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Clinical impact of endoscopic ultrasonography for small rectal neuroendocrine tumors

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Original Article

ABSTRACT

Background/Aims: Endoscopic ultrasonography (EUS) is helpful for evaluating the depth of tumor invasion and lymph node metastasis of rectal neuroendocrine tumors (NETs). The aim of this study was to clarify the clinical impact of EUS for rectal NETs less than 10 mm in diameter.

Materials and Methods: : A total of 76 rectal NETs treated at our hospital between June 2006 and March 2013 were reviewed retrospectively. All lesions were analyzed with EUS to evaluate the depth of tumor invasion. The lesions were resected by endoscopic submucosal resection with band ligation (ESMR-L) or endoscopic submucosal dissection (ESD) and examined histologically.

Results: Endoscopic ultrasonography findings showed that all lesions were confined to the submucosa and revealed no adjacent lymph node metastasis. Seventy-five of the 76 lesions were completely resected by ESMR-L. One lesion was resected by ESD and the resected deep margin of the lesion was histologically positive. Only one lesion exhibited lymphatic invasion.

Conclusion: EUS may not be essential for diagnosis and treatment planning for rectal NETs less than 10 mm in size.

Keywords: Endoscopic ultrasonography, neuroendocrine tumor, rectum

INTRODUCTION

Neuroendocrine tumors (NETs) are a group of solid malignant tumors that arise from neuroendocrine cells found throughout the body. The majority of NETs occur in the gastrointestinal (GI) tract (67.5%). In North America, most NETs within the gastrointestinal (GI) tract occur in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%) (1). In Korea and Japan, however, the rectum is the major site of GI NETs (48.0% and 51.0%, respectively) (2,3). During the last decade, the incidence of rectal NETs in Korea has increased (3). Prognosis of rectal NETs varies depending mainly on the tumor size (1,2,4), although other prognostic factors include depth of invasion, lymphovascular invasion, Ki-67 index, and mitotic rate (1,4,5). A broad consensus exists regarding rectal NETs smaller than 10 mm; it is generally assumed that invasion associated with these tumors is confined to the submucosa without lymphovascular invasion or lymph node metastasis.

Endoscopic ultrasonography (EUS) is known to be helpful for evaluating the depth of tumor invasion and adjacent lymph node metastasis of rectal NETs. However, in clinical practice it is not clear whether EUS is an effective method to evaluate rectal NETs less than 10 mm in size. The aim of this study was to clarify the clinical impact of EUS for rectal NETs less than 10 mm in diameter.

MATERIALS AND METHODS

We reviewed a total of 76 rectal NETs that were treated at our hospital between June 2006 and March 2013, retrospectively. A total of 81 patients with rectal NETs were originally enrolled; six patients were excluded for tumor size >10 mm and one patient had two synchronous lesions therefore 76 lesions were eligible for analysis. All patients were assessed with EUS to evaluate the depth of tumor invasion and echoic pattern. Abdominal computed tomography (CT) was also performed to evaluate lymph node metastasis or distant metastasis of tumors. Seventy-five lesions were resected by endoscopic submucosal resection with band-ligation (ESMR-L), and one lesion was resected by endoscopic submucosal

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dissection (ESD). Subsequently, all lesions were examined histologically.

The maximum size of each rectal NET was measured by pathologists using freshly resected specimens. This size was considered as the real size of the tumor. The resected tumors were examined histologically to evaluate the depth of invasion, lymphovascular invasion, and whether the resected margin of the specimen was positive or negative. Mitotic rate and Ki-67 index were also assessed according to World Health Organization (WHO) recommendations when possible. EUS examination was performed in all patients using a radial echoendoscope (GF-UM2000; Olympus Co., Tokyo, Japan); the depth of invasion was estimated according to the continuity between the lesion and adjacent normal rectal wall, and the echoic pattern was investigated to determine low or high attenuation. ESMR-L was performed using an endoscope equipped with a band ligator (Akita Sumitomo Bakelite Co., Ltd., Tokyo, Japan). This study was approved by the Kosin University Gospel Hospital Ethics Committee.

RESULTS

The mean age of the 75 patients was 53.6 years (range, 29-78 years), and 45 patients were male and 30 were female. The mean tumor size was 4.65 mm (range, 1-10 mm). All lesions were incidental colonoscopic findings. Macroscopically, most of the tumors were sessile type (74/76); the other two lesions were a semipedunculated type. All lesions were yellowish in color. On EUS findings, all 76 lesions were located in the submucosa; seven lesions were located in the mucosa and 69 lesions were located in the submucosa. This finding was consistent with histologic results. Sixty-nine lesions showed invasion within the upper two-thirds of the submucosa. Echoic patterns were hypoechoic homogenous for all lesions, and there was no adjacent lymph node metastasis. The EUS findings are summarized in Table 1.

