Factors predicting metastasis in patients with 10–20-mm sized rectal neuroendocrine tumor

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Research

Keywords: Rectal neuroendocrine tumor, metastasis, endorectal ultrasound, endoscopic resection

Posted Date: October 21st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-51218/v2

Abstract

Background: Rectal neuroendocrine tumors (NET) <10 mm are typically treated with endoscopic resection, while those >20 mm should be treated with radical surgical resection. However, the proper treatment methodology for 10-20-mm sized rectal NETs remains controversial. The purpose of this study was to investigate the appropriate treatment strategy for 10-20-mm sized rectal NETs by verifying factors that can predict metastasis.

Methods: A total of 24 patients with 10–20-mm sized NETs who were treated at Pusan National University Yangsan Hospital from January 2009 to September 2020 were included. The patients were divided into the metastasis and non-metastasis groups, and their respective data were analyzed.

Results: Seven patients had metastasis (29.2%) while 17 patients had no metastasis (70.8%). The tumor size, based on the endorectal ultrasound (EUS) findings, was significantly larger in the metastatic than in the non-metastatic group (14.4 vs. 10.2 mm, p = 0.029); however, the pathological tumor size did not show significant differences (13.3 vs. 11.8 mm, p = 0.065). Lymph node enlargement was observed in a single patient (14.3%) in the metastatic group, based on EUS and computed tomography (CT) imaging findings. The mitotic count (p = 0.017) and Ki-67 index (p = 0.014) were significantly higher in the metastatic group than in the non-metastatic group. The two groups also showed a significant difference in the proportion of patients with tumor grade 2 (71.4% vs. 5.9%, p = 0.003). In multivariate analysis, the tumor grade was the only independent metastasis-predicting factor (odds ratio = 49.25; 95% confidence interval = 2.55–950.83; p = 0.010).

Conclusions: Regarding the treatment of 10–20-mm sized rectal NETs, tumor grade 2 should be the most important factor to determine whether additional radical resection is necessary.

Background

Neuroendocrine tumor (NET), which originates from chromaffin-like cells, has neuroendocrine function and malignant potential [1]. The incidence of these tumors is on the rise, and case of rectal NETs showed the largest increase in recent years [2, 3]. Rectal NETs are known to have a better prognosis than NETs of the small bowel, colon, and other sites of the body [2, 4, 5]. In particular, a rectal NET <10 mm is considered an indolent lesion and is typically treated with endoscopic resection [6]. However, rectal NETs >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].

In contrast, the proper treatment strategies for 10–20-mm sized rectal NETs remain controversial [1, 3, 4, 9]. Endoscopic resection can be prioritized as a treatment method [2]. However, 10–15% incidence of metastasis was observed in patients with 10–20-mm sized rectal NETs; therefore, the risk of metastasis always exists following local excision [7]. Radical resection can be considered as another treatment option; however, in this case, the sacrifice of a huge portion of the rectum is inevitable, which leads to sequelae such as the 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 NETs is a fundamental issue that determines the prognosis and quality of life of the patient.

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

Methods

Patient population

Patients who underwent endoscopic resection, transanal excision, or radical surgery for rectal NETs (10–20-mm in size) at Pusan National University Yangsan Hospital from January 2009 to September 2020 were included. All data were taken from a prospectively maintained database. The exclusion criteria were as follows: pathologic tumor size <10 mm or ≥20 mm; follow-up period <30 months after endoscopic resection or transanal excision without radical surgery (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

The 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 the tumor size, involvement of muscularis propria, and lymph node enlargement. Lymph node enlargement and distant metastasis were checked using multiphase computed tomography (CT). Enlargement of the lymph node >5 mm was considered significant.

The tumor size, 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 the Ki-67 index, which were used to assess the tumor grade. In addition, the expressions of synaptophysin, chromogranin A, and CD56 were tested.

