



### Correspondence:

## Endoscopic ultrasonography is useful in the diagnosis and treatment of rectal neuroendocrine neoplasms: a case series<sup>\*#</sup>

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Rectal neuroendocrine neoplasms (NENs) are low-grade malignancies, which are slow-growing and usually become symptomatic late in the course of the disease (Basuroy et al., 2016). In recent years, rectal NENs are increasingly frequently detected, with the widespread availability and accessibility of endoscopy and cross-sectional imaging modalities (Kos-Kudla et al., 2017). Multiple studies have shown that endoscopic ultrasound (EUS) is an advanced endoscopic technique and is currently used in the diagnosis and preoperative assessment of NENs (Kim, 2012; Liu et al., 2013; Zhang et al., 2017). However, EUS imaging of rectal NEN and differential diagnosis with


other submucosal tumors (SMTs) has not been adequately reported. In this study, we reviewed and summarized the EUS imaging and pathological features of rectal NENs of 38 cases to improve preoperative diagnosis rate and reduce unreasonable treatment.

This retrospective study included 38 patients with rectal NEN confirmed by histopathology between January 2007 and December 2014. Clinical data, including patient attributes, EUS imaging performance, and immunohistochemistry examination, are shown in Table 1. Females comprised 47.4%, and the mean age was 48.6 years. Thirty patients were examined for clinical symptoms, including diarrhea, constipation, and mucous bloody stool. No patients were hospitalized for carcinoid syndrome. Then we analyzed images from colonoscopy and EUS. Under colonoscopy, the rectal carcinoid tumors were observed for the position of the lesions (away from anus), shape, color, integrity, and vascular change from the surface of the mucosa. EUS was performed to observe the depth (involving hierarchy) of the lesions, size, outline, border characteristics, internal echo intensity, and homogeneity. The lesions of all cases were solitary, located 2–13 cm from anus and 7.5 cm on average. Colonoscopy showed that most were hemispherical, hummocky submucous protrusions. Most of the mucosal surface was smooth and complete, with a normal or yellowish white color. In 18 cases, hyperplasia and dilation of the hemal net could be seen through the mucosa surface of lesions. Colonoscopic images of rectal NENs were shown in Fig. S1.

Under EUS, in this study, all cases of rectal NENs showed submucous protrusions. These protrusions and other SMTs were similar in shape; however, the color in 42.1% of cases was yellow-white, which significantly differed from stromal tumors and had similarities with esophageal granular cells (Xu et al.,

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**Table 1 Demographic characteristics of the patients**

Patient characteristics	Value
Gender (male/female)	20/18
Age (year)	48.6 (30–77)
Lesion characteristics	
Classification of NENs	
G1	33
G2	3
G3	1
Mixed gonadal neuroendocrine carcinoma	1
Location (distance from anus) (cm)	7.5 (2–13)
Shape	
Hemispherical	18
Hummocky	10
Nodular	6
Flat	3
Oval	1
Mucosal surface	
Normal	22
Yellowish white	16
Diameter	
Average (mm)	7.86±4.66
≤5 mm	11
5–10 mm	23
≥10 mm	4
EUS imaging performance	
Layers involved	
Layers 2 and 3	29
Layers 2, 3, and 4	4
Layer 2	3
Layers 2, 3, 4, and 5	1
Layer 3	1
Echo intensity	
Medium echo (Grade 4)	24
Medium to high echo (Grade 5)	12
Medium to hypo echoic (Grade 3)	2
Immunohistochemistry examination	
Total	23
Synaptophysin (SYN)	23 positive
Chromogranin A (CgA)	20 positive, 3 weakly positive
Pan-cytokeratin (CK-pan)	23 positive
Ki-67 proliferation index	23 positive (less than 3%)

NEN, rectal neuroendocrine neoplasm; EUS, endoscopic ultrasound. G1, mitotic count of <2 per 10 high-power fields (hpf) and/or Ki-67 index <3%; G2, mitotic count of 2–20 per 10 hpf and/or Ki-67 index 3%–20%; G3, mitotic count of >20 per 10 hpf and/or Ki-67 index >20%. Layers of rectum: Layer 1 is high-echo acoustic interface; Layer 2 is low-echo mucous layer; Layer 3 is high-echo submucous layer; Layer 4 is low-echo circular muscle layer; Layer 5 is high-echo fibrous connective tissue layer; Layer 6 is low-echo outer longitudinal muscle layer; Layer 7 is high-echo outer membrane layer. Lesions echo intensity criteria of rectal neuroendocrine tumors: Grade 0 is presented as equivalent to anechoic echo intensity (anechoic); Grade 1 is presented as between 0 and 2 echo intensity (extremely hypoechoic); Grade 2 is presented as equivalent to intrinsic muscle echo (hypoechoic); Grade 3 is presented as between 2 and 4 echo intensity (moderate hypoechoic); Grade 4 is presented as equivalent to deep mucosal echo (medium echo); Grade 5 is presented as between 4 and 6 echo intensity (moderate hyperechoic); Grade 6 is presented as equivalent to submucosa echo (hyperechoic). Data were expressed as number, mean (range), or mean±standard deviation (SD)

2012). Another noteworthy phenomenon was that on the surface of the lesions, the vascular network increased and thickened in more than one-third of the cases of rectal NEN. This manifestation was relatively specific, because an increased and thickened vascular network was rarely seen in other submucosal tumors.

