Tumor grade 2 as the independent predictor for lymph node metastasis in 10–20 mm sized rectal neuroendocrine tumor

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Purpose: Rectal neuroendocrine tumors (NETs) < 10 mm are endoscopically resected, while those ≥ 20 mm are treated with radical surgical resection. The choice of treatment for 10–20 mm sized rectal NETs remains controversial. This study aimed to verify factors predicting lymph node metastasis (LNM) of 10–20 mm sized rectal NET and utilize them to decide upon the treatment strategy.

Methods: Twenty-eight patients with 10–20 mm sized rectal NETs treated at Pusan National University Yangsan Hospital from January 2009 to September 2020 were divided into LNM (+) and LNM (–) groups, and their respective data were analyzed.

Results: Seven patients (25%) had LNM while 21 patients (75%) did not. Endorectal ultrasound findings showed tumor size was significantly larger in the LNM (+) than in the LNM (–) group (15 mm vs. 10 mm, $P=0.018$); however, pathologically, there was no significant difference in tumor size (13 mm vs. 11 mm, $P=0.109$). The mitotic count ($P=0.011$), Ki-67 index ($P=0.008$), and proportion of tumor grade 2 patients (5 cases, 71% vs. 1 case, 5%; $P=0.001$) were significantly higher in the LNM (+) group. In multivariate analysis, tumor grade 2 was the independent factor predicting LNM (odds ratio, 61.32; 95% confidence interval, 3.17–1,188.64; $P=0.010$).

Conclusion: Tumor grade 2 was the independent factor predicting LNM in 10–20 mm sized rectal NETs. Therefore, it could be considered as the meaningful factor in determining whether radical resection is necessary.

Keywords: Neuroendocrine tumors, Rectum, Lymphatic metastasis, Grade, Endoscopy

INTRODUCTION

Neuroendocrine tumor (NET), which originates from chromaf-

fin-like cells, has neuroendocrine function and malignant potential [1]. The incidence of these tumors is on the rise, and number of cases of rectal NETs have shown the largest increase in recent years [2]. Rectal NETs are known to have a better prognosis than NETs of the small bowel, colon, and other sites of the body. In particular, a rectal NET < 10 mm is considered an indolent lesion and is typically treated with endoscopic resection [3]. Whereas, rectal NETs > 20 mm have a 60%–80% chance of metastasis, in which case radical resection, such as low anterior resection (LAR) or abdominoperineal resection, is recommended for treatment.

In contrast, the proper treatment strategies for 10–20 mm sized rectal NETs remain controversial [3–5]. Endoscopic resection can be selected as one of the treatment options [3]. However, lymph node metastasis (LNM) was observed in 10%–15% of patients with 10–20 mm sized rectal NETs; therefore, the risk of metastasis always exists following local excision. 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

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chances of post-operational morbidity and mortality. Therefore, selecting the proper treatment method for 10–20 mm sized rectal NETs is a fundamental concern that determines the prognosis and quality of life of the patient.

To select an appropriate treatment method, predictive factors for LNM need to be determined in patients with rectal NET. To date, these identified factors include the tumor size, muscularis layer invasion, atypical endoscopic features, lymphovascular invasion, perineural invasion, mitotic count, Ki-67 index, and tumor grade [6–9]. However, because of inconsistency among the guidelines and studies, there is confusion regarding the determination of the appropriate treatment methods using those predicting factors [3,7,8]. Furthermore, most of the previous studies involved various sizes of rectal NETs. Only a limited number of studies on 10–20 mm sized rectal NETs are available. Therefore, the current study aimed to verify clinicopathologic factors that can predict LNM of 10–20 mm sized rectal NET and utilize them to decide upon the treatment strategy.

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; poorly differentiated neuroendocrine carcinoma [10]; follow-up period < 24 months after endoscopic resection or transanal excision without radical surgery

Fig. 1. Patient selection flowchart. NET, neuroendocrine tumor.

(Fig. 1). All the patients who underwent radical surgery were included regardless of follow-up period. We conducted this study in compliance with the principles of the Declaration of Helsinki. The study design was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 05-2020-079). Informed consent was waived.

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 LNM 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 tumor grade were based on the 2010 World Health Organization (WHO) classification [11]. 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, LNM was confirmed pathologically. In cases of endoscopic resection or transanal excision, negative LNM was considered when there was no evidence of recurrence or metastasis on CT and colonoscopy after at least 24 months of follow-up. CT was conducted every 6 months. Colonoscopy was performed at 1 year after the surgery, and repeated in 1–3 years according to the result.