Abdominal CT revealed neither lymph node metastasis nor distant metastasis for any lesion. Seventy-five of the total 76 lesions were completely resected by ESMR-L; one lesion was resected by ESD and the resected deep margin of the lesion was positive. Histologically, only one lesion showed lymphatic invasion, whereas the other 75 lesions showed neither vascular invasion nor lymphatic invasion. Ki-67 index was assessed in 24 lesions (24/76, 31.6%), and mitotic rate was assessed in 19 lesions (19/76, 25%). The Ki-67 index was <2% in all cases, and the mitotic rate was <2 per high-power field. The histologic findings are also summarized in Table 1.

To date, the average length of follow-up has been 16±10 months (range, 3-43) and 28 of the 75 (37.3%) patients have undergone follow-up colonoscopic examination. None of the patients have experienced recurrence. Nineteen of 75 (25.3%) patients have not undergone follow-up examination, and the remaining 28 (37.3%) patients were lost to follow-up.

DISCUSSION

This study showed that rectal NETs ≤10 mm in diameter have a very low possibility of invasion into the proper muscle layer and a low risk of adjacent lymph node metastasis. In this study, all 76 rectal NETs ≤10 mm in size were located in the submucosa and showed no lymph node or distant metastasis.

Only one lesion had a resected positive deep margin. This patient was a 64-year-old man with a sessile type, 10 mm diameter tumor with central dimpling (Figure 1a) who underwent ESD involving the rectal mucosa and submucosa (Figure 1b). There was no lymphatic invasion or vascular invasion. EUS performed before ESD did not show any evidence of lymphadenopathy (Figure 1c). Initial abdominal CT and positrom emission tomography-CT (PET-CT) of the patient showed negative findings; however, he was lost to follow-up after resection.

In addition, only one lesion showed positive findings of lymphatic invasion. The patient was a 61-year-old man with a yellowish sessile type, 5-mm diameter tumor (Figure 2a) who underwent ESMR-L (Figure 2b). Histologically, the resected deep or lateral margin of the lesion was negative. There was no vascular invasion. Initial EUS revealed no evidence of lymphadenopathy (Figure 2c). Initial abdominal CT and PET-CT of the patient also showed negative findings. He underwent a surveillance colonoscopy and abdominal CT one year later that revealed no evidence of recurrent disease.

Kobayashi et al. (6) reported 57 carcinoid tumors ≤10 mm in size that were all confined to the submucosa, in contrast to five of nine lesions ≥11 mm in size that had invaded the muscularis propria. Onozato et al. (7) reported that small carcinoid tumors less than 1 cm in size can be managed endoscopically with no recurrence or spread. However, according to a 2008 report by the American Society of Clinical Oncology, the rate of distant metastasis at diagnosis for rectal NETs is 5% (8). Some large studies have found that the rate of metastasis ranges from 1.7 to 5.5% for tumors ≤10 mm, 10 to 30% for those 10 to 20 mm, and 70% or higher for those >20 mm (2,9,10). Among published Japanese studies (1982-2001), 17 cases of rectal NETs ≤10 mm in size were reported with metastasis but no penetration of the submucosa, whereas more than 50% had a central depression or vascular invasion. In Korea, two such cases have been reported (11,12).

In this study, 75 of the total 76 lesions were completely resected by ESMR-L and one lesion was resected by ESD. Lee et al. (13) reported that ESMR-L is a useful alternative to conventional polypectomy for the removal of rectal NETs less than 10 mm in size. Choi et al. (14) found that, compared with ESD, ESMR-L resulted in a comparable histologically complete resection rate and took less time for removal of rectal NETs less than 10 mm in size. Historically, endoscopic resection has been considered curative in cases of rectal NETs ≤10 mm in size (1,15). However, several studies and case reports have reported metastasis of small rectal NETs

Figure 1. a-c. Appearance of rectal NET indicated a sessile type with a central dimpling **(a).** The tumor was resected by ESD **(b).** EUS showed that the tumor was confined to the submucosa with no adjacent lymphadenopathy **(c).**

