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The Morphologic Assessment of Rectal Neuroendocrine Tumors ☆ ☆



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KEYWORDS

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Video

Abstract

Background and aims: The histopathologic features of rectal neuroendocrine tumors (NETs), including size, lymphovascular invasion, invasion of proper muscle, and mitotic rate, have a limited role to play in determining a treatment plan preoperatively. We aimed to investigate the morphologic parameters associated with metastasis, and to evaluate their predictive value.

Methods: Between January 2000 and May 2011, the medical records and endoscopic findings of 468 patients presenting with rectal NETs at the Samsung Medical Center were analyzed retrospectively. All tumors were classified according to size and endoscopic features such as color, shape, contour, and surface change.

Results: Twenty-one of the 468 patients (4.5%) with rectal NETs had lymph node (LN) metastasis and 11 patients (2.4%) had distant metastasis. Risk factors for metastasis included tumor size (≥ 10 mm in diameter), hyperemic change, polypoid lesions, irregular contours, and surface ulceration ($p=0.000$). Independent risk factors that were predictive of metastasis on multivariate analysis included tumor size (≥ 10 mm in diameter), hyperemic change, and surface ulceration. As the number of independent risk factors for metastasis increased, the risk of metastasis rose.

Conclusions: Endoscopic features such as hyperemic change, polypoid lesions, irregular contours, and surface ulcers with tumor size ≥ 10 mm in diameter are associated with metastasis in rectal NETs. In particular, atypical endoscopic features including hyperemic

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change, and surface ulcer with tumor size ≥ 10 mm in diameter may help to predict the risk of metastasis of rectal NETs.

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Video related to this article

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1. Background

- Rectal neuroendocrine tumors (NETs) comprise 12.6% of all NETs [1]. A recent epidemiologic study showed that the incidence of rectal NETs has increased about tenfold over the last 35 years, and nowadays 50% or more rectal NETs are diagnosed as “incidentally” identified lesions due to the rapid development of screening sigmoidoscopy and colonoscopy [2,3].
- While the prognosis of patients with metastatic rectal NETs is no better than that of patients with metastatic rectal adenocarcinoma, rectal NETs without metastasis generally have an excellent five-year survival rate of 98.9-100% [3-5]. Small rectal NETs without infiltration to the proper muscle layer or lymph node (LN) metastasis can be treated effectively and safely through endoscopic resection. Hence, when deciding on the management of rectal NETs, the disease stage should be taken into consideration [3].
- Previous studies have reported several parameters that can be used to predict the metastatic spread of rectal NETs, including tumor size, histologic differentiation, muscular invasion, and lymphovascular invasion [6-9]. However, these parameters cannot play a role in determining strategies for treating rectal NETs preoperatively.
- Tumor size has long been regarded as a reliable and easily obtained parameter [3,9]. However, several studies have reported that rectal NETs smaller than 10 mm have metastasis ranging from 1.7% to 9.7%, illustrating that the risk of metastasis is not governed by primary tumor size alone [5,7,10-12].

2. Aims of the study

- To investigate the morphologic parameters associated with metastasis in patients with rectal NETs.
- To assess the risk of metastasis according to the morphologic parameters that assist in

determining treatment plans for rectal NETs preoperatively.

3. Study design

- Between January 2000 and May 2011, the medical records and endoscopic findings of 468 patients presenting with rectal NETs at Samsung Medical Center were analyzed retrospectively. Specific data extracted from the medical records included patients' age and sex, tumor size, tumor site, method of resection, and the presence of LN or distant metastasis.
- Diagnosis of NETs was confirmed by pathology. Tumor size was measured using open biopsy forceps (8 mm in width, FB-24Q-1; Olympus, Tokyo, Japan) during endoscopy. LN or distant metastasis was diagnosed based on the results of a biopsy or surgical resection, or radiologic findings consistent with metastasis.
- All endoscopic features were reviewed by the authors using photographs of each tumor. All tumors were classified according to size and endoscopic features such as color, shape, contour, and surface change.

