

Retrospective Study

Clinical impact of atypical endoscopic features in rectal neuroendocrine tumors

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Abstract

AIM: To validate the association between atypical endoscopic features and lymph node metastasis (LNM).

METHODS: A total of 247 patients with rectal neuroendocrine tumors (NETs) were analyzed. Endoscopic images were reviewed independently by two endoscopists, each of whom classified tumors by sized and endoscopic features, such as shape, color, and surface change (kappa coefficient 0.76 for inter-observer agreement). All of patients underwent computed tomography scans of abdomen and pelvis for evaluation of LNM. Univariate and multivariate analyses were performed to identify the factors associated with LNM. Additionally, the association between endoscopic atypical features and immunohistochemical staining of tumors was analyzed.

RESULTS: Of 247 patients, 156 (63.2%) were male and 15 (6.1%) were showed positive for LNM. On univariate analysis, tumor size ($P < 0.001$), shape ($P < 0.001$), color ($P < 0.001$) and surface changes ($P < 0.001$) were significantly associated with LNM. On multivariate analysis, tumor size (OR = 11.53, 95%CI: 2.51-52.93, $P = 0.002$) and atypical surface (OR = 27.44, 95%CI: 5.96-126.34, $P < 0.001$) changes were independent risk factors for LNM. The likelihood of atypical endoscopic features increased

as tumor size increased. Atypical endoscopic features were associated with LNM in rectal NETs < 10 mm ($P = 0.005$) and 10-19 mm ($P = 0.041$) in diameter. Immunohistochemical staining showed that the rate of atypical endoscopic features was higher in non L-cell tumors.

CONCLUSION: Atypical endoscopic features as well as tumor size are predictive factors of LNM in patients with rectal NETs.

Key words: Rectal neuroendocrine tumor; Colonoscopy; Lymph node metastasis

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Core tip: We were studied about association between endoscopic atypical features in rectal neuroendocrine tumor and metastasis in 2008. Thus, our study was designed to validate the association between atypical endoscopic features and lymph node metastasis (LNM). Our study showed that the atypical endoscopic features, such as size > 10 mm, surface changes, were risk factors for LNM. Additionally, rectal neuroendocrine tumors which showed atypical endoscopic features were associated with non L-cell tumors. When we examined rectal neuroendocrine tumor using colonoscopy, atypical endoscopic features help to predict the treatment plan.

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INTRODUCTION

Increases in rate of screening colonoscopy have resulted in increases in incidence and prevalence of rectal neuroendocrine tumors (NETs). Most rectal NETs are slow growing tumors that originate from enterochromaffin cells and rarely metastasize^[1,2]. A recent consensus guideline suggests that tumor size is the most powerful predictor of lymph node metastasis (LNM) of rectal NETs^[3,4]. Guideline of the National Comprehensive Cancer Network recommend that NETs ≤ 2 cm in diameter be excised transanally or endoscopically excision and that NETs > 2 cm in diameter undergo radical resection^[5]. However, LNMs have been reported in patients with NETs < 6 mm in diameter^[6], suggesting that tumor size alone is not predictive of LNM.

Colonoscopy is the most useful method of diagnosing and treating rectal NETs. Although typical NETs appear as yellowish, sessile, submucosal tumors^[7,8], some are morphologically unusual, having irregular surfaces

or being pedunculated or hyperemic. These unusual features have been associated with LNM, suggesting an association between endoscopic findings and LNM^[9].

Study was designed to validate the association between endoscopically atypical features and LNM. In addition, the association between endoscopically atypical features and the immunohistochemistry of these tumors was analyzed^[10].