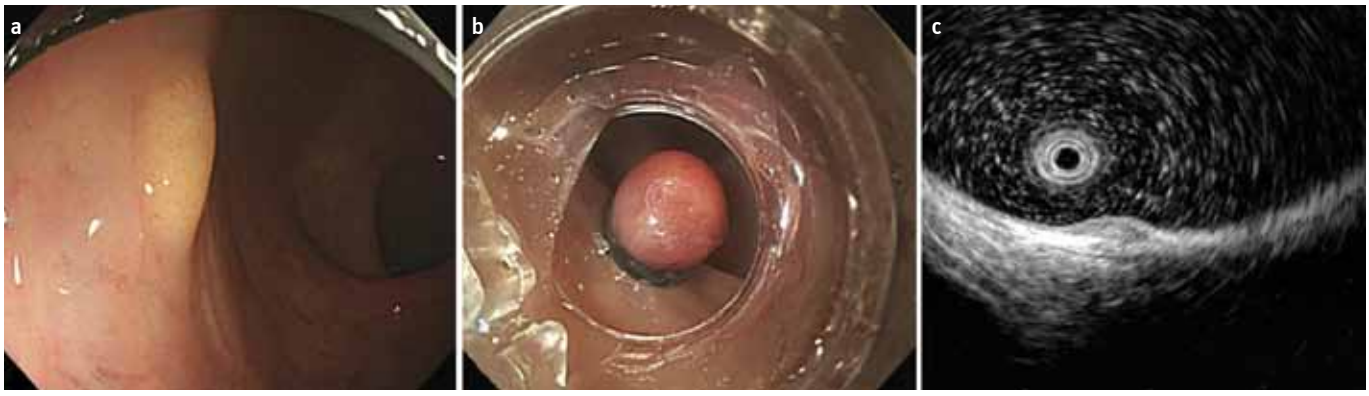

Figure 2. a-c. Appearance of rectal NET indicated a yellowish sessile type **(a).** The tumor was resected by ESMR-L **(b).** EUS showed that the tumor was confined to the submucosa with no adjacent lymphadenopathy **(c).**

Table 1. Histologic and EUS findings

	Histologic findings (n=76)	EUS findings (n=76)
Depth of invasion		
Confined to the mucosa	7	7
Confined to the submucosa	69	69
Echoic pattern		
Hypoechoic homogenous		76
Other pattern		0
Adjacent lymph node		0
Lymphatic invasion	1	
Vascular invasion	0	
Positive resection margin	1	
Ki-67 index	<2% (n=24)	
Mitotic rate (per 10 HPF)	<2 (n=19)	

HPF: high-power field

(16-19). We performed EUS for all 76 lesions before endoscopic resection. All lesions had a homogenous hypoechoic internal echo. None of the lesions penetrated the submucosa or showed adjacent lymph node metastasis. Some studies reported that rectal NETs ≤10 mm in size that were examined by EUS before endoscopic resection were correctly diagnosed as confined to the submucosa (6,14,20). Although EUS is a useful method for evaluating the depth of invasion, its necessity is questionable in cases of rectal NETs ≤10 mm in size. As shown in this study, rectal NETs smaller than 10 mm have a very low possibility of invasion to the proper muscle layer and a low risk of adjacent lymph node metastasis. Furthermore, the cost of EUS is prohibitive (450 United States dollar for each EUS examination in Korea).

This study has some limitations. First, this study was retrospective; therefore we could not avoid selection bias when collecting information on all rectal NETs less than 10 mm. Second, the number of rectal NETs included in this study is too small to conclude that rectal NETs less than 10 mm in diameter have an extremely low possibility of invasion to the proper muscle or risk of metastasis and further studies including a larger number of rectal NETs less than 10 mm in size are needed to verify our findings. Third, only 28 of our patients (37.3%) have undergone follow-up colonoscopic examination. Therefore, we do not know the follow-up results of all patients, including the patient with a positive resection margin. Fourth, this study did not include examination of Ki-67 or mitotic count for all lesions.

In conclusion, information provided by EUS can be helpful in diagnosis and to evaluate the possibility of invasion and adjacent lymph node metastasis for rectal NETs, but rectal NETs

less than 10 mm in diameter appear to have a very low risk of invasion to the proper muscle layer or adjacent lymph node metastasis. We believe that EUS may not be essential for diagnosis and determination of a treatment strategy for rectal NETs smaller than 10 mm.

Ethics Committee Approval: Ethics committee approval was received for this study from Institutional Review Board of Kosin University Gospel Hospital.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

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