SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 7: 476-480, 2017

# Evaluation of treatment for rectal neuroendocrine tumors sized under 20 mm in comparison with the WHO 2010 guidelines

NOBUHISA MATSUHASHI[1], TAKAO TAKAHASHI[1], HIROYUKI TOMITA[2], HIROSHI ARAKI[3], TAKASHI IBUKA[3], KAORI TANAKA[1], TOSHIYUKI TANAHASHI[1], SATOSHI MATSUI[1], YOSHIYUKI SASAKI[1], YOSHIHIRO TANAKA[1], NAOKI OKUMURA[1], KAZUYA YAMAGUCHI[1], SHINJI OSADA[1] and KAZUHIRO YOSHIDA[1]

Departments of [1]Surgical Oncology, [2]Tumor Pathology and [3]Gastroenterology, Gifu University School of Medicine, Gifu 501-1194, Japan

Received February 23, 2016; Accepted July 4, 2017

DOI: 10.3892/mco.2017.1326

**Abstract.** Rectal neuroendocrine tumor (NET) is a relatively rare lesion of the gastrointestinal tract, but the prospective examination with colonofiberoscopy or endoscopic ultrasound has increased the frequency of its detection. It is often difficult to determine the optimal treatment for NETs sized <20 mm in the clinical setting. Other clinicopathological variables are not considered in the current guidelines and staging systems. Although the effects of lymphovascular invasion are not covered by the World Health Organization (WHO) 2010 guidelines or tumor-node-metastasis (TNM) staging system, this may be promising for the establishment of improved guidelines and staging systems, particularly for early-stage colorectal carcinoids. The aim of the present study was to evaluate rectal NETs sized <20 mm in comparison with the WHO 2010 guidelines. Between January 2005 and December 2013, 40 consecutive patients [26 men and 14 women; median age, 59.3 years (range, 34-81 years)] who underwent endoscopic resection of rectal NETs, and 12 patients undergoing surgical resection of rectal NETs, were enrolled in this retrospective study. The median tumor size was 7.4 mm (range, 3-15 mm). The locations of the NET were the rectosigmoid colon (n=3), the upper rectum (n=13), and the lower rectum (n=25). The NETs were classified by size as 0-5 (n=7), 6-10 (n=29) and 11-15 mm (n=4). The surgical procedures performed included low anterior resection plus esophagectomy (n=1), laparoscopic low anterior resection (n=7) and laparoscopic intersphincteric resection (n=4). Only 1 patient had lymph node metastasis (tumor sized 6-10 mm, with lymphovascular invasion). NET recurrence was not detected in any of the patients. According to the WHO guidelines, the tumors were classified as grade (G)1 (n=8), G2 (n=3) and G1/G2 (n=1). The tumor in the patient with lymph node metastasis was G1. NETs sized <10 mm may be curatively treated by endoscopic resection. However, NETs with either lymphovascular invasion or sized >1 cm carry a risk for metastasis equivalent to that of adenocarcinomas. Therefore, it is mandatory to histologically examine lymphovascular invasion in specimens retrieved via endoscopic resection to determine the necessity for further radical surgery with regional lymph node dissection. The treatment of NETs sized <20 mm as presently defined in the WHO 2010 guidelines requires further evaluation.

*Correspondence to:* Professor Kazuhiro Yoshida, Department of Surgical Oncology, Gifu University School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan
E-mail: kyoshida@gifu-u.ac.jp

*Key words:* rectal neuroendocrine tumor, size under 20 mm, World Health Organization 2010 guidelines

## Introduction

Due to their generally good prognosis, small (≤1 cm) and well-differentiated neuroendocrine neoplasms of the stomach, duodenum, appendix, or rectum may be considered as 'early' tumors. The new 2010 World Health Organization (WHO) classification refers to these neoplasms as neuroendocrine tumors (NETs)/carcinoids, grade (G)1 or 2, whereas poorly differentiated neuroendocrine carcinomas are classified as G3 (1,2). Over the past 35 years, the age-adjusted incidence of NETs in the USA has risen by ~700%. Colorectal carcinoids display different biological behaviors compared with other tumors (3,4). Colorectal carcinoids are defined by the WHO classification as benign when confined within the submucosa, are ≤20 mm in size, and are not associated with vascular invasion. However, several reports are critical of this definition (5-7). Histological lymph node involvement in G1-G2 differentiated rectal NETs/carcinoids 1-2 cm in size has not been extensively investigated and, thus, its clinical significance is not well known worldwide.