4. Materials

- Colonoscope: CF-Q260AI, Olympus Corporation, Tokyo, Japan.
- Single band ligator: Stiegmann-goff Clearvue Endoscopic Ligator, ConMed, New York, USA.
- Knives.
 - Needle knife: KD-10Q-1, Olympus Corporation, Tokyo, Japan.
 - Hook knife: KD-620LR, Olympus Corporation, Tokyo, Japan.
 - Flex knife: KD-630L, Olympus Corporation, Tokyo, Japan
- Electrosurgical unit: ERBE VIO 300 D, ERBE Elektromedizin GmbH, Tübingen, Germany.

5. Endoscopic procedure

- A total of 369 patients were treated with endoscopic resection (ER) including conventional endoscopic

mucosal resection (EMR) or EMR with precutting (EMR-P), EMR with a ligation device (EMR-L) and endoscopic submucosal (SM) dissection with or without snaring (ESD-S or ESD) [13]. ER was performed using a single-channel colonoscope.

- Conventional EMR was performed by snare polypectomy with a blended electrosurgical current

after SM injection of a hypertonic saline solution mixed with a small amount of indigo-carmin and diluted epinephrine (1:10,000). EMR-P was performed by snare polypectomy after circumferential mucosal incision using a needle knife or hook knife.

- EMR-L was performed by snare polypectomy with an attached single-band ligator. Snare polypectomy

Table 1 Demographic and clinical features of patients with rectal neuroendocrine tumors.

Total number of patients, <i>n</i> (tumors, <i>n</i>)	468 (468)
Age, median (range), years	49.0 (19-80)
Sex	
Male	308 (65.8%)
Female	160 (34.2%)
Size of rectal neuroendocrine tumor, mean \pm SD (mm)	7.3 \pm 5.67 (range, 1-80)
Distance from anal verge, mean (cm)	7.4 (range, 2-18)
Treatment, <i>n</i>	
Endoscopic resection	369
Surgical resection	91
Chemotherapy	8

SD, standard deviation.

Table 2 Predictive factors of metastasis on univariate analysis.

	Total (<i>n</i> =468)	Metastasis (<i>n</i> =21)			<i>P</i> value
		LN (<i>n</i> =21)	Distant (<i>n</i> =11)	Total (<i>n</i> =21)	
Size					0.000
< 10 mm	368 (78.6%)	3 (0.8%)	1 (0.3%)	3 (0.8%)	
\geq 10 mm	100 (21.4%)	18 (18.0%)	10 (10.0%)	18 (18.0%)	
Color					0.000
Yellowish	413 (88.2%)	6 (1.5%)	2 (0.5%)	6 (1.5%)	
Hyperemic	55 (11.8%)	15 (27.3%)	9 (16.4%)	15 (27.3%)	
Shape					0.000
Sessile	313 (66.9%)	5 (1.6%)	2 (0.6%)	5 (1.6%)	
Polypoid	155 (33.1%)	16 (10.3%)	9 (5.8%)	16 (10.3%)	
Contour					0.000
Regular	385 (82.3%)	7 (1.8%)	1 (0.3%)	7 (1.8%)	
Irregular	83 (17.7%)	14 (16.9%)	10 (12.0%)	14 (16.9%)	
Surface change					0.000
Smooth	411 (87.8%)	9 (2.2%)	2 (0.5%)	9 (2.2%)	
Depression or erosion	41 (8.8%)	0 (0%)	0 (0%)	0 (0%)	
Ulceration	16 (3.4%)	12 (75.0%)	9 (56.2%)	12 (75.0%)	

Table 3 Predictive factors for metastasis on multivariate analysis.

	Odds ratio (95% CI)	P value
Size (≥ 10 mm)	5.920 (1.204-29.107)	0.029
Hyperemic change	4.837 (1.315-17.790)	0.018
Polypoid lesion	1.126 (0.261-4.856)	0.874
Irregular contour	2.388 (0.634-8.990)	0.198
Surface ulceration	10.825 (2.091-56.033)	0.005

Table 4 The risk of metastasis by number of predictive factors.