In the previous literature, most reports of EUS diagnosis and treatment of the rectal carcinoid or NEN are hypoechoic submucosal lesions (Basuroy et al., 2016; Kos-Kudla et al., 2017). Earlier, Yoshikane et al. (1993) studied 17 cases of rectal carcinoid endoscopic ultrasonography, and the ultrasonogram characteristics showed that the lesions are well defined, homogeneous, and have oval hypoechoic areas, which mainly located in the submucosa, and the mucosa covering thereon could not be separated from the tumor at the junction boundary. With the accumulation of the number of cases and progress of EUS technology, Kobayashi et al. (2005) studied the characteristics of EUS of 53 cases of rectal carcinoid tumors, showing that rectal carcinoid tumors are well defined and uniformly internal isoechoic to hypoechoic lesions. Isoecho, referring to the echo intensity, was similar to normal deep mucosa, ranging from hypoechoic (submucosa) to hyperechoic (muscularis propria). In this study, the shape of the rectal NEN section and boundary whether clear or not had no significant difference between stromal tumors or other SMTs, but there were fundamental differences in the lesions involving layers and the echo intensity. In these 38 cases of rectal NEN, the majority of lesions (89.4%) involved mucosa, submucosa, and even deeper layers. This two-layer-involved characteristic differs from single-layer involvement of the general SMT, which could help to differentiate rectal SMT.

As for differential diagnosis with other SMTs, stromal tumors and lipomas are both single-layer originated, originating from submucosa or muscularis propria. In addition to the inherent muscle, leiomyoma could also originate from the muscularis mucosa, but there is clear boundary with the submucosa. When the rectal mucosa NEN located in deep mucosa without submucosa being involved, it required identification with leiomyoma theoretically. However, rectal leiomyoma was rarely reported. EUS showed rectal NEN lesions completely located in submucosa, which was similar to stromal tumors. In this case echo intensity was required for lesion identification.

EUS can provide detailed information about five layers on ultrasound images of gastrointestinal and adjacent organs. These layers are parallel to the mucosal surface in the image and are distinguished by their different echo textures and intensities (Aibe et al., 1986; Kimmey et al., 1989). In addition, the echo intensity of the normal gastrointestinal wall layer could be used to evaluate the lesion in the same layer. Okanobu et al. (2005) first proposed a digestive tract tumor gastrointestinal echo intensity classification based on normal five-layer structure. The biggest advantage of this classification was that the evaluation of echo intensity was relatively objective and convenient. In this group, we classified 38 cases according to rectal NEN echo intensity, and found that the majority of cases belonged to moderate echo intensity equal to deep mucosa level (Grade 4); nearly one-third of the cases had medium to hyper echo, stronger than that of deep mucosa but weaker than that of submucosa. It was noticeable that rectal NEN EUS echo intensity was significantly higher than that of the stromal tumor and leiomyoma (muscularis propria relatively hypoechoic echo intensity, Grade 2), consistent with the study of Okanobu et al. (2005).

As for histopathologic characteristics, the gross pathological sections showed solid, grey-yellow or grey-red, homogeneous, hard, clear boundaries, and with no capsule. Under the microscope, the tumor cells were infiltrating into the submucosa and mostly arranged in a nest or cord. They were mostly rounded, medium-sized, of consistent shape, and ill-defined, and contained acidic particles in the cytoplasm. Nuclei have round or oval shape, uniform size, inconspicuous nucleoli, and rare mitoses.

In conclusion, the characteristic features of EUS images of rectal NENs include a well-defined boundary, and homogeneous echo in submucosa or deep mucosa, and most of rectal NENs are isoechoic or hyperechoic nodules. These EUS characteristic features facilitate the early diagnosis and different diagnoses with rectal NEN and other rectal SMTs, especially the layer involved and the echo intensity.

### Contributors

Qing GU, Yi-ming LIN, and Li CEN contributed to the study design and data analysis, and wrote the manuscript. Min XU, Hong-zhang LI, and Xian-chu LIN contributed to the table and supplemental figure design. Chao LU checked and revised the manuscript. All authors read and approved the final manuscript.

### Compliance with ethics guidelines

Qing GU, Yi-ming LIN, Li CEN, Min XU, Hong-zhang LI, Xian-chu LIN, and Chao LU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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### List of electronic supplementary materials

Fig. S1 Colonoscopic images of rectal NENs

### 中文概要

**题目:** 直肠神经内分泌肿瘤的超声内镜表现及其临床价值: 病例分析

**概要:** 随着内镜技术的提高, 直肠神经内分泌肿瘤(NEN)检出率逐年提高。目前关于直肠 NEN 的研究比较有限, 尤其在我国的。本文回顾性收集 2007 年至 2014 年在浙一医院就诊, 病理确诊为直肠 NENs 的患者的临床信息、普通肠镜及超声内镜(EUS)的镜下表现、病理等方面资料, 并进行对比分析。本文显示直肠 NEN 的 EUS 镜下表现主要为边界清晰, 回声均匀, NEN 位于粘膜层或粘膜下层, 且多为等回声或高回声。此外, EUS 对直肠 NEN 的诊断具有较显著的临床价值。

**关键词:** 直肠神经内分泌肿瘤; 超声内镜; 诊断