ANTICANCER RESEARCH *39*: 505-510 (2019)
doi:10.21873/anticanres.13141

Essentiality of Imaging Diagnostic Criteria Specific to Rectal Neuroendocrine Tumors for Detecting Metastatic Lymph Nodes

MICHIHIRO KUDOU, TOMOHIRO ARITA, MASAYOSHI NAKANISHI, YOSHIAKI KURIU, YASUTOSHI MURAYAMA, KATSUTOSHI SHODA, TOSHIYUKI KOSUGA, HIROTAKA KONISHI, RYO MORIMURA, ATSUSHI SHIOZAKI, HISASHI IKOMA, TAKESHI KUBOTA, HITOSHI FUJIWARA, KAZUMA OKAMOTO and EIGO OTSUJI

Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

Abstract. *Background/Aim: The present study aimed to clarify an accurate diagnostic method for lymph node metastasis (LN+) in rectal neuroendocrine tumors (rNETs). Patients and Methods: This was a retrospective study of 14 rNETs and 45 rectal adenocarcinoma patients undergoing rectal resection. The short axis of LNs was measured using CT and pathological findings (43 paraffin-fixed LNs in rNETs and 786 LNs in adenocarcinoma). Results: The size of LN+ in CT and pathological findings was smaller in rNETs than adenocarcinoma (p=0.082 and p<0.001, respectively). The AUC values of ROC curves for detecting LN+ using LN sizes on CT were 0.837 for rNETs and 0.885 for adenocarcinoma (Cut-off values: 5 mm for rNETs, 7 mm for adenocarcinoma). rNETs were diagnosed with high accuracy using the cut-off value of rNETs (5 mm) (sensitivity: 80.0%, and specificity: 87.5%). Conclusion: The size of LN+ was smaller in rNETs than in adenocarcinoma, suggesting the essentiality of diagnostic criteria specific for rNETs.*

Rectal neuroendocrine tumors (rNETs) are epithelial tumors derived from endocrine cells with malignant potential, such as invasion to deep layers or metastasis, which develops in the deep portions of glands (1). In recent years, the number of patients with rNETs has markedly increased because of recent advances in preventive screening for colorectal disease, which has resulted in increasing attention to its pathophysiology by many clinicians and more focused research (2, 3). Based on this recent background, a new classification system has been established, in which rectal carcinoids are classified as rNETs, and are staged according to tumor size, lymph node metastasis (LN+), distant metastasis, the mitotic count, and Ki-67 labeling index (4). The clinical utility of this classification system has been already reported (5). Despite an increase in incidence, rNETs are still rare tumors; their incidence was previously reported to be only 1-2% of all rectal tumors (6). Their clinicopathological and biological characteristics have gradually been clarified; however, their rarity prevents the establishment of clinical guidelines with strong statistical power.

The behavior of LN+ in rNETs is specific, which complicates decision-making by clinicians. Previous studies reported that LN+ was sometimes detected in small rNETs, with diameters less than 10 mm (7, 8). The survival of rNET cases with LN+ was previously reported to be as poor as that of rectal cancer cases with LN+ (9, 10). Therefore, similar to surgical indications for rectal cancer, radical rectal resection with lymphadenectomy has been strongly recommended for rNETs with potential LN+. Although risk factors for rNETs with potential LN+ currently remain unclear, the criteria of surgical indications for rNETs are generally recognized as the following: 1) rNETs with diameters of 20 mm or larger in the primary tumor, 2) 10-20 mm with a suspected invaded muscularis propria (MP) and lymph ductal invasion, and 3) suspected LN+ on computed tomography (CT) or magnetic resonance imaging (MRI) findings (11, 12). Tumor size or invasion depth may be evaluated with high accuracy using endoscopic ultrasonography (13). However, a precise diagnostic method for detecting LN+ has not yet been established; therefore, it may often be evaluated using the diagnostic criteria of CT or MRI, which were established based on clinicopathological data in rectal adenocarcinoma, despite the diagnostic accuracy of these criteria for LN+ not being demonstrated in rNETs.