Standard management

All the patients underwent EUS together with the multiphase abdomen and pelvis CT to assess the tumors' progress and determine its clinical stage. Afterward, endoscopic or 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 to carry out endoscopic resection based on the results of endoscopy and

EUS. If it was judged possible, endoscopic resection was performed right after EUS. The type of endoscopic resection was selected based on the size of the rectal NET and preference of the endoscopist. We did not conduct colonoscopic biopsy before endoscopic resection because biopsy can cause fibrosis that would complicate removal of the NET. Afterward, surgical resection was decided by an experienced colorectal surgeon and gastroenterologist in consideration of the patient's condition and intention. Transanal excision was performed in case of wide submucosal lesion where endoscopic resection would be challenging, and positive resection margin after endoscopic resection. LAR was performed in the following cases: (1) suspicious involvement of muscularis propria, as observed on EUS; (2) suspicious LNM, as observed on EUS or CT; (3) positive lymphovascular invasion, perineural invasion, or tumor grade ≥ 2 based on pathological findings; (4) positive resection margin after transanal excision; or (5) patient's decision to undergo surgery due to the fear of metastasis. When distant metastasis was observed on CT, metastasectomy was performed with LAR if 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 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.

Table 1. Clinical characteristics of all patients with 10–20 mm sized rectal neuroendocrine tumor

Parameter	Total (n = 28)	LNM (+) (n = 7)	LNM (–) (n = 21)	P-value
Age (yr)	57 (46–61)	60 (45–61)	56 (42–62)	0.577
Sex				> 0.999
Male	19 (68)	5 (71)	14 (67)	
Female	9 (32)	2 (29)	7 (33)	
Final treatment methods				< 0.001
Endoscopic resection	17 (61)	0	17 (81)	
Transanal excision	3 (11)	0	3 (14)	
Radical resection	8 (28)	7 (100)	1 (5)	
Follow-up periods (mo)	39 (24–60)	16 (1–31)	52 (31–60)	0.012

Values are presented as median (interquartile range) or number (%).

LNM, lymph node metastasis.

RESULTS

Patient clinical characteristics

In total, 28 patients presenting 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 (25%) had LNM and 21 (75%) had no LNM (Table 1). The median age was 60 and 56 years in the LNM (+) and the LNM (–) groups, respectively. Radical resection was performed in all seven patients of the LNM (+) group, while 17 (81%), three (14%), and one (5%) patients in the LNM (–) group underwent endoscopic resection, transanal excision, and radical resection, respectively.

Relationship between imaging results and LNM

The tumor surface was smooth in four (57%) and ulcerated in two (29%) patients in the LNM (+) group (Table 2). In the LNM (–) group, 16 (76%) patients had tumors with a smooth surface, and no cases of ulceration were observed ($P = 0.076$). While the two groups showed no significant difference in the tumor size when examined endoscopically, the tumor size based on the EUS findings was significantly larger in the LNM (+) group than in the LNM (–) (15 mm vs. 10 mm, $P = 0.018$). Furthermore, EUS images showed the proportion of patients with tumor size ≥ 15 mm was higher in the LNM (+) group ($P = 0.043$). They also revealed more frequent involvement of muscularis propria in the LNM (+) group ($P = 0.038$). EUS and CT imaging showed lymph node enlargement in a single patient (14%) of the LNM (+) group.

Table 2. Relationship between imaging results and lymph node metastasis in 10–20 mm sized rectal neuroendocrine tumor

Parameter	LNM (+) (n = 7)	LNM (–) (n = 21)	P-value
Tumor surface			0.076
Smooth	4 (57)	16 (76)	
Central depression	1 (14)	5 (24)	
Ulcerated	2 (29)	0	
Tumor size on endoscopy (mm)	15 (13–15)	12 (9–15)	0.326
Tumor size on EUS (mm)	15 (13–17)	10 (6–14)	0.018
Tumor size on EUS			0.043
< 15 mm	3 (43)	18 (86)	
≥ 15 mm	4 (57)	3 (14)	
MP involvement on EUS (+)	3 (43)	1 (5)	0.038
LN enlargement on EUS (+)	1 (14)	0	0.250
LN enlargement on CT (+)	1 (14)	0	0.250

Values are presented as median (interquartile range) or number (%).

LNM, lymph node metastasis; EUS, endorectal ultrasound; MP, muscularis propria; LN, lymph node; CT, computed tomography.

Relationship between pathological features and LNM

Pathologically, there was a tendency for the tumor to be larger in the LNM (+) group (13 mm vs. 11 mm, $P=0.109$) (Table 3). Lymphovascular invasion tended to have higher frequencies among patients in the LNM (+) group than among those in the LNM (–) group. However, the differences were not statistically significant ($P=0.145$); whereas, perineural invasion was significantly more frequent in the LNM (+) group ($P=0.038$). A mitotic count of 2–20 was observed more frequently in the LNM (+) group than in the LNM (–) group (3 cases, 43% vs. 0 cases, 0%; $P=0.011$). The Ki-67 index of 3%–20% was significantly higher in the LNM (+) group (4 cases, 57% vs. 1 case, 5%; $P=0.008$). The proportion of

patients with tumor grade 2 was also significantly higher in the LNM (+) group (5 cases, 71% vs. 1 case, 5%; $P=0.001$). The numbers of positive cases with chromogranin A, synaptophysin, and CD56 expression were not significantly different between the two groups.

