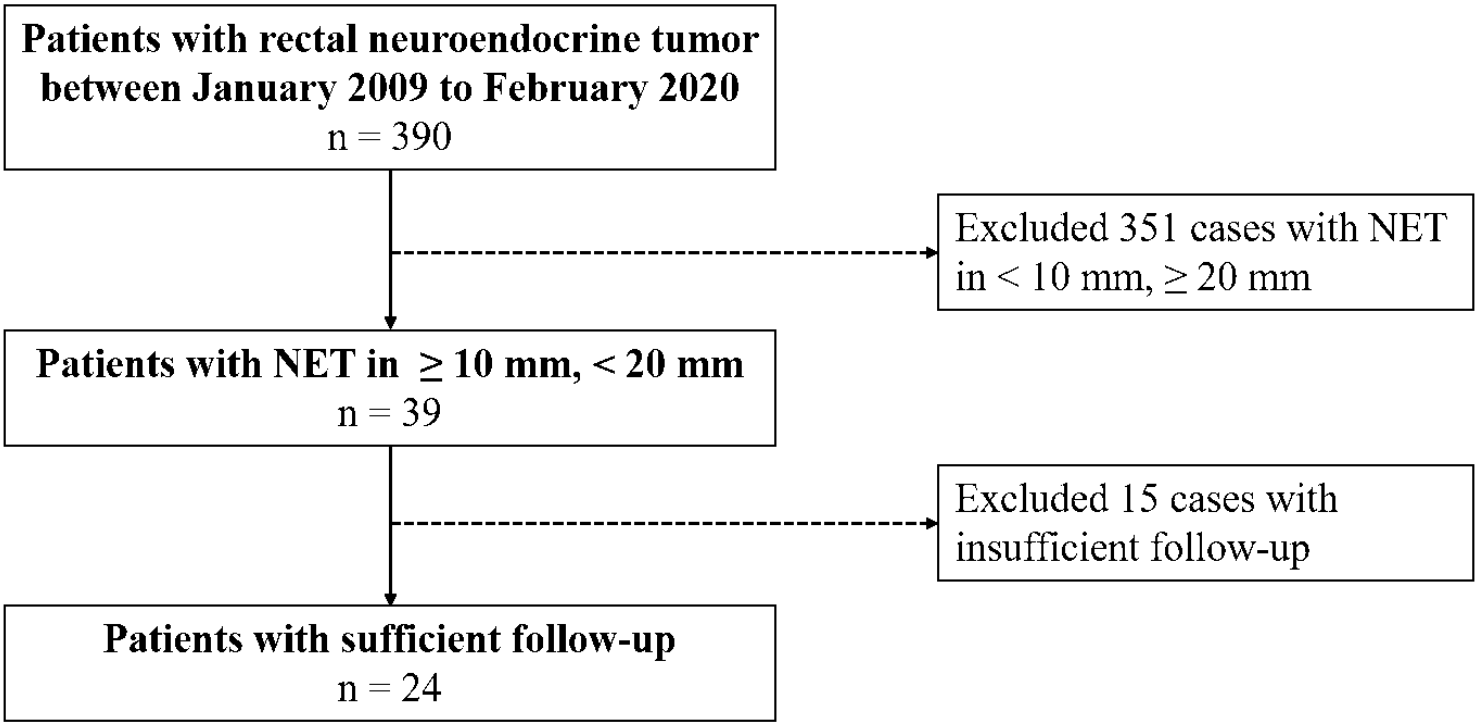

Figure 1

Patient Selection Flow

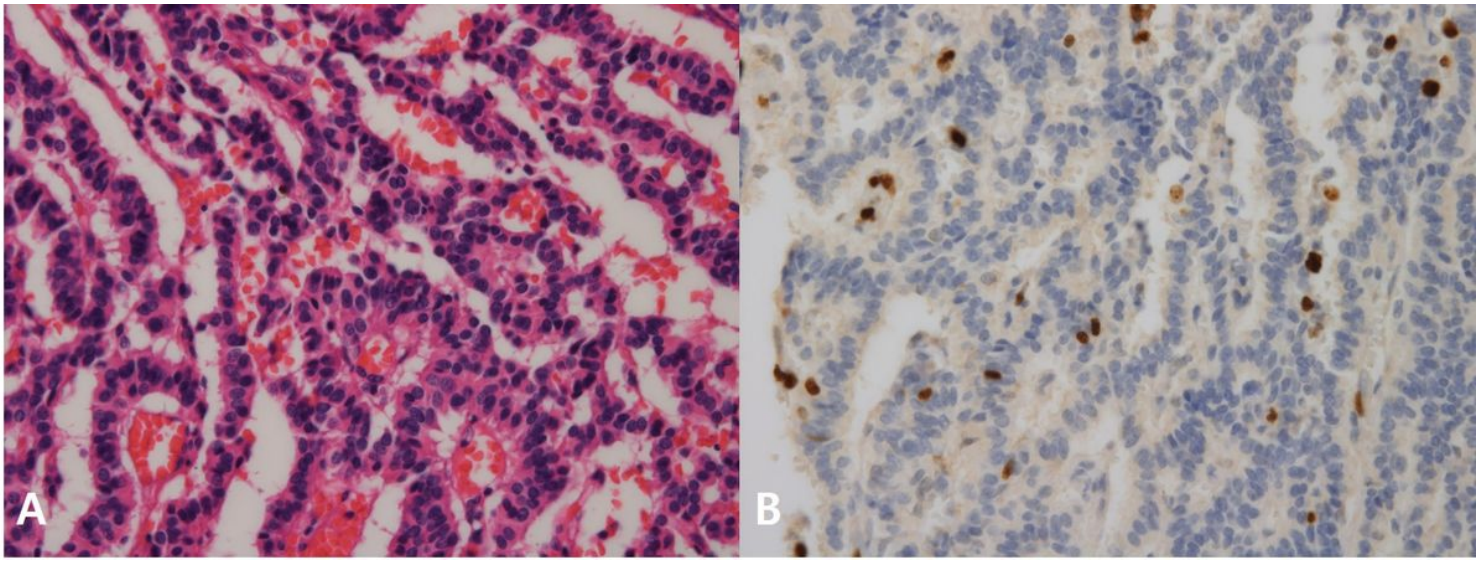

Figure 2

Rectal neuroendocrine tumor (Case 2) with liver and two lymph node metastases. A: Haematoxylin and eosin (H&E) staining (x400 magnification), B: Immunohistochemical staining for Ki-67 at x400 magnification (Ki-67 index = 11%)