The mitotic count, categories of the Ki-67 index, and grading criteria were based on the 2019 WHO classification [12]. The definition of the grading criteria of rectal NET was as follows: 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%
In the case of radical resection, the presence or absence of lymph node metastasis was examined pathologically. In cases of endoscopic resection or transanal local excision, no lymph node metastasis was considered, when there was no evidence of recurrence or metastasis on CT and colonoscopy after at least 30 months of follow-up.

Standard management

Every patient underwent EUS together with the multiphase abdomen and pelvis CT to assess the tumors' progress and determine its clinical stage. Afterward, endoscopic and surgical resections were selected as treatment methods. Endoscopic mucosal resection or endoscopic submucosal dissection was conducted for endoscopic resection. Transanal excision and LAR were performed for the surgical resection.

First, an experienced gastroenterologist checked whether it was possible to apply endoscopic resection, as judged based on the results of endoscopy and EUS. The indication for endoscopic resection was as follows: (1) tumor size on EUS < 10 mm; (2) no evidence of involvement of muscularis propria on EUS; (3) no evidence of metastasis to lymph node or distant organ, as observed using EUS and CT. Afterward, surgical resection was selected by an experienced colorectal surgeon and gastroenterologist in consideration of the patient's condition and intention. The indication for transanal local resection was as follows: (1) tumor size on EUS ≥10 mm with patients' intention to the surgery; (2) wide submucosal lesion where endoscopic resection would be challenging; (3) positive resection margin after endoscopic resection. The indication for LAR was as follows: (1) tumor size on EUS ≥10 mm with patients' strong intention to the surgery; (2) suspicious involvement of muscularis propria, as observed EUS; (3) suspicious metastasis to lymph node, as observed EUS; (4) suspicious metastasis to lymph node or distant organ, as observed CT; (5) positive lymphovascular or perineural invasion in the pathological findings; (6) positive resection margin after transanal local resection. When distant metastasis was observed on CT, metastasectomy was performed with LAR where resection was possible.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 26; IBM Corp., Armonk, NY, USA). The independent-samples t-test was used to analyze normally distributed continuous variables. The 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 <0.05 was considered statistically significant.

Results

Patient clinical characteristics

In total, 24 patients with 10–20-mm sized rectal NETs from January 2009 to September 2020 were included in the present study (Fig. 1). Of these, seven patients had metastasis (metastatic group, 29.2%) and 17 had no metastasis (non-metastatic group, 70.8%). Patient characteristics are summarized in Table 1. The mean age was 55.6 and 52.1 years in the metastatic and the non-metastatic group, respectively. Radical resection was performed in all seven patients of the metastatic group, while 76.5% and 23.5% of the patients in the non-metastatic group underwent endoscopic resection and transanal local excision, respectively.

Endoscopic and imaging results

A smooth surface of tumors and ulceration was observed in 57.1% and 28.6% of patients in 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 = 0.113). While the two groups showed no significant difference in the endoscopic tumor size, the EUS tumor size was statistically larger in the metastatic than in the non-metastatic group (14.4 vs. 10.2 mm, p = 0.029). Furthermore, the proportion of patients with EUS tumor size ≥13 mm was higher in the metastatic group (85.7% vs. 14.3%, p = 0.023). Involvement of muscularis propria involvement was a higher in the metastatic group (42.9% vs. 5.9%, p = 0.059) than in the non-metastatic group. Lymph node enlargement was observed in a single patient (14.3%) from the metastatic group in each of the EUS and CT imaging. Liver metastasis was observed in two patients (28.6%) of the metastatic group, based on CT findings.

Pathological features

There was no significant difference in the pathological tumor size between the two groups (13.3 vs. 11.8 mm, p = 0.087) (Table 3). Lymphovascular and perineural invasions tended to have higher frequencies among patients in the metastatic group than among those in the non-metastatic group. However, the differences were not statistically significant. In the metastatic group, 42.9% of the patients showed a mitotic count of 2–20, which was not observed in the non-metastatic group (p = 0.017). The Ki-67 index was 3–20% in 57.1% and 5.9% of the patients in the metastatic and non-metastatic groups, respectively. This difference between the groups was statistically significant (p = 0.014). The two groups also showed a statistically significant difference in the proportion of patients with tumor grade 2 (71.4% vs. 5.9%, in the patients of the metastatic and non-metastatic groups, respectively, p = 0.003). The numbers of positive cases with chromogranin A, synaptophysin, and CD56 expression were not significantly different between the two groups.