In the present study, we examined whether the size of regional LNs in rNETs may be evaluated using the same diagnostic criteria of contrast-enhanced CT (CECT) as rectal

Correspondence to: Tomohiro Arita, MD, Ph.D., Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan. Tel: +81 752515527, Fax: +81 752515522, e-mail: t-art@koto.kpu-m.ac.jp

Key Words: Rectal neuroendocrine tumor, pre-operative staging, lymph node metastasis.

adenocarcinoma through a retrospective analysis of non-metastatic and metastatic LN sizes on CECT and in paraffin-fixed specimens. Furthermore, the cut-off value for the size of LN with metastasis in pre-operative CECT findings was calculated. The present study aimed to establish an appropriate diagnostic method for LN+ in rNETs using pre-operative CECT through a retrospective analysis, in order to provide rNET patients with more curative treatments based on a precise clinical diagnosis.

Patients and Methods

Patients. This study included 14 rNET cases that underwent curative surgery between April 2006 and March 2017 in the Division of Digestive Surgery of Kyoto Prefectural University of Medicine (KPUM), Kyoto, Japan. Pathological diagnoses were made by two expert pathologists based on the UICC/AJCC classification system (14). This study was approved by the Research Ethics Committee of Kyoto Prefectural University of Medicine (No. ERB-C-1178).

Middle and lower rectal adenocarcinoma patients undergoing curative surgery between April 2013 and March 2017 in KPUM where included in the analysis. Patients receiving neoadjuvant chemotherapies or radiotherapies or with a previous history of rectal resection were excluded from the present study. Therefore, 45 rectal adenocarcinoma cases were ultimately selected.

Preoperative evaluation by CECT. All eligible cases underwent CECT in the 2 months before rectal resection. CECT was mainly performed in KPUM or an affiliated medical center. CT examinations were performed using a multidetector CT with 64 or 320 layers. Briefly, all patients fasted for more than 6 h, and received an intravenous injection of 510 mg/kg iopamidol (Bayer, Osaka, Japan) or iohexol (Daiichi-Sankyo, Tokyo, Japan) over 45 sec. A CT scan was then performed for 100 sec after the contrast material injection in order to obtain equilibrium phase images. The sizes of LNs were evaluated in the short axis on horizontal CECT images by at least one radiologist and two or more digestive surgeons.

Evaluation of LN sizes in paraffin-fixed specimens. LNs were sampled from surgically resected specimens by digestive surgeons and were subsequently embedded in paraffin after 12 h of formalin fixation. They were sliced at the maximum cut surface by expert technicians, and samples were then re-fixed on slide glasses. The short axes of all re-fixed LNs derived from eligible rNETs and adenocarcinoma tumors were measured.

Surgical procedures. All surgeries were performed or supervised by surgeons with sufficient experience in rectal resection. A surgical method was selected in a preoperative conference by an expert rectal surgical team according to the Japanese colorectal cancer guidelines (15, 16). Briefly, anal preservation surgery was performed for rectal tumors that were without invasion to the anal canal. In tumors with invasion to the anal canal, intersphincteric resection (ISR) was performed if the tumor was localized to the mucosal and submucosal layers and it was possible to secure a surgical margin. If not, anterior perineal resection was performed. Lateral LN dissection was basically performed for lower rectal adenocarcinoma and rNETs with invasion to the mesorectum or with suspected LN metastases. Clinically suspected LN+ in the perirectal and lateral regions were defined as 7 mm and 5 mm or larger in the short diameter, respectively (17). Temporary diverting ileostomy was simultaneously constructed in ISR and super low anterior resection. Diverting ileostomy was closed 3 months after initial surgery.

Statistical analysis. Comparisons were performed between both groups using the Student's *t*-test or chi-squared test. *p*-Values of less than 0.05 were regarded as significant. Receiver operating characteristic (ROC) curves were generated to evaluate diagnostic performance for detecting LN+ using measurements of the LN short diameter on CECT. Corresponding sizes under the ROC curve (AUC), sensitivities, specificities, and accuracies were calculated. Statistical analyses were performed using JMP version 10.