## Patients and methods

*Patients.* Between January 2005 and December 2013, 40 consecutive patients undergoing endoscopic resection of rectal NETs and 12 patients undergoing surgical resection of rectal NETs were enrolled in this retrospective study. The criterion for the performance of endoscopic resection [including endoscopic mucosal

resection (EMR) and endoscopic submucosal dissection (ESD)] at the Gifu University Hospital is a tumor size of <20 mm. In addition, the criteria for surgical resection are a tumor size of ≥20 mm, a positive resection margin, and lymphatic or venous invasion in patients who receive local treatment.

All the patients were examined prior to surgery by pelvic computed tomography (CT) at a slice thickness of 5 mm. A diagnosis of lymph node metastasis was made if lymph nodes were detected on this scan. The resected tissue specimens underwent conventional processing and staining with hematoxylin and eosin to evaluate invasion depth, lymphatic and venous invasion, and lymph node metastasis. Clinical and surgical data were correlated with pathological findings. Patient follow-up included clinical assessment, assessment of laboratory data, chest radiography, abdominal ultrasonography, and CT or magnetic resonance imaging for early detection of tumor recurrence, at least every 6 months until 5 years. Survival time was calculated from the endoscopic resection to the time of the last follow-up examination or the patient's death.

Written informed consent was obtained from all the patients enrolled in the present study. The study protocol conformed to the the ethical guidelines of the 1975 Declaration of Helsinki after the approval of the Institutional Review Board of the Gifu University Graduate School of Medicine.

*Immunohistochemical staining for Ki-67.* An LSAB2 kit (LSAB2 System-HRP; Dako, Carpinteria, CA, USA) was used for Ki-67 immunohistochemical staining. The 4-$\mu$m tissue sections were placed on slides and then deparaffinized and dehydrated. The sections were then placed in 0.01 M citrate buffer (pH 6.0) and heated in a microwave (MI-77; Azumaya, Tokyo, Japan) for 40 min at 400 W and at 95˚C for antigen retrieval. Following pretreatment at room temperature with 0.3% $H_2O_2$ in methanol to quench endogenous peroxidase activity, the sections were blocked with Protein Block Serum-Free (Dako, USA) for 30 min and incubated for 1 h with anti-Ki-67 antibody (dilution, 1:50; clone MIB-1; cat. no. M7240; Dako, Carpinteria, CA, USA). The sections were then incubated for 15 min with biotinylated secondary antibody (pooled goat anti-mouse/anti-rabbit antibody, 1:1, LSAB2 System-HRP, Dako, USA) and washed with phosphate-buffered saline prior to a 20-min treatment with peroxidase-conjugated streptavidin. The sections were visualized by incubation for 3 min in 3,3'-diaminobenzidine tetrahydrochloride with 0.05% $H_2O_2$ (Liquid DAB+Substrate Chromogen System; Dako, USA) and counterstaining with Carazzi's hematoxylin.

*Statistical analysis.* The data are presented as means ± standard deviation and were evaluated with the Student's t-test, Wilcoxon's signed-rank test, Kaplan-Meier method, a log-rank test, and the Pearson product-moment correlation coefficient, as appropriate. A P-value of <0.05 was considered to indicate statistically significant differences.

## Results

*Patient characteristics.* The study comprised 26 men and 14 women, with a median age of 59.3 years (range, 34-81 years). The median tumor size was 7.4 mm (range, 3-15 mm). The locations of the NETs were the rectosigmoid colon (n=3), the upper rectum (n=13), and the lower rectum (n=25) (Table I).