Multivariate analysis of predicting factor for metastasis

In multivariate analysis, tumor grade 2 was identified as a significant independent factor for predicting metastasis (odds ratio [OR] = 49.25, 95% confidence interval [CI] = 2.55–950.83, p = 0.010) (Table 4).

Clinicopathologic patient characteristics in the metastatic group

The clinicopathologic characteristics of the patients in the metastatic group are summarized in Table 5. Metastasis was observed in seven patients. Among them, there were seven and two cases of lymph node and liver metastasis, respectively. Two patients had both type of metastases. Of these, five and two cases were of tumor grade 2 and 1, repectively. In one of the patients with tumor grade 1 (Case 3), lymphovascular and perineural invasions were identified. In Case 6, in which tumor grade 1 was assigned, lymph node metastasis was suspected from the results obtained using EUS. Haematoxylin and eosin (H&E) and immunohistochemical staining for Ki-67 in Cases 1 and 2 are shown in Figures 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 NETs. The mitotic count and Ki-67 index itself were also meaningful; however, it was less significant than the tumor grade. The EUS tumor size was significant in univariate analysis. Pathological tumor size, lymphovascular invasion, and perineural invasion showed no statistically significant differences.

The tumor grade was the most significant factor to predict metastasis in the present study. Several previous studies and guidelines have also stated that mitotic count and the Ki-67 index were significant in predicting metastasis risk and prognosis [10, 13]. In contrast, some other studies have reported that the tumor grade was a significant predictor, assessed by combining the mitotic count and Ki-67 index [6, 11, 14]. In the present study, we focused on patient with on 10–20-mm sized rectal NETs, and the grade was an independent predictive factor for metastasis in multivariate analysis. In particular, 71.4% of the patients with metastasis had 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 could be determined when the tumor grade has been used as the main factor to predict metastasis in post-operative biopsy while referring to the results of imaging and other pathological tests.

It is surprising that the tumor size, as determined by EUS, was a more significant factor than the pathological tumor size in predicting metastasis. There was a possibility that the biopsy results may not have accurately reflected the original tumor properties, as tissue deformation may occur during and after resections. Conversly, it can be thought that EUS retains the original shape before the manipulation and better reflects the tumor's original size. This reasoning seems to be more conspicuous, as the accuracy of the measurements obtained with the EUS machine has improved with 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 the pathological tumor size.

Lymphovascular and perineural invasion had no statistical significance in the present study; however, they were observed in higher percentage (28.6% and 42.9%, respectively) in patients with metastasis (vs. 5.9% in those in the non-metastatic group). A meta-analysis showed that lymphovascular invasion was a risk factor for lymph node metastasis [15]. Concerning the small sample size in the present study, type II error might occur, and an increase in the sample size may demonstrate a statistical significance for these factors. As aforementioned, one case with metastasis was determined as tumor grade 1, in which lymphovascular and perineural invasions were identified. The significance may be lower than that of the tumor grade, but lymphovascular and perineural invasions may certainly be considered as clinically meaningful tests.

Immunohistochemical methods for rectal NET diagnosis 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 standards [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 test [16]. In the present study, tests for chromogranin A, synaptophysin, and CD56 were performed. In addition, this study also investigated whether immunohistochemical tests can be used for diagnosis and for determining the treatment method. However, none of these immunochemical tests for NET diagnosis could be identified to have an association with lymph node metastasis. Synaptophysin and CD56 were expressed in all patients in the 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 NETs. As previous studies have focused on various sizes of rectal NETs, the predictors of metastasis of 10–20-mm sized rectal NETs could not be directly identified. The current study suggested that the tumor grade is the most important factor in determining the radical treatment of 10–20-mm sized rectal NETs. In addition, it is considered essential to examine the tumor size, lymph node enlargement, and muscularis propria involvement using EUS and to examine lymph node enlargement using CT. Thereafter, when the tumor size defined with EUS is ≥13 mm, muscularis propria has been infiltrated, and lymph node enlargement has been identified based on EUS and CT findings, radical resection should be considered as the first option. In other cases, endoscopic resection may be considered at first choice; afterward, radical resection is suggested for tumor grade 2 or higher in pathological examination.