Results

Clinicopathological characteristics of rNET and adenocarcinoma patients. Patient characteristics are summarized in Table I. rNET patients were significantly younger than rectal adenocarcinoma patients (Mean: 54.6 *vs*. 66.2, $p<0.001$). Tumor sizes were significantly smaller for rNETs than for rectal adenocarcinomas (Mean: 9.9 *vs*. 44.2, $p<0.001$). rNETs were more frequently located on the lower rectum than rectal adenocarcinomas (11/14 *vs*. 14/45, $p<0.001$). More cases were undergoing preceding endoscopic resection, such as endoscopic mucosal resection or endoscopic submucosal dissection, among rNETs cases than adenocarcinoma cases (2/45 *vs*. 8/14: $p<0.001$). A permanent stoma was not constructed in rNET cases. D3 LN dissection was more frequently performed for rectal adenocarcinoma than for rNETs ($p<0.001$). The pathological invasion depth was significantly deeper in rectal adenocarcinoma cases than in rNET cases ($p<0.001$). Lymph ductal or venous invasion were more frequently observed in adenocarcinoma cases ($p=0.034$ and 0.016, respectively). Seventeen rectal adenocarcinoma and 5 rNET cases were pathologically diagnosed with LN+. All rNET tumors with LN+ had some vessel invasion, and LN+ was also detected in all rNET tumors with invasion to the MP. The Ki-67 labeling index of rNET cases was 0.9-19.5% (data not shown).

Comparison of regional LN sizes in rNETs and adenocarcinomas on CT images. The short axis of the greatest LN in the circumrectal region on pre-operative CECT images was measured and compared between rectal rNETs and adenocarcinomas (Table II). LN sizes were slightly smaller in rNET cases with LN+ than in carcinoma cases (Mean: 6.0 *vs*. 8.8 mm, $p=0.082$). Moreover, LN sizes were smaller in rNETs without LN+ than in adenocarcinoma cases (2.7 *vs*. 4.5 mm, $p=0.026$). A ROC curve was used to select the cut-off value for LN size in LN+. The AUC values of ROC curves were used to detect the LN+ of rNETs and adenocarcinomas. By measuring the short axis of the greatest LN on CT images the AUCs for rNETs and adenocarcinomas were 0.837 and 0.885, respectively. The cut-off values for adenocarcinomas and rNETs were 7 and 5 mm, respectively.

Table I. *Patient characteristics*.

	rNETs 14	Adenocarcinoma 45	*p*-Value
Gender			
Male	8	32	0.250
Female	6	12	
Age			
Mean±SD	54.6±10.6	66.2±10.3	<0.001
Tumor size	9.9±4.9	44.4±16.9	<0.001
Tumor location			
Middle	3	31	<0.001
Lower	11	14	
Pre-treatment			
None	6	43	<0.001
EMR	5	2	
ESD	3	0	
Surgical approach			
open	1	2	0.688
lap	13	43	
Surgical method			
ISR	1	4	0.415
LAR	13	33	
APR	0	6	
Hartmann	0	2	
Stoma	0	8	<0.001
Lymph node dissection			
D2	14	13	<0.001
D3	1	32	
Lateral dissection	0	5	
Pathological invasion depth			
SM	12	2	<0.001
MP	3	14	
SS	0	29	
Pathological lymph node metastasis			
Positive	5	17	0.889
Lymph ductal invasion			
Positive	6	25	0.034
Venous invasion			
Positive	5	28	0.016
Distant metastasis	0	5	0.192

rNETs: Rectal neuroendocrine tumors; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; ISR: intersphincteric resection; LAR: lower anterior resection; APR: abdominoperineal resection; SM: submucosa; MP: muscularis propria; SS: subserosa.

Comparison of regional LN sizes in rNETs and adenocarcinoma in paraffin-fixed specimens. As previously described (18), LN+ sizes were smaller in rNETs than in rectal adenocarcinoma in the present study; however, there was a limitation due to the small number of rNETs cases examined. Thus, the sizes of all dissected LNs fixed by paraffin were measured in order to validate the hypothesis that the LN+ of rNETs are smaller than those of rectal adenocarcinomas (Table III). The total numbers of dissected LNs in rNETs and adenocarcinoma were 143 and 786, respectively. In these LNs, the numbers of LN+ in rNETs and adenocarcinomas were 8 (5.5%) and 28 (3.5%), respectively. The metastatic or non-metastatic LNs of rNETs were significantly smaller than those of rectal adenocarcinomas, which was consistent with CT findings.

Table II. *Size of lymph nodes evaluated by CT findings in rectal adenocarcinoma and neuroendocrine tumors*.

Lymph nodes	rNETs	Adenocarcinoma	*p*-Value
n			
Total	14	45	
Metastasis	5	17	
Non-metastasis	9	28	
Short diameter			
Total	4.0±2.6	6.1±3.2	0.032
Metastasis	6.0±3.2	8.8±2.9	0.082
Non-metastasis	2.7±1.0	4.5±2.0	0.026

rNETs: Rectal neuroendocrine tumors.