*NET classification and outcome.* The NETs were classified by size as 0-5 (n=7), 6-10 (n=29) and 11-15 mm (n=4). The surgical procedures performed included low anterior resection (plus esophagectomy) in 1 patient, laparoscopic low anterior resection in 7 patients, and laparoscopic intersphincteric resection in 4 patients. Lymph node metastases were present in only 1 patient (tumor size, 6-10 mm, with associated lymphovascular invasion). NET recurrence was not detected in any of the patients. According to the WHO guidelines, the tumors were classified as G1 (n=8), G2 (n=3), and as G1/G2 (n=1) (1). The tumor in the patient with lymph node metastasis was classified as G1 (Table II). No patient received adjuvant chemotherapy. At the time of writing of this manuscript, with the exception of 1 patient who succumbed to heart disease, all the patients remained alive and recurrence-free.

## Discussion

Historically, the term 'carcinoid' has been used to label NETs originating in the gut. There is an international consensus towards the use of the term 'NET' rather than 'carcinoid', although the latter term is still widely used clinically and in the literature (8,9). A NET is a well-differentiated, neuroendocrine neoplasm comprised of cells with characteristics similar to those of normal gut endocrine cells. According to its location, NETs express general markers of neuroendocrine differentiation (generally diffuse and intense chromogranin A and synaptophysin expression) and hormones (generally intense but not always diffuse) and exhibit mild-to-moderate nuclear atypia with few mitoses [<20 per 10 high-power fields (HPF)]. G1 and G2 are defined on the basis of proliferation fraction and histology (Table III). This definition also covers neoplasms termed 'carcinoid tumor' in the WHO 2000 classification (8). In the WHO 2010 classification, these tumors are generically referred to as NETs of the well-differentiated type and rough division and neuroendocrine carcinoma in poorly differentiated neuroendocrine cancer (3,4) that have the characteristics and expression pattern of the endocrine system and gut tumors. NETs are identified as neuroendocrine neoplasms based on the number of mitotic figures showing the proliferative capacity, and by the Ki-67 index as G1 and G2 tumors (3,4) (Table IV). Ito *et al* reported that it is important to understand the background of the patients, particularly their epidemiological background, and to be aware of the differences in epidemiology between Japanese and Western patients (10).

Soga *et al* calculated the rate of 1,914 gastrointestinal (GI) submucosal (SM) carcinoids (among a total of 6,799 GI carcinoids) in 10 growth sites and ranked them in descending order from the highest (44.4% in the rectum; n=849) to the lowest (0% in the gallbladder). Despite an overall ratio of GI carcinoids to all GI carcinoids of 28.2% (1,914/6,799), the incidence rate of SM carcinoids at each of the 10 sites varied widely, from 0% (gallbladder) to 51.0% (rectum), with 37.8% in the duodenum, 36.0% in the stomach, 27.1% in the esophagus, and 11.3% in the jejunoileum (11-13).

Identification of the site distribution of colorectal carcinoids among 90,057 cases of tumors registered between 1984

Table I. TNM classification for NETs of the colon and rectum.

| TNM | Characteristics |
|---|---|
| Primary tumor | |
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor invades mucosa or submucosa<br>T1a size <1 cm<br>T1b size 1-2 cm |
| T2 | Tumor invades muscularis propria or size >2 cm |
| T3 | Tumor invades subserosa/pericolic/perirectal fat |
| T4 | Tumor directly invades other organs/structures and/or perforates the visceral peritoneum |
| Regional LNs | |
| Nx | Regional LN status cannot be assessed |
| N0 | No regional LN metastasis |
| N1 | Regional LN metastasis |
| Distant metastasis | |
| Mx | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

NET, neuroendocrine tumor; TNM, tumor-node-metastasis; LN, lymph node.