This study had a few limitations. First, there was small numbers of patients included in the study. The incidence of 10–20-mm sized rectal NETs was low and that of metastasis was even lower, which led to further limitation of the sample size. To compensate for this limitation, we extended the study period to 11 years. Another limitation was the retrospective design of this study; therefore, the possibility for selection bias existed. In the future, prospective studies could

obtain more significant results. Moreover, lymph node metastasis was not pathologically confirmed in all patients. To exclude potential errors that could not be identified with imaging, despite lymph node metastasis, we only included patients who were followed-up for at least 30 months in case of receiving endoscopic resection with no pathologically identified lymph node metastasis. Patients who underwent only endoscopic resection with a follow-up duration of <30 months were excluded.

Conclusions

For the treatment of 10–20-mm sized rectal NETs, tumor grade 2 should be the most important factor to determine whether additional radical resection is necessary.

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 analyzed 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.

Funding

This study was supported by the Research Institute for Convergence of Biomedical Science and Technology (61-2020-002), Pusan National University Yangsan Hospital.

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 critically revised the manuscript.

Acknowledgements

Abbreviations

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

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Tables

Table 1. Clinical patient characteristics

Parameters	Metastasis (n = 7)	Non-metastasis (n = 17)	p-value
Age (years)	55.6 ± 11.5	52.1 ± 13.0	0.539
Sex			
Male	5 (71.4)	12 (70.6)	>0.999
Female	2 (28.6)	5 (29.4)	
Treatment methods			
Endoscopic resection	0 (0)	13 (76.5)	<0.001
Transanal excision	0 (0)	4 (23.5)	
Radical resection	7 (100)	0 (0)	
Follow-up periods (months)	19.9 ± 21.70	47.8 ± 18.1	0.004

The results are expressed as mean ± standard deviation or numbers with percentages in parentheses, as appropriate.

Table 2. Endoscopic, EUS, and CT imaging results

Parameters	Metastasis (n = 7)	Non-metastasis (n = 17)	p-value
Tumor surface			
Smooth	4 (57.1)	12 (70.6)	0.113
Central depression	1 (14.3)	5 (29.4)	
Ulcer	2 (28.6)	0 (0)	
Tumor size on endoscopy (mm)	14.0 ± 1.9	12.1 ± 5.6	0.237
Tumor size on EUS (mm)	14.4 ± 3.4	10.2 ± 3.9	0.029
Tumor size on EUS			
<13 mm	1 (14.3)	12 (70.6)	0.023
≥13 mm	6 (85.7)	5 (29.4)	
MP involvement on EUS (+)	3 (42.9)	1 (5.9)	0.059
LN enlargement on EUS (+)	1 (14.3)	0 (0)	0.292
LN enlargement on CT (+)	1 (14.3)	0 (0)	0.292
Liver metastasis on CT (+)	2 (28.6)	0 (0)	0.076

The results are expressed as mean ± standard deviation or numbers with percentages in parentheses, as appropriate. MP, muscularis propria; LN, lymph node; EUS, endorectal ultrasound; CT, computed tomography