Number of risk factors	Odds ratio (95% CI)	P value
0	1	
1	5.897 (0.970-35.837)	0.054
2	73.286 (13.561-396.054)	0.000
3	427.500 (69.955-2612.485)	0.000

Risk factors: ≥ 10 mm, hyperemic change, surface ulceration.

Table 5 The risk stratification of metastasis by endoscopic features.

Stratification of risk factors	Odds ratio (95% CI)	P value
< 10 mm, No hyperemic change, no ulceration	1	
< 10 mm With hyperemic change or ulceration	7.435 (0.650-85.070)	0.107
≥ 10 mm With hyperemic change or ulceration	5.344 (0.739-38.628) 73.286 (13.561-396.054)	0.097 0.000
With both hyperemic change and ulceration	427.500 (69.955-2612.485)	0.000

was performed below the band using a blended electrosurgical current after SM injection of a hypertonic saline solution mixed with a small amount of indigo-carmin and diluted epinephrine (1:10,000).

- ESD was performed using a needle knife or hook knife with an electrosurgical unit after SM injection. A mixture of 10% glycerin, 5% fructose, and 0.9% saline was used as the SM injection solution. After lifting the tumor, a mucosal incision and SM dissection was made with a needle knife or flex knife. ESD-S involved initially performing ESD and then using snaring for the final resection step. SM dissection progressed circumferentially only to the degree

that the undissected SM tissue was about 1 cm or less in diameter. The attached, narrowed SM tissue was then snared and resected using an electric current.

6. Statistical analysis

- For the analysis of risk factors for metastasis, the relationship between each clinicopathological variable and the presence of metastasis was evaluated using univariable and multivariable logistic models.
- P values of < 0.05 were considered statistically significant.

7. Results

- The mean age at diagnosis was 49 years (range, 19–80 years) and 65.8% of patients were male. Rectal NETs were located a mean of 7.4 cm (range, 2–18 cm) from the anal verge and measured a mean 7.3 ± 5.67 mm in maximal diameter. A total of 369 patients were treated with endoscopic resection and 91 patients (10 of whom underwent surgery after initial endoscopic resection) were treated with surgery (Table 1).
- Twenty-one of the 468 patients (4.5%) with rectal NETs had LN metastasis and 11 patients (2.4%) had distant metastasis, mainly in the liver. Risk factors for metastasis identified by univariate analysis included tumor size (≥ 10 mm in diameter), hyperemic change, polypoid lesions, irregular contours, and surface ulceration (Table 2). Independent factors that were predictive of metastasis on multivariate analysis included tumor size (≥ 10 mm in diameter), hyperemic change, and surface ulceration (Table 3).
- None of the 244 patients (52.1%) with rectal NETs that satisfied five endoscopic morphology of < 10 mm in diameter, no hyperemic change, sessile lesions, regular contours, and smooth surface, had metastasis. As the number of independent risk factor for metastasis increased, the risk of metastasis also rose (Table 4).
- The risk of metastasis was stratified according to tumor size and morphologic predictive factors (Table 5). The larger the tumor size and the more morphologic predictive factors appeared, the more the risk of metastasis increased. The presence of endoscopic features such as hyperemic change and surface ulceration was important as a part of initial risk stratification for metastasis, along with tumor size.

8. Discussion

The results of the present study were consistent with those of earlier studies that reported that tumor size is an indicator of metastasis [7,8,14]. However, in our study, three of the 368 patients with rectal NETs < 10 mm had LN metastasis. Among them, one patient even presented with multiple hepatic metastasis. This study showed that in addition to tumor size, general shape, color, contour, and surface changes of tumors on endoscopic observation also correlate with regional LN or distant metastasis. In particular, hyperemic change and the surface ulceration of tumors with tumor size

were excellent predictors of metastasis. Moreover, as the number of predictive factors for metastasis including ≥ 10 mm in diameter, hyperemic changes and surface ulceration of tumors increased, the risk of metastasis also rose.