Table II. Grading of gastrointestinal neuroendocrine neoplasms according to proliferative activity (WHO 2010 classfication).

| Grade | Mitotic count (/10 HPFs) | Ki-67 (%) |
|---|---|---|
| G1 | <2 | ≤2 |
| G2 | 2-20 | 3-20 |
| G3 (NEC) | <20 | <20 |
| Mixed adenoneuroendocrine carcinoma | | |

Modified according to reference, MIB1 and antibody, % of 100 tumor cells in areas of highest nuclear labeling. WHO, World Health Organization; HPF, high-power field; NEC, neuroendocrine carcinoma.

Table III. Patient characteristics (n=40).

| Characteristics | No. |
|---|---|
| Age at treatment, years | |
| Median | 59.8 |
| Range | 34-81 |
| Sex | |
| Male | 26 |
| Female | 14 |
| Tumor size, mm | |
| Median | 7.4 |
| Range | 3-15 |
| Tumor location | |
| Rs | 3 |
| Ra | 13 |
| Rb | 25 |
| Categories by size, mm | |
| 0-5 | 7 |
| 6-10 | 29 |
| 11-15 | 4 |

Rs, rectosigmoid; Ra, upper rectum; Rb, lower rectum.

Table IV. Surgical parameters (n=12).

| Variables | Mean | Range |
|---|---|---|
| Age, years | 55.9 | (40-69) |
| Submucosal, $\mu$m | 1,816.7 | (100-4,500) |
| Max tumor size, mm | 8.5 | (5-14) |
| Operative time, min | 458 | (275-643) |
| Blood loss, ml | 423 | (5-1,770) |
| Lymph node dissection, no. site | 8.6 | (2-19) |

and 1998 in Japan showed 345 cases of carcinoids, all from the Asian population. After excluding 2 cases of unknown sites, the sites were distributed as follows: 3 (0.9%) in the ileum, 8 (2.3%) in the appendix, 28 (8.2%) in the colon, and 304 (88.6%) in the rectum, indicating a high prevalence for carcinoids in the rectum in the Japanese population. Colon carcinoids were most often present in the cecum (9/28, 32%), sigmoid colon (8/28, 28%), transverse colon (5/28, 18%), ascending colon (4/28, 14%), and descending colon (2/28, 7%). The majority of the rectal carcinoids occurred in the lower rectum (267/304, 88%) (14,15).

Fahy *et al* also reported on the effect of lymphovascular invasion in rectal NETs by investigating 70 rectal NETs surgically resected at a single institution to assess the association between various clinicopathological variables and poor oncological outcomes. The authors observed a strong association of the presence of lymphovascular invasion with metastasis and poor relapse-free and disease-specific survival (16,17). When selecting the appropriate treatment, it is often particularly difficult to evaluate NETs sized <20 mm in the clinical setting. Other clinicopathological variables are not addressed in the current guidelines and staging systems.

At present, the surgical techniques of EMR and ESD are spreading in Japan, and several endoscopic therapies are being performed for rectal NETs. The malignant potential of NETs sized ≥2 cm is high, similar to that of colorectal cancer. The possibility of lymph node metastasis in NETs of this size is also high. However, the management of G1 NETs sized 1-2 cm

Table V. Surgical parameters (n=12) mitotic count and Ki-67.

| No. | Depth | SM invasion, $\mu$m | Size, mm | Lymphatic invasion | Vascular invasion | Mitotic count, n[a] | Ki-67, %[a] | WHO 2010 |
|---|---|---|---|---|---|---|---|---|
| 1 | SM | 2,000 | 7 | 0 | 1 | 1 | 0.4 | G1 |
| 2 | SM | 100 | 8 | 1 | 0 | 0 | 1.0 | G1 |
| 3 | SM | 1,000 | 8 | 0 | 0 | 1 | 2.4 | G2 |
| 4 | SM | 1,000 | 8 | 0 | 1 | 1 | 3.0 | G2 |
| 5 | SM | 2,200 | 10 | 1 | 0 | 0 | 1.0 | G1 |
| 6 | SM | 500 | 14 | 0 | 0 | 1 | 3.0 | G2 |
| 7 | SM | 4,000 | 11 | 1 | 0 | 1 | 3.2 | G2 |
| 8 | SM | 4,500 | 10 | 0 | 1 | 1 | 2.0 | G1 |
| 9 | SM | 2,000 | 7 | 0 | 0 | 0 | 1.4 | G1 |
| 10 | SM | 2,000 | 7 | 0 | 1 | 1 | 2.0 | G1 |
| 11 | SM | 1,000 | 5 | 0 | 1 | 0 | 2.0 | G1 |
| 12 | SM | 1,500 | 7 | 0 | 0 | 0 | 1.0 | G1 |