MATERIALS AND METHODS

Patients

Data from 287 patients with rectal NETs diagnosed and treated at the National Cancer Center (Goyang, South Korea) and Daehang Hospital (Seoul, South Korea) between January 2008 and December 2010 were retrospectively reviewed^[10]. Eight patients with synchronous colorectal cancer, eight who underwent multiple biopsies before visiting our institutions and 24 whose endoscopic images were unavailable were excluded from this study. Finally, 247 patients with rectal NETs were analyzed (Figure 1). Of these 247 lesions, 208 were endoscopically resected, 22 were removed transanally, and 16 were treated with radical surgery. One patient received only palliative chemotherapy, because he had multiple unresectable liver and peritoneal metastases. Clinicopathologic variables were retrospectively collected from the patients' medical records. This study was approved by the Institutional Review Board of the National Cancer Center of Korea (NCC2014-0104).

Evaluation

All patients underwent endoscopic examination with video colonoscopes (Olympus CF-Q240, CF-Q260 or CF-H260; Olympus, Tokyo, Japan) for diagnosis and treatment. Endoscopic images were reviewed independently by two endoscopists, resulting in kappa coefficient of 0.76 for interobserver agreement. Any disagreements between the two endoscopists were resolved by open discussions with all expert endoscopists.

All patients underwent computed tomography (CT) scans of the abdomen and pelvis for evaluation of LNM. Patients were considered positive for LNM if CT scans revealed nodes > 3 mm in diameter in the perirectal area or nodes > 1 cm in diameter in the pelvis^[10-12]. Tumor sizes were confirmed by pathology reports, except for the one patient who did not undergo curative resection because of extensive liver metastases. All tumors were classified by size (longest diameter), and then by endoscopic features such as shape, color, and surface changes, including depression, erosion and ulceration. Of the 247 lesions, 217 were also assessed immunohistochemically.

Statistical analysis

Interobserver agreement on endoscopic findings

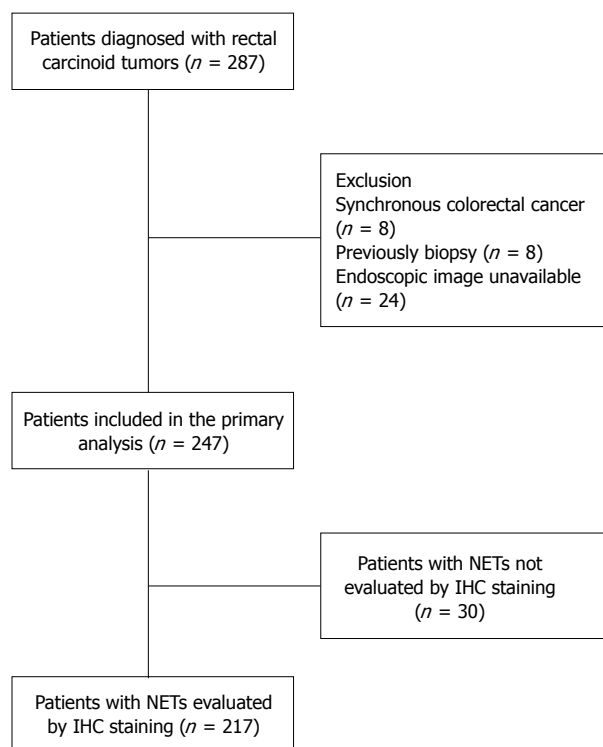


Figure 1 Study flow chart. NETs: Neuroendocrine tumors; IHC: immunohistochemistry.

was analyzed by calculating the kappa coefficient. The associations between endoscopic findings and LNM were analyzed by χ^2 or Fisher’s exact tests. Multivariate analysis using a logistic regression model was performed to identify associations between all potential parameters and LNM. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 14.0 (SPSS Inc., Chicago, IL). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the baseline clinicopathological characteristics of the 247 patients with rectal NETs. Of these patients, 91 (36.8%) were male and 156 (63.2%) were female. Mean age at diagnosis was 51.6 \pm 10.7 years and mean tumor size was 5.76 \pm 2.65 mm. Two patients had liver metastases at diagnosis, with one also having peritoneal seeding and 15 (6.1%) were diagnosed with LNM.