Table III. *Size of lymph nodes evaluated using paraffin-fixed specimens in rectal adenocarcinoma and neuroendocrine tumors*.

Lymph nodes	rNETs	Adenocarcinoma	*p*-Value
n			
Total	143	786	
Metastasis	8	28	
Non-metastasis	135	758	
Short diameter			
Total	2.1±1.2	2.6±1.5	<0.001
Metastasis	3.5±0.7	6.4±2.4	<0.001
Non-metastasis	2.0±1.2	2.5±1.2	<0.001

rNETs: Rectal neuroendocrine tumors.

Diagnostic accuracy of CT for detecting LN+ using cut-off values calculated by ROC curves. The diagnostic accuracy of CT was evaluated using novel size criteria based on the calculated cut-off values (Table IV). When defining LN+ as 7 mm or larger in the short axis, the sensitivity, specificity, and accuracy of CT were 82.4%, 82.1%, and 82.2%, respectively, for rectal adenocarcinoma and 20.0%, 100.0%, and 71.4%, respectively, for rNETs. The sensitivity of the cut-off value of 7 mm in the short axis calculated by the ROC curve of rectal adenocarcinoma was insubstantial for rNETs. In contrast, LN+ was diagnosed with high accuracy using the cut-off value of 5 mm in the short axis calculated by data obtained for rNETs (sensitivity: 80.0%, specificity: 87.5%, and accuracy: 84.6%).

Table IV. *Diagnostic accuracy of CT in detecting lymph node metastasis using cut-off values calculated by a ROC analysis.*

	Cut-off value	cN (+)	pN (+)	Sensitivity	Specificity	Accuracy
Adenocarcinoma	≥7 mm	19/45	17/45	82.4%	82.1%	82.2%
rNETs	≥7 mm	1/14	5/14	20.0%	100.0%	71.4%
	≥5 mm	5/14	5/14	80.0%	87.5%	84.6%

Cut-off value: The value calculated by the ROC curve for detecting lymph node metastasis using CT (adenocarcinoma: minor axis of 7 mm or larger, NETs; minor axis of 5 mm or larger); cN(+): clinically diagnosed metastasis of lymph nodes by pre-operative CT; pN(+): pathologically diagnosed metastasis of lymph nodes after surgery; rNETs: rectal neuroendocrine tumors.

Discussion

The size of LN+ in rNETs has been previously examined. Fujimoto *et al*. performed a retrospective analysis of their rNETs cases and reported that regional LNs with a minor axis of 5 mm or greater needs to be regarded as metastasis (19). Kim BC *et al*. showed that LN size alone is not a sufficient predictor of tumor metastasis through a retrospective analysis on paraffin-fixed LN+ derived from rNETs, because of wide variations in the sizes of LNs with metastasis, with some being very small (18). Although this evaluation method of LNs using paraffin-fixed specimens had the advantage of allowing the analysis of a higher number of resected LNs, difficulties were associated with calculating precise cut-off values for LN sizes with metastasis in clinical settings because the dewatering process by formalin, which was used in the preparation of pathological specimens, may reduce the size of LNs (20). In contrast, although only a small number of LNs may be evaluated in pre-operative CECT findings, these sizes may be examined in actual clinical settings. Based on these advantages and disadvantages, we examined LN sizes in rNETs using LN data derived from CECT findings and paraffin-fixed specimens.

LN+ in rNETs is often diagnosed in clinical settings using the criteria of rectal adenocarcinoma despite the diagnostic accuracy of these criteria for LN metastasis not being demonstrated for rNETs. In order to clarify this ambiguous point, we compared LN+ sizes in rNETs and adenocarcinomas. To the best of our knowledge, this is the first study to show an appropriate diagnostic method for LN+ using CECT in rNETs through a comparison with rectal adenocarcinoma.

The results of the present study revealed that the sizes of LN+ were smaller in rNETs than in rectal adenocarcinoma using CECT and pathological findings. Moreover, the cut-off values for the LN minor axis of the LN+ of rNETs and adenocarcinoma on CECT images were calculated as 5 and 7 mm, respectively, in the present study. The diagnostic accuracy of CECT was not satisfactory (sensitivity: 20.0%, and accuracy: 71.4%) when applying the cut-off value for rectal adenocarcinoma (7 mm) to rNETs. However, the LN+ of rNETs were diagnosed with very high accuracy (sensitivity: 80.0%, accuracy: 84.6%) by CECT when the cut-off value was defined as 5 mm or larger in the minor axis. These results suggest that the diagnostic criteria of LN+ for rectal adenocarcinoma cannot be applied to rNETs in clinical settings. We considered the evaluation of LNs in preoperative CECT findings using as criterion for assessing the existence of LN+ in rNETs "a short axis of 5 mm or greater", to potentially decrease the rate of false-staging in pre-operative settings and avoid misleading over or under-treatments.