[a]per 10 high-power fields. SM, submucosal; WHO, World Health Organization; G, grade.

continues to be a subject of debate (18-20). Unfortunately, controlled prospective studies comparing the endoscopic and surgical approach for NETs of this size have not been performed. Due to the particular biology of G1 NETs of this size, the endoscopic approach is preferable to open surgery in patients with significant comorbidities and in elderly patients at high surgical risk.

Evaluation of the grade of malignancy and the choice of an appropriate treatment for colorectal NETs may be difficult in the clinical setting. Even tumor size and invasion depth are apparently not adequate for stratifying the risk of this rare tumor, and the current guidelines and staging systems do not address other clinicopathological variables. However, several recent studies have reported the effect of lymphovascular invasion on outcome in patients with colorectal NET. The presence of lymphovascular invasion is one of the strongest risk factors for metastasis, as are tumor size and depth of invasion. Furthermore, tumors sized <1 cm with submucosal invasion and no lymphovascular invasion are at minimal risk for metastasis, as reported in studies from Japan and the USA showing 100% 5-year survival (5,6).

This suggests that such tumors may be treated curatively with endoscopic resection or transanal local excision. By contrast, the risk for metastasis of colorectal carcinoids with lymphovascular invasion or a tumor size of >1 cm is equivalent to that of adenocarcinomas. Thus, it is important to emphasize the mandatory histological examination of lymphovascular invasion in specimens obtained by endoscopic resection or transanal local excision, in order to determine the need for additional radical surgery with regional lymph node dissection. Although the effects of lymphovascular invasion are not covered by the present guidelines and the TNM staging system, this may be promising for improving the guidelines and staging systems, particularly for early-stage colorectal NETs (7).

The present study evaluated rectal NETs sized <20 mm in comparison with the WHO 2010 guidelines. An open surgical procedure was performed in 12 patients to evaluate the presence of lymphatic or venous invasion. According to the WHO guidelines, 8 of our patients had G1 NETs, with 1 patient having lymph node metastasis; 4 patients had G2 NETs, and 1 patient had G1/G2 NET. ESD and EMR were performed in 28 patients, all of whom had G1 NETs (data not shown).

According to their mitotic index or Ki-67 index, NETs may be subdivided into either G1 or G2. Although this revised classification is a simple and useful grading system based on proliferative activity, the assessment of tumors with a Ki-67 index of >2 and ≤3% remains unclear. Despite this, inter-observer differences in mitotic counts remain larger compared with those of the Ki-67 index, and it is difficult to routinely scan at least 50 HPFs (1 HPF=2 $mm^2$), as required by the WHO 2010 classification for evaluation of the mitotic index. Thus, the validity and reproducibility of the Ki-67 index are superior to those of the mitotic index (21). A tumor with a a Ki-67 index of <2% is classified as G1, whereas a tumor with an index of 3-20% is classified as G2. As only one cut-off value was used to divide continuous values into two groups, the Ki67 index criteria of G1 NETs of the WHO 2010 classification were validated to elucidate the assessment of tumors with a Ki-67 index of 2-3%.

Yamaguchi *et al* reported that analysis of a Ki-67 index between 2 and 3% confirmed 2.8% to be the best Ki-67 index cut-off value for predicting metastasis or recurrence. However, none of our patients with G1/G2 and G2 NETs had lymph node metastasis (22). Only 1 of 12 (8.3%) patients had lymphatic or venous invasion, which is a low rate compared with that of other reports.