Fifty-five patients (22.3%) had rectal NETs with one or more atypical features (Figure 2), whereas the other 192 patients (77.7%) had rectal NETs with endoscopically typical features such as being sessile and having a smooth surface covered with normal or yellowish mucosa (Figure 3). On univariate analysis, tumor size, tumor shape, surface changes, and color were significantly associated with LNM. On multivariate analysis, tumor size (OR = 11.53, 95%CI: 2.51-52.93), atypical surface changes (OR = 27.44, 95%CI:

Table 1 Characteristics of the 247 patients with rectal neuroendocrine tumor *n* (%)

	Value
Age, mean \pm SD (range), yr	51.56 \pm 10.69 (27-76)
Sex	
Male	91 (36.8)
Female	156 (63.2)
Tumor size, mean \pm SD (mm)	5.76 \pm 2.76
Resection type	
Endoscopic resection	208 (84.2)
TEM or TAE	22 (8.9)
Radical resection	16 (6.5)
None	1 (0.4)
Distant organ metastasis at diagnosis	
Negative	245 (99.2)
Positive	2 (0.8)
LN metastasis	
Negative	232 (93.9)
Positive	15 (6.1)

TEM: Transanal endoscopic microsurgery; TAE: Transanal excision; LN: Lymph node.

5.96-126.34), and any type of atypical feature (OR = 4.38, 95%CI: 0.92-20.80) were independent risk factors for LNM (Table 2). Moreover, atypical features correlated with increased tumor size (Table 3).

Table 4 shows the association between endoscopic features and metastasis in rectal NETs < 10 mm and 10-19 mm in diameter were evaluated in Table 4, respectively. Tumor shape and color were not associated with LNM for either size range of rectal NETs. However, tumor surface changes were associated with LNM in patients with NETs < 10 mm ($P = 0.005$) and 10-19 mm ($P = 0.041$) in diameter. Ulceration was not observed in any tumor < 20 mm in diameter.

Table 5 shows the association between atypical features and the results of immunohistochemical staining results. L-cell phenotype and GLP1 were associated with atypical features, whereas non-L cell phenotype was associated with surface changes and color of NETs (Table 6).

DISCUSSION

Risk factors predictive of LNM of rectal NETs were assessed by univariate and multivariate analyses, with the latter showing that tumor size and atypical surface changes were significant independent predictors of LNM. The ability to predict the likelihood of LNM is important for managing patients requiring radical surgery to prevent tumor progression. Recent studies have reported that risk factors for LNM of rectal NETs include tumor size > 10 mm; atypical features; pathologic T stage; and muscular, perineural or lymphovascular invasion^[9,13-16]. Two studies recommended radical lymph node dissection for patients with rectal NETs > 10 mm and lymphatic invasion^[16,17]. Lymphatic invasion, however, cannot be evaluated