Multivariate analysis of predicting factors for LNM

In multivariate analysis, tumor grade 2 was identified as an independent factor for predicting LNM (odds ratio, 61.32; 95% confidence interval, 3.17–1,188.64; $P=0.010$) (Table 4).

Clinicopathologic patient characteristics in the LNM (+) group

Seven patients had metastasis to the regional lymph node (Table 5). Among them, there were two patients with liver metastasis. Five patients had tumor grade 2, while in two patients (cases 3 and 6) (Table 5), it was grade 1. Among these two patients, lymphovascular invasion and perineural invasion were identified in the case 3 patient, while the EUS image of the patient in case 6 showed lymph node enlargement that was indicative of metastasis. Hematoxylin and eosin and immunohistochemical staining for Ki-67 in cases 1 and 2 are shown in Figs. 2 and 3, respectively.

DISCUSSION

In this study, tumor grade 2 was the independent predictor for LNM in patients with 10–20 mm sized rectal NETs. Therefore, tumor grade 2 could be considered as the meaningful factor to determine whether radical resection is required for the treatment of such NETs. The mitotic count and Ki-67 index itself were also meaningful; however, they were less significant than the tumor grade. The EUS images showing tumor size and perineural invasion were significant in univariate analysis. Pathologically, however, tumor size and lymphovascular invasion showed no significant differences among the two groups.

This study focused on the appropriate treatment choice for 10–20 mm sized rectal NETs. Most previous studies have included various sizes of rectal NETs. Because majority (80%–90%) of rectal

Table 3. Relationship between pathologic features and lymph node metastasis in 10–20 mm sized rectal neuroendocrine tumor

Parameter	LNM (+) (n = 7)	LNM (–) (n = 21)	P-value
Tumor size (mm)	13 (12–15)	11 (10–14)	0.109
Tumor size			0.622
< 15 mm	5 (71)	17 (81)	
≥ 15 mm	2 (29)	4 (19)	
MP involvement (+)	1 (14)	0	0.250
Lymphovascular invasion (+)	2 (29)	1 (5)	0.145
Perineural invasion (+)	3 (43)	1 (5)	0.038
Mitotic count ^a			0.011
< 2	4 (57)	21 (100)	
2–20	3 (43)	0	
Ki-67 index (%)			0.008
< 3	3 (43)	20 (95)	
3–20	4 (57)	1 (5)	
Tumor grade			0.001
1	2 (29)	20 (95)	
2	5 (71)	1 (5)	
Chromogranin A (+)	3 (43)	5 (24)	0.374
Synaptophysin (+)	7 (100)	21 (100)	> 0.999
CD56 (+)	7 (100)	21 (100)	> 0.999

Values are presented as median (interquartile range) or number (%).

LNM, lymph node metastasis; MP, muscularis propria.

^aMitotic count is per 10 high-power fields.

Table 4. Logistic regression analysis of the predictive factors for lymph node metastasis in 10–20 mm sized rectal neuroendocrine tumor

Predictor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Tumor size ≥ 15 mm on EUS	8.00 (1.16–55.26)	0.035	3.30 (0.12–92.26)	0.483
MP involvement	15.00 (1.23–183.63)	0.034	5.87 (0.13–267.77)	0.364
Perineural invasion	15.00 (1.23–183.63)	0.034	20.85 (0.77–565.33)	0.071
Tumor grade 2	50.00 (3.74–668.35)	0.003	61.32 (3.17–1,188.64)	0.010

OR, odds ratio; CI, confidence interval; EUS, endorectal ultrasound; MP, muscularis propria.

NETs were less than 10 mm [12], previous study reports could not directly define predictors of LNM of 10–20 mm sized rectal NETs. Although Fields et al. [3] analyzed 10–20 mm sized rectal NETs to identify prognostic factors, this study did not include analysis of immunohistochemical results such as tumor grade, the Ki-67 index, and lymphovascular invasion. We analyzed exclusively 10–20

mm sized rectal NETs including immunohistochemical results, and tumor grade 2 was an independent predictive factor for LNM in multivariate analysis. Therefore, our study results present a clear understanding of the features and predictive factors for LNM of 10–20 mm sized rectal NETs.