Previous studies have focused on histopathologic features such as depth of invasion, lymphovascular invasion, histologic differentiation, and mitosis to predict metastasis or outcomes. However, these histopathologic features have a limited role to play in determining a treatment plan because they are difficult to assess before surgery or endoscopic resection. Few studies have reported characteristic endoscopic features that correlate with metastasis in rectal NETs. Shim et al. [15] reported 15 rectal carcinoid tumor patients with atypical endoscopic appearance. However they could not demonstrate the prognostic value of atypical endoscopic appearance because they focused on the rate of correct endoscopic diagnosis and the sample size was too small [15]. They suggested only that ulceration may be a useful prognostic factor because invasion into the muscularis propria or metastasis was significantly more common in cases with tumor ulceration (three of the four patients whose tumors showed ulceration). Recently, Kim et al. demonstrated the relationship between endoscopic features and metastasis in rectal NETs. They showed that atypical endoscopic features including tumor shape, surface change and color were correlated with metastasis in rectal NETs [12]. However, in their study, 9 out of 9 patients with tumors ≥ 20 mm in diameter and none of 93 patients with tumors < 10 mm in diameter presented with metastasis. Therefore, they insisted that primary tumor size is the best parameter for predicting the behavior of rectal NETs measuring < 10 or ≥ 20 mm in diameter and they focused on tumors 10–19 mm in diameter. Of the atypical endoscopic features, only atypical surface change exhibited an association with metastasis in rectal NETs 10–19 mm in diameter. In contrast, in the present study, three of 368 patients with rectal carcinoid tumor < 10 mm in diameter presented with metastasis. Therefore, primary tumor size alone is insufficient when it comes to predicting the behavior of rectal NETs. Hence we classified all rectal carcinoid tumors according to endoscopic features such as color, shape, contour, and surface change. These endoscopic features were correlated with the presence of metastasis, and atypical endoscopic features such as hyperemic change, polypoid lesions, irregular contours, and surface ulceration occurred more frequently as the size of the tumor increased (35.6% in tumors < 10 mm in diameter, 82.6% in tumors 10–19 mm in diameter and 100% in tumors ≥ 20 mm in diameter, $p=0.000$). However, none

of these endoscopic features alone completely predicted the presence of metastasis. On the other hand, it was noteworthy that none of patients with rectal NETs that satisfied all of five endoscopic morphology of <10 mm in diameter, no hyperemic change, sessile lesions, regular contours, and smooth surface, had metastasis. Thus, we tried to combine these endoscopic features into a risk assessment of metastasis for rectal NETs. As expected, as the number of predictive factors for metastasis increased, the risk of metastasis also rose.

Based on these results, we determined the risk stratification of metastasis. Even though it was not statistically significant, the risk of metastasis was higher in rectal NETs <10 mm in diameter with atypical endoscopic features than in rectal carcinoid tumor <10 mm in diameter without atypical endoscopic features (odd ratio, 7.435 vs. 1, $p=0.107$). In rectal NETs ≥ 10 mm in diameter, the risk of metastasis increased as the number of the number of predictive factors for metastasis increased (odd ratio, 5.344 vs. 73.286 vs. 427.500, $p=0.097$ vs. 0.000 vs. 0.000, Table 5).

The current study was a retrospective single center study. The sample size in the metastasis group was small. However, compared with previous studies and considering the rate of metastasis of rectal carcinoid tumors, the sample size was not insufficient. The present study is meaningful in that we focused on morphologic parameters and stratified these features in detail, according to the risk of metastasis. Although the total sample size of our study was not insufficient, to establish this risk stratification using endoscopic features, further prospective and large scale studies are needed.

In conclusion, this study suggested that endoscopic features such as hyperemic change, polypoid lesions, irregular contours, and surface ulcers with a tumor size ≥ 10 mm in diameter are associated with regional LN or distant metastasis of rectal NETs. In particular, atypical endoscopic features including hyperemic change, and surface ulcers with a tumor size ≥ 10 mm in diameter may help predict the risk of metastasis of rectal NETs and may assist in determining treatment plans for these rectal NETs preoperatively.

8.1. Take-home messages

- In addition to tumor size, the shape, color, contour, and surface change of tumor are correlated with metastasis of rectal neuroendocrine tumors (NETs).