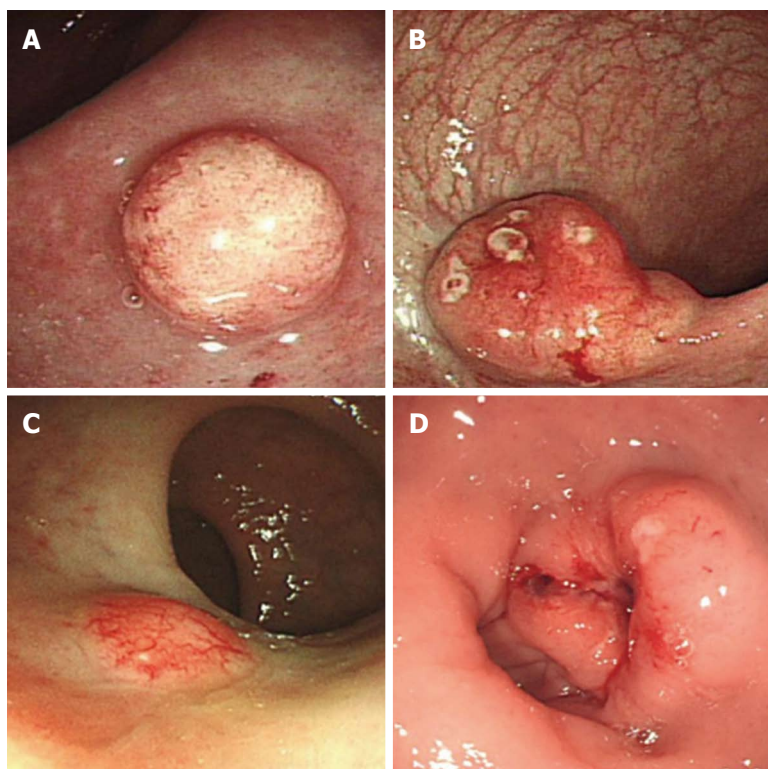


Figure 2 Endoscopic findings of atypical carcinoids. A: Semipedunculated type with hyperemia; B: Semipedunculated type with erosion and hyperemia; C: Sessile type with hyperemia; D: An ulcerofungating types mimicking rectal cancer.



Figure 3 Endoscopic image of a typical carcinoid, which was a sessile tumor with a yellow, smooth surface.

before resection of rectal NETs. On colonoscopy, the size of rectal NETs was the only predictor of LNM. We previously reported an association between atypical features of rectal NETs and LNM^[9]. Moreover, the incidence of atypical features was found to be associated with increased tumor size, suggesting that atypical features may be useful in determining treatment for tumors 11-19 mm in diameter. This study was performed to validate the predictive value of atypical features of NETs in a separate patient cohort.

The cutoff value for carcinoid tumor size that can determine the treatment plan and assess patient prognosis has not been definitively established. Tumors ≤ 10 mm in diameter are locally resected,

by methods such as endoscopic resection, transanal excision or transanal endoscopic microsurgery. The American Joint Committee on Cancer staging system has recommended that patients with tumors ≥ 20 mm undergo radical resection with lymph node dissection^[3,18]. However, the proper method of removing rectal NETs 11-19 mm in size remains undetermined, and no controlled prospective trials have assessed treatment plans for these patients. We found that all three patients with tumors ≥ 20 mm in diameter, 6 (27.3%) of 22 with tumors 10-19 mm, and 3 (1.4%) of 222 with tumors < 10 mm presented with LNM. Although, surprisingly, 3 patients with tumors < 10 mm in diameter had LNM, two studies observed metastases to lymph nodes and distant organs in patients with rectal NETs ≤ 10 mm in size^[6,19]. Thus, size of rectal NETs alone is insufficient to predict LNM and determine treatment plans.

The Surveillance, Epidemiology, and End Results registry database has shown that the incidence of rectal NETs has increased over the last 35 years^[20]. Most rectal NETs are diagnosed incidentally, with the increase in incidence likely due to increases in screening sigmoidoscopy and colonoscopy^[1]. Although size of rectal NETs incidentally diagnosed during lower endoscopy was the only factor associated with LNM, this study found that atypical features, especially surface changes, were strongly predictive of LNM. One of 3 patients with rectal NETs ≤ 10 mm and LNM had a semipedunculated lesion with surface erosion,

Table 2 Univariate and multivariate analyses of clinical factors associated with lymph node metastasis in patients with rectal neuroendocrine tumors *n* (%)