Furthermore, the present study revealed an interesting characteristic of regional LNs in rNETs; they were significantly smaller than in rectal adenocarcinoma regardless of metastasis. This may have been due to the following differences in the characteristics between each tumor. Colorectal cancer tissues generally induce inflammation through the production of proinflammatory cytokines, which often facilitate cancer proliferation or metastasis (21). This inflammatory reaction spreads in the tissue surrounding a tumor, resulting in the swelling of LNs. Therefore, some large LNs regardless of metastasis are often detected around cancer tissues and exhibit strong inflammatory reactions. In contrast, the relationship between rNETs and inflammation has not yet been examined. This difference in the strength of inflammation derived from a tumor may result in various LN sizes irrespective of metastasis.

There were some limitations that need to be addressed. This was a retrospective and single-institution study with a small sample size, which may limit statistical power and generate a statistical bias. Furthermore, the study included cases undergoing pre-operative non-thin slice CT. In one rNET case with pathologically diagnosed LN+ among the present cases, non-thin slice CECT (slice thickness: 5 mm) did not reveal swollen regional LNs, such as 5 mm or larger in the minor axis, in pre-operative screening. These LNs may have been detected if thin-slice CECT was used for the pre-operative evaluation of this case. Another limitation is that the sizes of fresh samples, unaffected by formalin fixation, were not analyzed just after surgery in the present study because of the lack of these data in our Institution. However, a previous study reported that radiographic tumor sizes were

significantly smaller than post-resection fresh tumor sizes (22). It is not, therefore, evident whether radiologic findings of LN size are consistent with those of fresh samples. In addition, it was not possible to examine the diagnostic accuracy of LN+ in rNETs by MRI in the present study because there were some cases without pre-operative MRI, which has recently been regarded as one of the indispensable pre-operative examinations in surgery for rectal tumors. Further investigations of its diagnostic accuracy for rNETs are needed. Nevertheless, the present study demonstrated the essentiality of diagnostic criteria specific to rNETs, and the diagnostic accuracy of the clinical staging of rNETs. The results of the present study need to be validated in studies with large sample sizes for a precise clinical diagnosis and appropriate decision-making regarding surgical indications for rNETs.

Conclusion

The present study revealed that the sizes of LN+ were smaller in rNETs than in rectal adenocarcinoma on CECT and in pathological findings, suggesting that the imaging criteria of LNs used for rectal adenocarcinoma in clinical evaluations of regional LNs cannot be applied to rNETs. Furthermore, in consideration of many limitations, LN+ in rNETs may be clinically evaluated with a high accuracy when defining it with a minor axis of 5 mm or greater on CT images.

Conflicts of Interest

The Authors of this article have no relevant financial relationships with commercial interests to disclose.

References

1 Shimizu T, Tanaka S, Haruma K, Kitadai Y, Yoshihara M, Sumii K, Kajiyama G and Shimamoto F: Growth characteristics of rectal carcinoid tumors. Oncology *59(3)*: 229-237, 2000.

2 Soga J: Carcinoids of the rectum: An evaluation of 1271 reported cases. Surg Today *27(2)*: 112-119, 1997.

3 Ito T, Sasano H, Tanaka M, Osamura RY, Sasaki I, Kimura W, Takano K, Obara T, Ishibashi M, Nakao K, Doi R, Shimatsu A, Nishida T, Komoto I, Hirata Y, Nakamura K, Igarashi H, Jensen RT, Wiedenmann B and Imamura M: Epidemiological study of gastroenteropancreatic neuroendocrine tumors in japan. J Gastroenterol *45(2)*: 234-243, 2010.

4 Edge SB and Compton CC: The American Joint Committee on Cancer: The 7th edition of the ajcc cancer staging manual and the future of tnm. Ann Surg Oncol *17(6)*: 1471-1474, 2010.