It remains debatable whether rectal NETs sized 10-19 mm require radical lymph node dissection or can be treated with local resection. As reported by Mani *et al*, the lymphatic spread of NETs sized 10-19 mm was clear in 10-15% of their patients. Guidelines from UKNET also recommend that lesions sized <10 mm may be adequately treated with complete endoscopic removal (23).

However, Konishi *et al* reported a 7% incidence of lymph node metastasis in tumors sized ≤10 mm, and Soga *et al* reported a 9.7% rate of metastasis of early-stage rectal carcinoids sized ≤10 mm. Fahy *et al* indicated that invasion depth, lymphovascular invasion and mitotic rate, all correlate with prognosis. Konishi *et al* found the risk factors for lymph node metastasis of colorectal carcinoids to be tumor size ≥11 mm and lymphatic invasion. Our patient with lymph node metastasis developed lymphatic invasion of a 10-mm tumor. In their evaluation of specimens from endoscopic resection, Fijimoto *et al* reported that 70% of the patients had lymph node metastasis with tumor sizes of 0-30 mm. The incidence of lymph node metastasis in the present study is significantly higher compared with that in previous reports, suggesting that the Fujimoto's criteria for radical resection are appropriate (24). Of note, two of three lesions sized <10 mm with lymph node metastasis were accompanied by lymphovascular invasion, confirming that lymphovascular invasion may be an important predictor of lymph node metastasis. The absence of lymphovascular invasion is key to confirming a favorable outcome in patients with a colorectal NET (Table V). To the best of our knowledge, this is the first study to report a comparison between lymphovascular invasion and Ki-67 in regard to rectal NETs. Further evaluation should be undertaken to determine whether mandatory histological examination of lymphovascular invasion is necessary in specimens obtained by endoscopic resection or transanal local excision, as histological examination can provide useful information to aid in determining the necessity of additional radical surgery with regional lymph node dissection.

The findings of the present study suggest that NETs sized <10 mm may be curatively treated by endoscopic resection. However, NETs with either lymphovascular invasion or sized >1 cm carry a risk for metastasis equivalent to that of adenocarcinomas. Therefore, it is mandatory to histologically examine lymphovascular invasion in specimens retrieved via endoscopic resection to determine the necessity for further radical surgery with regional lymph node dissection. The treatment of NETs sized <20 mm, as presently defined in the WHO 2010 guidelines, requires further evaluation.