	Univariate analysis			Multivariate analysis	
	Metastasis (-)	Metastasis (+)	<i>P</i> value	OR (95%CI)	<i>P</i> value
Gender			0.183	-	-
Male	144 (92.3)	12 (7.7)			
Female	88 (96.7)	3 (3.3)			
Age (yr)			1.000	-	-
≤ 50	113 (94.2)	7 (5.8)			
> 50	119 (93.7)	8 (6.3)			
Size (mm)			< 0.001	11.53 (2.51-52.93)	0.002
< 10	219 (98.6)	3 (1.4)			
≥ 10, < 20	13 (59.1)	9 (40.9)			
≥ 20	0 (0)	3 (100)			
Tumor shape			< 0.001	-	-
Sessile	205 (97.6)	5 (2.4)			
Semipedunculated	27 (77.1)	8 (22.9)			
Ulcerofungating	0 (0)	2 (100)			
Surface change			< 0.001	27.44 (5.96-126.34)	< 0.001
Smooth	222 (97.8)	5 (2.2)			
Depressed/eroded	10 (55.6)	8 (44.4)			
Ulcerated	0 (0)	2 (100)			
Color			< 0.001	-	-
Normal or yellow	210 (96.8)	7 (3.2)			
Hyperemia	22 (73.3)	8 (26.7)			
Atypical features, any			< 0.001	4.38 (0.92-20.80)	0.064
Typical features	189 (98.4)	3 (1.6)			
Atypical features	43 (78.2)	12 (21.8)			

Table 3 Atypical features of rectal neuroendocrine tumors according to tumor size *n* (%)

	Typical (<i>n</i> = 192)	Atypical (<i>n</i> = 55)	<i>P</i> value
Tumor size (mm)			< 0.001
< 10	186 (83.8)	36 (16.2)	
≥ 10, < 20	6 (27.3)	16 (72.7)	
≥ 20	0 (0)	3 (100)	

while all 9 patients with tumors > 10 mm in size and LNM had lesions with one or more atypical features. The presence of atypical features can help determine treatment plans for patients with rectal NETs 11-19 mm in diameter. We suggest that rectal NTEs 11-19mm in diameter, which showed atypical features in endoscopic findings, should be performed the CT or EUS to evaluate the LNM.

In 2010, the World Health Organization (WHO) classified rectal NETs as malignant^[21], with L-cell, glucagon-like peptide producing and pancreatic polypeptide/peptide YY (PPY/PYY) producing NETs defined as borderline malignant or of uncertain malignant potential. Although most rectal NETs are L-cell tumors, the L-cell phenotype was not associated with biologically favorable characteristics^[10]. That study, with a population overlapping our study, recommended that clinical management of rectal NETs should depend on tumor size. Our analysis of the association between atypical features and immunohistochemical staining results found that L-cell phenotype and GLP1 were associated with atypical features. These

Table 4 Association between endoscopic features and metastasis in rectal neuroendocrine tumors < 10 mm and 10-19 mm in diameter *n* (%)

	Metastasis (-)	Metastasis (+)	<i>P</i> value
< 10 mm in diameter			
Shape			0.155
Sessile	199 (99.0)	2 (1.0)	
Semipedunculated	20 (95.2)	1 (4.8)	
Surface change			0.005
Smooth	212 (99.1)	2 (0.9)	
Depression/erosion	7 (87.5)	1 (12.5)	
Color			0.627
Yellow	203 (98.5)	3 (1.5)	
Hyperemia	16 (100)	0 (0)	
10-19 mm in diameter			
Shape			0.548
Sessile	6 (66.7)	3 (33.3)	
Semipedunculated	7 (53.8)	6 (46.2)	
Surface change			0.041
Smooth	10 (76.9)	3 (23.1)	
Depression/erosion	3 (33.3)	6 (66.7)	
Color			0.665
Yellow	7 (63.6)	4 (36.4)	
Hyperemia	6 (54.5)	5 (45.5)	

findings suggested that increased tumor size may be associated with atypical features as well as non L-cell type. Prospective observational studies in large cohorts of patients are required to clarify these associations.