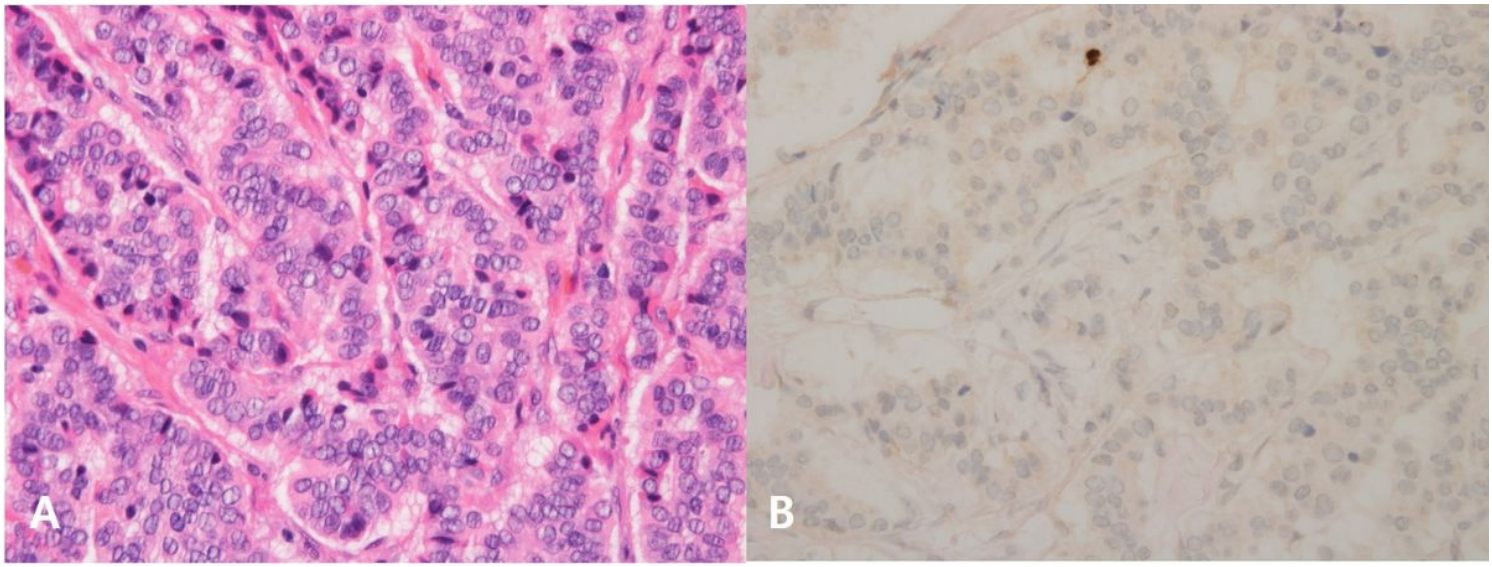

Figure 3

Rectal neuroendocrine tumor (Case 1) with three lymph node metastases. A: Haematoxylin and eosin (H&E) staining (x400 magnification), B: Immunohistochemical staining for Ki-67 at x400 magnification (Ki-67 index = 2%)