## References


1. Konishi T, Watanabe T, Kishimoto J, Kotake K, Muto T and Nagawa H; Japanese Society for Cancer of the Colon and Rectum: Prognosis and risk factors of metastasis in colorectal carcinoids: Results of a nationwide registry over 15 years. Gut 56: 863-868, 2007.
2. Konishi T, Watanabe T, Muto T, Kotake K and Nagawa H; Japanese Society for Cancer of the Colon and Rectum: Site distribution of gastrointestinal carcinoids differs between races. Gut 55: 1051-1052, 2006.
3. Konishi T, Watanabe T, Nagawa H, Oya M, Ueno M, Kuroyanagi H, Fujimoto Y, Akiyoshi T, Yamaguchi T and Muto T: Treatment of colorectal carcinoids: A new paradigm. World J Gastrointest Surg 2: 153-156, 2010.
4. Rindi G, Arnold R and Bosman F: Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH (eds). WHO Classification of Tumours of the Digestive System. IARC Press, Lyon, 2010.
5. Hamilton SR and Aaltonen LA: World Health Organization, International Agency for Research on Cancer. Pathology and genetics of tumours of the digestive system. IARC Press, Lyon, pp105-111, 2000.
6. Pelosi G, Bresaola E, Bogina G, Pasini F, Rodella S, Castelli P, Iacono C, Serio G and Zamboni G: Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin sections is an independent predictor for malignancy: A comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index, and other clinicopathologic variables. Hum Pathol 27: 1124-1134, 1996.
7. Vilar E, Salazar R, Pérez-Garcia J, Cortes J, Oberg K and Tabernero J: Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. Endocr Relat Cancer 14: 221-232, 2007.
8. Klöppel G, Perren A and Heitz PU: The gastroenteropancreatic neuroendocrine cell system and its tumors: The WHO classification. Ann N Y Acad Sci 1014: 13-27, 2004.
9. Modlin IM, Kidd M, Latich I, Zikusoka MN and Shapiro MD: Current status of gastrointestinal carcinoids. Gastroenterology 128: 1717-1751, 2005.
10. Ito T, Tanaka M, Sasano H, Osamura YR, Sasaki I, Kimura W, Takano K, Obara T, Ishibashi M, Nakao K, *et al*: Preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors. J Gastroenterol 42: 497-500, 2007.
11. Soga J: Endocrinocarcinomas (carcinoids and their variants) of the duodenum. An evaluation of 927 cases. J Exp Clin Cancer Res 22: 349-363, 2003.
12. Soga J: Carcinids and their variant endocrinomas. An analysis of 11842 reported cases. J Exp Clin Cancer Res 22: 517-530, 2003.
13. Soga J: Carcinoids of the rectum: An evaluation of 1271 reported cases. Surg Today 27: 112-119, 1997.
14. Soga J: Gastric carcinoids: A statistical evaluation of 1,094 cases collected from the literature. Surg Today 27: 892-901, 1997.
15. Soga J: Carcinoids of the small intestine: A statistical evaluation of 1102 cases collected from the literature. J Exp Clin Cancer Res 16: 353-363, 1997.
16. Fahy BN, Tang LH, Klimstra D, Wong WD, Guillem JG, Paty PB, Temple LK, Shia J and Weiser MR: Carcinoid of the rectum risk stratification (CaRRS): A strategy for preoperative outcome assessment. Ann Surg Oncol 14: 396-404, 2007.
17. Fahy BN, Tang LH, Klimstra D, Wong WD, Guillem JG, Paty PB, Temple LK, Shia J and Weiser MR: Carcinoid of the rectum risk stratification (CaRRs): A strategy for preoperative outcome assessment. Ann Surg Oncol 14: 1735-1743, 2007.
18. Tanaka S, Oka S, Kaneko I, Hirata M, Mouri R, Kanao H, Yoshida S and Chayama K: Endoscopic submucosal dissection for colorectal neoplasia: Possibility of standardization. Gastrointest Endosc 66: 100-107, 2007.
19. Sakata H, Iwakiri R, Ootani A, Tsunada S, Ogata S, Ootani H, Shimoda R, Yamaguchi K, Sakata Y, Amemori S, *et al*: A pilot randomized control study to evaluate endoscopic resection using a ligation device for rectal carcinoid tumors. World J Gastroenterol 12: 4026-4028, 2006.
20. Nagai T, Torishima R, Nakashima H, Ookawara H, Uchida A, Kai S, Sato R, Murakami K and Fujioka T: Saline-assisted endoscopic resection of rectal carcinoids: Cap aspiration method versus simple snare resection. Endoscopy 36: 202-205, 2004.
21. Hasegawa T, Matsuno Y, Shimoda T and Hirohashi S: Gastrointestinal stromal tumor: Consistent CD117 immunostaining for diagnosis, and prognostic classification based on tumor size and MIB-1 grade. Hum Pathol 33: 669-676, 2002.
22. Yamaguchi T, Fujimori1 T, Tomita S, Ichikawa K, Mitomi H, Ohno K, Shida Y and Kato H: Clinical validation of the gastrointestinal NET grading system: Ki67 index criteria of the WHO 2010 classification is appropriate to predict metastasis or recurrence. Diagn Pathol 8: 65, 2013.
23. Mani S, Modlin IM, Ballantyne G, Ahlman H and West B: Carcinoids of the rectum. J Am Coll Surg 179: 231-248, 1994.
24. Fujimoto Y, Oya M, Kuroyanagi H, Ueno M, Akiyoshi T, Yamaguchi T and Muto T: Lymph-node metastases in rectal carcinoids. Langenbecks Arch Surg 395: 139-142, 2010.