Table 3. Pathological features

Parameters	Metastasis (n = 7)	Non-metastasis (n = 17)	p-value
Tumor size (mm)	13.3 ± 1.3	11.8 ± 2.4	0.065
Tumor size			
<13 mm	2 (28.6)	12 (70.6)	0.085
≥13 mm	5 (71.4)	5 (29.4)	
MP involvement (+)	1 (14.3)	0 (0)	0.292
Lymphovascular invasion (+)	2 (28.6)	1 (5.9)	0.194
Perineural invasion (+)	3 (42.9)	1 (5.9)	0.059
Mitotic count[a]			
<2	4 (57.1)	17 (100)	0.017
2-20	3 (42.9)	0 (0)	
Ki-67 index (%)			
<3	3 (42.9)	16 (94.1)	0.014
3-20	4 (57.1)	1 (5.9)	
Tumor grade			
1	2 (28.6)	16 (94.1)	0.003
2	5 (71.4)	1 (5.9)	
Chromogranin A (+)	3 (42.9)	4 (23.5)	0.374
Synaptophysin (+)	7 (100)	17 (100)	>0.999
CD 56 (+)	7 (100)	17 (100)	>0.999

The results are expressed as mean ± standard deviation or numbers with percentages in parentheses, as appropriate. MP, muscularis propria; LN, lymph node; EUS, endorectal ultrasound

[a]Mitotic count is per 10 high-power fields.

Table 4. Multivariate analysis of predicting factor for metastasis

Predictor	Odds ratio	95% CI	p-value
MP involvement	5.20	0.12–217.92	0.387
Lymphovascular invasion	5.21	0.07–376.09	0.450
Perineural invasion	16.82	0.63–448.27	0.092
Tumor grade 2	49.25	2.55–950.83	0.010

CI, confidence interval; EUS, endorectal ultrasound; MP, muscularis propria

Table 5. 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	Metastasi
1	35	M	Ulcerated	15.0	O	X	X	13.0	X	X	3	2	2	LN
2	61	M	Ulcerated	15.0	O	X	X	15.0	X	O	10	11	2	Liver and LN
3	61	M	Smooth	17.2	X	X	X	13.0	O	O	0	<1	1	LN
4	69	F	Smooth	18.7	X	X	O	15.0	O	X	5-7	5	2	Liver and LN
5	58	F	Smooth	8.0	O	X	X	12.0	X	X	0	3	2	LN
6	45	M	Central depression	13.9	X	O	X	12.0	X	X	1	<1	1	LN
7	60	M	Smooth	13.0	X	X	X	13.0	X	O	10	5	2	LN