Tumor grade 2 was the independent factor to predict LNM in

Table 5. Characteristics of the patients with the lymph node metastasis from 10–20 mm sized rectal neuroendocrine tumor

Case	Age (yr)	Sex	Tumor 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	Location of metastasis
1	35	M	Ulcerated	15.0	+	–	–	13	–	–	3	2	2	LN
2	61	M	Ulcerated	15.0	+	–	–	15	–	+	10	11	2	LN and liver
3	61	M	Smooth	17.2	–	–	–	13	+	+	0	< 1	1	LN
4	69	F	Smooth	18.7	–	–	+	15	+	–	5–7	5	2	LN and liver
5	58	F	Smooth	8.0	+	–	–	12	–	–	0	3	2	LN
6	45	M	Central depression	13.9	–	+	–	12	–	–	1	< 1	1	LN
7	60	M	Smooth	13.0	–	–	–	13	–	+	10	5	2	LN

EUS, endorectal ultrasound; MP, muscularis propria; LN, lymph node; CT, computed tomography; LVI, lymphovascular invasion; PI, perineural invasion; M, male; F, female.

Fig. 2. Rectal neuroendocrine tumor (case 1) with three lymph node metastases. (A) H&E staining, ×400. (B) Immunohistochemical staining for Ki-67 at ×400 (Ki-67 index, 2%).

Fig. 3. Rectal neuroendocrine tumor (case 2) with liver and two lymph node metastases. (A) H&E staining, ×400. (B) Immunohistochemical staining for Ki-67 at ×400 (Ki-67 index, 11%).

the present study. There have been fewer studies regarding the tumor grade than other factors because these grades were first described in the WHO classification of digestive system tumors in 2010 [11]. While some studies have reported that the tumor grade was a significant predictor [6,9,13], others have concluded that the tumor grade did not play a part in prediction of LNM [14]. In this study, 83% (5/6) of the patients with tumor grade 2 had LNM. Therefore, it would be acceptable to proceed with radical surgery in cases of grade 2 rectal NETs.

LNM occurred in two patients with tumor grade 1. One of them had lymphovascular and perineural invasion, and the other had lymph node enlargement on EUS. Therefore, it seems that the decision to perform radical resection could be determined by the tumor grade which has been used as the main factor to predict LNM after local excision, followed by referring to the results of imaging and other pathological tests.

The question of what happens if LNM occurs with NET grade 1 then arises. A case report by Kim et al. [15] provides a hypothesis suggesting that if the NET has low Ki-67 proliferation index and mitotic activity, the metastatic lesion may grow very slowly. If this is true, in cases of NET with lower grade and other risk factors for metastasis like lymphovascular invasion, delayed radical surgery could be decided to perform if metastasis was suspected on follow-up image examinations. This hypothesis was supported by the results of a systematic review that rectal NET patients treated with endoscopic resection had good prognosis despite positive lymphovascular invasion [16], which in turn, substantiates our results that the tumor grade should be the most significant factor in determining the need for radical resection.

Lymphovascular invasion and perineural invasion were not considered predictors for LNM by multivariate analysis in the current study; however, they were observed in higher percentages (29% vs. 5% lymphovascular invasion and 43% vs. 5% perineural invasion) in patients with the metastasis. Several studies including a meta-analysis showed that lymphovascular invasion was a risk factor for LNM [16,17]. 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. However, clinical implication is still doubtful, because several studies showed excellent prognosis after the endoscopic resection of rectal NETs despite lymphovascular invasion [16,18].

Surprisingly, the tumor size, as determined by EUS, was a more significant factor than the pathological tumor size for predicting LNM in 10–20 mm sized rectal NETs. There was a possibility that the biopsy results might not have accurately reflected the original tumor properties because tissue deformation may occur during and after resections. Conversely, it can be thought that EUS retains

the original shape before manipulation and better reflects the tumor's original size. This reasoning seems to be more valid as the accuracy of the measurements obtained with the EUS machine has improved with technological advancement [1]. Moreover, the risk of LNM can be assessed before treatments, such as endoscopic resection. Thus, the tumor size defined by EUS could be considered a more significant factor in determining the need for radical resection rather than the pathological tumor size.

This study had a few limitations. First, there were small numbers of patients included in the study. The incidence of 10–20 mm sized rectal NETs was very 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. In addition, LNM was not pathologically confirmed in all patients. To exclude potential errors that small-sized LNM might not be identified with imaging, we only included patients who were followed up for at least 24 months in case of receiving local excision such as endoscopic resection or transanal excision. Most patients underwent local excision had follow-up period of ≥ 36 months except for three patients (median period: 47 months).

In conclusion, tumor grade 2 was the independent factor to predict LNM in 10–20 mm sized rectal NETs. Therefore, tumor grade 2 could be considered as the meaningful factor in determining whether radical resection is necessary in the treatment of 10–20 mm sized rectal NETs. Further research is needed to confirm this result.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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