5 Kim MS, Hur H, Min BS, Baik SH, Lee KY and Kim NK: Clinical outcomes for rectal carcinoid tumors according to a new (AJCC 7th edition) tnm staging system: A single institutional analysis of 122 patients. J Surg Oncol *107(8)*: 835-841, 2013.

6 Jetmore AB, Ray JE, Gathright JB Jr., McMullen KM, Hicks TC and Timmcke AE: Rectal carcinoids: The most frequent carcinoid tumor. Dis Colon Rectum *35(8)*: 717-725, 1992.

7 Heah SM, Eu KW, Ooi BS, Ho YH and Seow-Choen F: Tumor size is irrelevant in predicting malignant potential of carcinoid tumors of the rectum. Tech Coloproctol *5(2)*: 73-77, 2001.

8 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(5)*: 153-156, 2010.

9 Konishi T, Watanabe T, Kishimoto J, Kotake K, Muto T, Nagawa H and 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(6)*: 863-868, 2007.

10 Anthony LB, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR, Wiseman GA, Benson AB, 3rd and Pommier RF: The nanets consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): Well-differentiated nets of the distal colon and rectum. Pancreas *39(6)*: 767-774, 2010.

11 Kulke MH, Shah MH, Benson AB, 3rd, Bergsland E, Berlin JD, Blaszkowsky LS, Emerson L, Engstrom PF, Fanta P, Giordano T, Goldner WS, Halfdanarson TR, Heslin MJ, Kandeel F, Kunz PL, Kuvshinoff BW, 2nd, Lieu C, Moley JF, Munene G, Pillarisetty VG, Saltz L, Sosa JA, Strosberg JR, Vauthey JN, Wolfgang C, Yao JC, Burns J and Freedman-Cass D: Neuroendocrine tumors, version 1.2015. J Natl Compr Canc Netw *13(1)*: 78-108, 2015.

12 Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, Corrie P, Davar J, Davies AH, Lewington V, Meyer T, Newell-Price J, Poston G, Reed N, Rockall A, Steward W, Thakker RV, Toubanakis C, Valle J, Verbeke C and Grossman AB, UK and Ireland Neuroendocrine Tumour Society: Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut *61(1)*: 6-32, 2012.

13 Varas MJ, Gornals JB, Pons C, Espinos JC, Abad R, Lorente FJ and Bargallo D: Usefulness of endoscopic ultrasonography (eus) for selecting carcinoid tumors as candidates to endoscopic resection. Rev Esp Enferm Dig *102(10)*: 577-582, 2010.

14 Edge S, Byrd D and Compton C: Ajcc cancer staging manual seventh edition. New York: Springer-Verlag, 2009.

15 Japan Neuroendocrine tumor siciety (JNETs), Guidelines for the management of gastroenteropancreatic neuroendocrine tumor ver1.1, 2015

16 Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K, Japanese Society for Cancer of the C and Rectum: Japanese society for cancer of the colon and rectum (jsccr) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol *23(1)*: 1-34, 2018.

17 Pomerri F, Maretto I, Pucciarelli S, Rugge M, Burzi S, Zandona M, Ambrosi A, Urso E, Muzzio PC and Nitti D: Prediction of rectal lymph node metastasis by pelvic computed tomography measurement. Eur J Surg Oncol *35(2)*: 168-173, 2009.

18 Kim BC, Kim YE, Chang HJ, Lee SH, Youk EG, Lee DS, Lee JB, Lee EJ, Kim MJ, Sohn DK and Oh JH: Lymph node size is not a reliable criterion for predicting nodal metastasis in rectal neuroendocrine tumours. Colorectal Dis *18(7)*: O243-251, 2016.

19 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(2)*: 139-142, 2010.

20 Goldstein NS, Soman A and Sacksner J: Disparate surgical margin lengths of colorectal resection specimens between *in vivo* and *in vitro* measurements. The effects of surgical resection and formalin fixation on organ shrinkage. Am J Clin Pathol *111(3)*: 349-351, 1999.

21 Klampfer L: Cytokines, inflammation and colon cancer. Curr Cancer Drug Targets *11(4)*: 451-464, 2011.

22 Tran T, Sundaram CP, Bahler CD, Eble JN, Grignon DJ, Monn MF, Simper NB and Cheng L: Correcting the shrinkage effects of formalin fixation and tissue processing for renal tumors: Toward standardization of pathological reporting of tumor size. J Cancer *6(8)*: 759-766, 2015.

Received November 22, 2018
Revised November 28, 2018
Accepted November 29, 2018