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

Figures

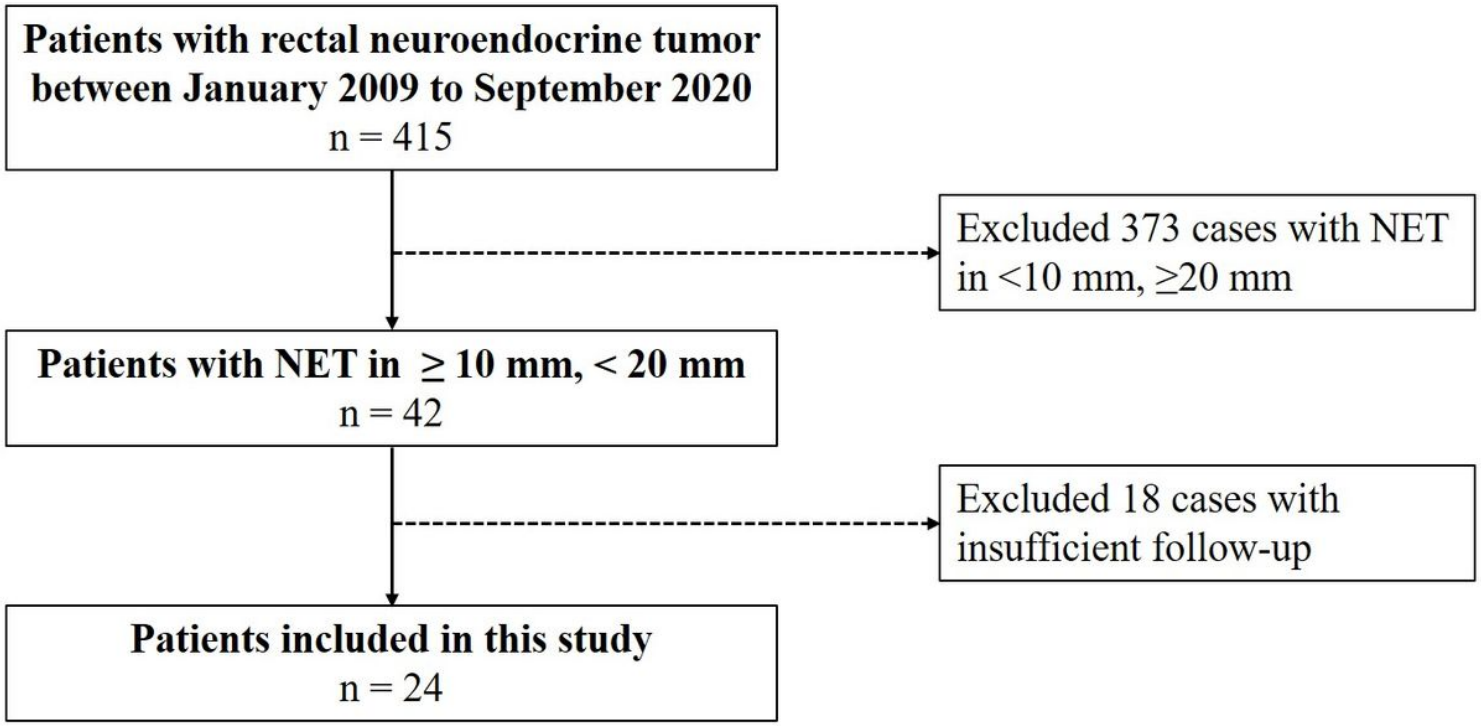

Figure 1

Patient selection flowchart

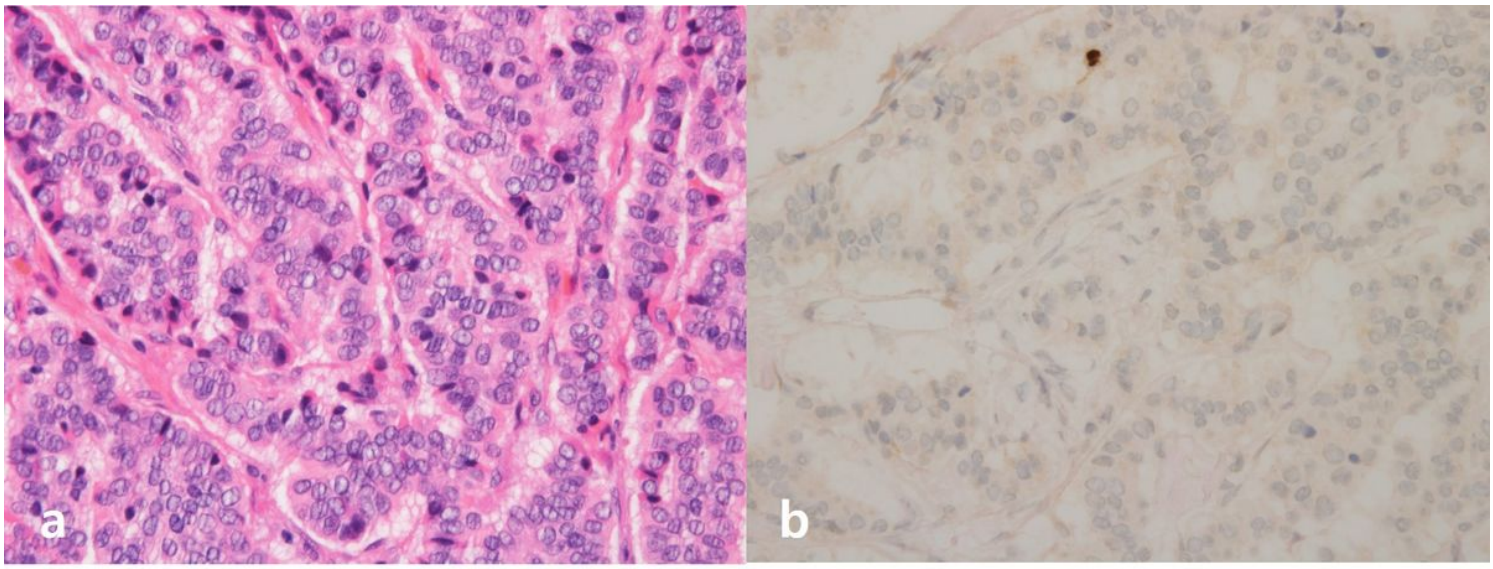

Figure 2

Rectal neuroendocrine tumor (Case 1) with three lymph node metastases. a: H&E staining (×400 magnification), B: Immunohistochemical staining for Ki-67 