Although we analyzed a relatively large patient cohort, our study had the inherent limitations of a retrospective study. To minimize such biases, we did not include and analyze consecutive patients with

Table 5 Association between atypical endoscopic features of rectal neuroendocrine tumors and immunohistochemical staining results *n* (%)

	Typical feature	Atypical feature	<i>P</i> value
L-cell			0.008
(-)	27 (62.8)	16 (37.2)	
(+)	142 (81.6)	32 (18.4)	
EC-cell			0.464
(-)	162 (78.3)	45 (21.7)	
(+)	7 (70.0)	3 (30.0)	
Serotonin			0.306
(-)	161 (78.5)	44 (21.5)	
(+)	8 (66.7)	4 (33.3)	
Somatostatin			1.000
(-)	161 (77.8)	46 (22.2)	
(+)	8 (80.0)	2 (20.0)	
GLP1			0.021
(-)	57 (69.5)	25 (30.5)	
(+)	112 (83.0)	23 (17.0)	
PYY1			0.513
(-)	72 (75.8)	23 (24.2)	
(+)	97 (79.5)	25 (20.5)	
PPY1			0.443
(-)	88 (75.9)	28 (24.1)	
(+)	81 (80.2)	20 (19.8)	

rectal NETs. Second, we investigated LNM by radiologic imaging or pathologic reports. Most patients with rectal NETs underwent local excision, such as transanal excision, transanal endoscopic microsurgery, and endoscopic procedures, rather than radical resection. Although the LNM status of patients who underwent local excision was evaluated by abdominopelvic CT, CT was used only to evaluate lymph node status. To evaluate the lymph node status, we were using criteria that distinguished positive node which showed > 3 mm in diameter in perirectal area or > 1 cm in diameter in the pelvis^[11,12]. These criteria showed about a sensitivity of 73% and a specificity of 58%. Thus, we have to consider a difference between CT finding and pathology. Third, we did not perform survival analysis. Median follow-up time of our study patients was 44 mo (range 0-78 mo), which, while longer than in other studies, was too short to assess distant metastases or tumor recurrence. Prospective long term follow-up studies are needed for survival analyses.

In conclusion, the present study, along with a previous study performed at our institution, suggests that rectal NETs ≤ 10 mm in diameter can be treated by local excision, whereas tumors ≥ 20 mm in diameter should be treated by radical resection with lymph node dissection. Atypical endoscopic features may help select the optimal treatment plans for patients with rectal NETs 11-19 mm in diameter.

COMMENTS

Background

Increases in rate of screening colonoscopy have resulted in increases in incidence and prevalence of rectal neuroendocrine tumors (NETs). The treatment plan of rectal NETs have been decided depends on tumor size.

Table 6 Association between atypical features and L-cell type in rectal neuroendocrine tumors *n* (%)

	L-cell (-)	L-cell (+)	<i>P</i> value
Tumor shape			0.107
Sessile	34 (18.4)	151 (81.6)	
Semipedunculated	8 (25.8)	23 (74.2)	
Ulcerofungating	1 (100)	0 (0)	
Surface change			0.022
Smooth	36 (18.0)	164 (82.0)	
Depression/erosion	6 (37.5)	10 (62.5)	
Ulceration	1 (100)	0 (0)	
Color			< 0.001
Normal or yellow	31 (16.1)	162 (83.9)	
Hyperemia	12 (50.0)	12 (50.0)	

Previously, the authors had proposed the possible association between endoscopic atypical features and lymph node metastasis (LNM) in rectal NETs.

Research frontiers

Tumor size, tumor shape, color and surface change were significantly related to LNM in univariate analysis. In multivariate analysis, tumor size and atypical surface change were independent risk factors for LNM [odds ratios with 95% confidence interval were 11.5 (2.5-52.9) and 27.4 (5.9-126.3), respectively]. The rate of atypical endoscopic feature was increased as tumor size increase (16.2% in less than 10 mm, 72.7% in 10-19 mm, 100% in 20 mm or over in diameter, *P* < 0.001).

Innovations and breakthroughs

In this study, the authors found atypical endoscopic features as well as tumor size were predictive factors for LNM in rectal NETs.

Applications

This study suggested that NETs which showed atypical endoscopic feature helpful for determining proper treatment.

Peer-review

The paper is an interesting analysis of the association between atypical features and LNM in rectal NETs. The atypical features of rectal NETs are important findings to determine the treatment plan during colonoscopy.

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