- Hyperemic change and surface ulceration with a tumor size ≥ 10 mm in diameter are excellent parameters predicting metastasis.
- The risk stratification combining these endoscopic features with tumor size may help in determining treatment plans for rectal NETs preoperatively.

9. Scripted voiceover

Voiceover Text

The incidence of the rectal neuroendocrine tumors has increased. The histologic features of rectal neuroendocrine tumors have a limited role to play in determining treatment plan.

Between January 2000 and May 2011, the medical records of 468 patients with rectal neuroendocrine tumors were analyzed. All tumors were classified according to size and endoscopic features. The study aimed to investigate the morphologic parameters associated with metastasis, and to assess the risk of metastasis.

It is reported that rectal neuroendocrine tumors smaller than 10mm rarely metastasize. However, in this case, despite of small size of rectal tumor being only 6mm, the patient presented with multiple hepatic metastasis. Therefore, it is insufficient to predict the behavior of rectal neuroendocrine tumors by primary tumor size alone.

Generally, rectal neuroendocrine tumors appear as smooth, yellowish and round sessile lesion.

Tumor size is one of the most important risk factor. In our study, tumor size is less than 10mm in 78.6%.

Also, we classified all rectal neuroendocrine tumors according to endoscopic features: color, shape, contour, and surface changes. In our study, 88% of rectal tumors have yellowish color, 12% show hyperemic changes, ...

... 67% appear sessile, 33% are polypoid, ...

... 82% of these tumors have regular contour.

The surface changes are classified under smooth (88%), depression or erosion (8.8%), and ulceration (3.4%).

This study show that in addition to tumor size, general shape, color, contour, and surface changes of tumor were correlated with regional lymph node or distant metastasis. On multivariate analysis, hyperemic change and surface ulceration of tumors with tumor size are excellent parameters predicting metastasis.

Voiceover Text

Furthermore, this table show that as the number of independent predictive factors for metastasis increased, the risk of metastasis also rose.

The risk of metastasis is stratified according to tumor size and predictive morphologic parameters. The larger the tumor size and more morphologic predictive factors appeared, the more the risk of metastasis increased.

This is a 34-year-old female patient referred for rectal neuroendocrine tumor. There is a smooth yellowish submucosal tumor, it is small and show typical morphologic finding of rectal neuroendocrine tumor. It can be easily managed with endoscopic treatment.

After submucosal injection, the mucosa around the neuroendocrine tumor is incised by needle knife. The lifted submucosal tissue beneath the lesion is dissected from the muscle layer. The attached, narrowed submucosal tissue is then snared and resected by using an electric current.

This is another rectal neuroendocrine tumor. This is a 30-year-old male patient. The tumor shows the depression on the surface. Even though the tumor size was smaller than 10 mm, we performed CT scan before endoscopic treatment. After confirmation of non-metastatic disease, we performed endoscopic resection. When endoscopic resection is done, it is important that the deep resection margin be as close to the proper muscle as possible.

Endoscopic submucosal dissection are provided a higher pathologic complete resection rate compared with endoscoic mucosa resection. Now, tumor is resected by snaring after submucosal dissection. Endoscopic submuocsal dissection is technically difficult and requires highly skilled endoscopists.

The recent studies reported that both the en bloc resection rate and the histologically complete resection rate for the lesions of <20 mm were not different for ESD vs. ESD with snaring. Therefore, ESD with snaring can be a good alternative to ESD for en bloc resection of rectal neuroendocrine tumors.

As a result, risk factors for metastasis include tumor size, hyperemic change, polypoid lesion, irregular contour, and surface ulceration. Independent risk factors for metastasis include tumor size, hypermic change, and surface ulceration. As the number of independent risk factor for metastasis increased, the risk of metastasis also rose.

Voiceover Text

To sum up, in addition to tumor size, the shape, color, contour, and surface change of tumors are correlated with metastasis of rectal neuroendocrine tumors. Hyperemic change and surface ulceration with a tumor size are excellent parameters predicting metastasis. The risk stratification combining these endoscopic features with tumor size may help in determining treatment plans for rectal neuroendocrine tumors preoperatively.

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None.

Conflict of interest

None.

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