at ×400 magnification (Ki-67 index = 2%) H&E, hematoxylin and eosin

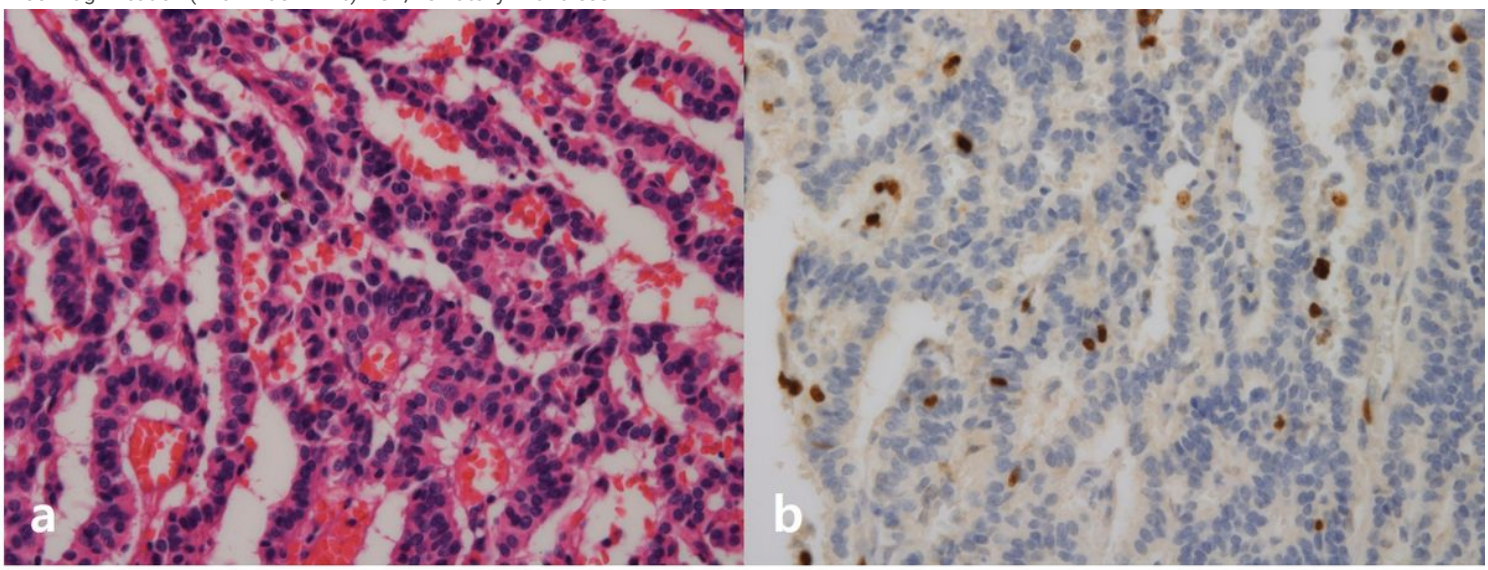

Figure 3

Rectal neuroendocrine tumor (Case 2) with liver and two lymph node metastases. a: H&E staining (×400 magnification), b: Immunohistochemical staining for Ki-67 at ×400 magnification (Ki-67 index = 11%) H&E, hematoxylin and eosin