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Lymph Node Size on Computed Tomography Images Is a Predictive Indicator for Lymph Node Metastasis in Patients with Colorectal Neuroendocrine Tumors

TOSHIAKI TANAKA[1], HIROAKI NOZAWA[1], KAZUSHIGE KAWAI[1], KEISUKE HATA[1], TOMOMICHI KIYOMATSU[2], TAKESHI NISHIKAWA[1], KENSUKE OTANI[1], KAZUHITO SASAKI[1], KOJI MURONO[1] and TOSHIAKI WATANABE[1]

[1]*Department of Surgical Oncology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;*
[2]*Division of Colorectal Surgery, Department of Surgery, National Center for Global Health and Medicine, Tokyo, Japan*

Abstract. *Background: Colorectal neuroendocrine tumors (NET) are a rare manifestation of colorectal neoplasia, requiring for radical dissection of the regional lymph nodes along with colorectal resection similar to that required for colorectal cancer. However, thus far, no reports have described the ability of computed tomography (CT) to predict lymph node involvement. In this study, we revealed the prediction rate of lymph node metastasis using contrast-enhanced CT. Patients and Methods: A total of 21 patients with colorectal NET undergoing colorectal resection were recruited from January 2010 to June 2016. We compared the CT findings between samples with or without pathologically proven lymph node metastasis, in each field (pericolic/perirectal and intermediate nodes). Results: Within the pericolic/perirectal field, any lymph node larger than 5 mm in the CT images was a predictive indicator of lymph node metastasis with a sensitivity, specificity, and area under ROC curve (AUC) of 66.7%, 87.5%, and 0.844, respectively. Within the intermediate field, any visible lymph node on the CT was a predictive indicator of lymph node metastasis with a sensitivity, specificity, and AUC of 100%, 76.4%, and 0.890, respectively. In addition, when we observed lymph nodes larger than 3 mm on the CT images, the sensitivity and specificity were 100% and 82.4%, respectively, with an AUC of 0.8971. Conclusion: CT images provide predictive information for lymph node metastasis with a high rate of accuracy.*

Correspondence to: Toshiaki Tanaka, MD, Ph.D., Department of Surgical Oncology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, 113-8655,Tokyo, Japan. Tel: +81 358008653, Fax: +81 338116822, e-mail: toshi-t@venus.dti.ne.jp

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Neuroendocrine tumors (NET) are a rare malignancy arising from amine precursor uptake and decarboxylation of cells (1). According to WHO classification released in 2010, they are categorized into three groups according to their pathological features (2). The incidence of NETs in each organ is unclear. However, a population-based study revealed that the gastrointestinal tract is the most common site (54.5%) of NET G1, which is the major NET subtype. Moreover, within the gastrointestinal tract, colon and rectum (36.3%) are the second most common gastrointestinal sites following the small intestine (3). The survival of a patient with NET differs among each pathological grade. Patients with colorectal NET G1 have the most beneficial 5-year survival from 92.1% to 100% (2, 4), followed by those with NET G2. Even patients with neuroendocrine carcinoma (NET G3), the most aggressive subtype of NET, have a postoperative 5-year survival of 26.3-57.4% when distant metastasis is absent (5). Thus, we consider that a radical resection along with an appropriate regional lymphadenectomy is necessary for NET. The indication of lymphadenectomy is commonly determined by the tumor size, the depth of the tumor, lympho-vascular invasion, along with lymph node metastasis proven by the clinical images (6, 7).

The manifestation of lymph node metastasis observed *via* clinical images is routinely performed by contrast-enhanced computed tomography (CT) in colorectal cancer. In previous findings, it was reported that lymph nodes with a diameter larger than 1 cm, three or more clustered lymph nodes regardless of their size, and irregular surface, were predictive factors for lymph node involvement (sensitivity: 66-96.3% and specificity: 35-81%) (8-18). On the other hand, thus far, there has only been a single report stating the lymph node

involvement of rectal NETs predicted by CT (19), and there have been no reports concerning colorectal NETs.

In this study, we examined our experience of colorectal NETs and revealed the accuracy of lymph node staging on preoperative CT imaging. We revealed that the size and number of lymph nodes were the predictive factors for lymph node involvement in the intermediate field. Moreover, size was the single predictive factor for the pericolic/perirectal region.

Materials and Methods

Patient recruitment and data. This was a retrospective study carried out in the Department of Surgical Oncology at the University of Tokyo Hospital, Tokyo, Japan. We reviewed our registry from January 2010 to June 2016. A total of 24 patients consulted at our department during this period. Three of these patients underwent a transanal resection and presented no risk factors of lymph node metastasis in the resected specimen. Therefore, they did not undergo a colorectal resection and were excluded from our study. Another 21 patients had clinical or pathological risk factors prior to the operation (6, 7, 20), and we performed a colorectal resection with a complete regional lymph node dissection (pericolic/perirectal, intermediate and apical lymph node). No morbidity or mortality were observed in the postoperative course. For each patient, we collected perioperative clinical data (*i.e.* age, gender, location of the primary tumor, preceding therapy before the operation and approach of operation) along with pathological data (*i.e.* the surgical margin, the number of harvested lymph nodes, pathological grade, depth of the tumor and the extent of lymph nodes metastasis). All data were registered in our database and approved by the review board. We obtained written informed consent from patients before registry.

Lymph node measurement on CT. We performed contrast-enhanced CT as a routine examination before the operation. The CT images were obtained via spiral multidetector computed tomography (MDCT) and an expert radiologist determined the staging. In addition, we reviewed the CT images to obtain additional information regarding this study (*e.g.* the number of visible lymph nodes, location, diameter, internal heterogeneity, shape and the surface of the lymph node). The location was categorized into three fields: 1) the region between the colorectal wall and the distal end of feeding artery as the pericolic/perirectal field, 2) region along the feeding artery was characterized as the intermediate, and 3) the area proximal to the intermediate region as the apical field. The diameter was calculated for all the lymph nodes in each case, and the largest one was used as an indicator. The internal pattern was categorized as either 'hetero' or 'iso'. If there were any lymph nodes presenting with a heterogeneous internal pattern, the case was categorized as 'hetero'. The shape was categorized as 'round' or 'ellipse' (ratio of long/short axis <0.8), and any lymph nodes that presented with a round shape were categorized as 'round'. The margin of the lymph node was categorized as either regular or irregular, and any that presented with an irregular surface were categorized as 'irregular'. All of these indicators were measured without knowing the pathological findings, except for the location of the primary tumor.

Statistics. Each variable was measured on the CT images and analysed in relation to the lymph node involvement that was proven pathologically. A Fisher's exact test was used to assess the categorized variables. A one-tailed *t*-test was used to assess the continuous variables among the groups. The predictive accuracy of the indicator was assessed by the specificity and sensitivity, and the area under the receiver operating characteristic curve (ROC) was calculated. Data were analysed using JMP ver. 12.0 software (SAS Institute, Tokyo, Japan).

Table I. *Patient characteristics*.

	No. of cases
Gender	
Male/Female	13/8
Age (years)	58±14.9
Location	
Rectum	18
Colon	2
Appendix	1
Preceding therapy	
ESD/EMR	9
TAR	2
None	10
Laparoscopic Surgery	
Yes	19
No	2
Resection	
R0	20
R1	0
R2	1
No. of harvested LNs	16±12
Histology	
G1	15
G2	3
G3 (NEC)	3
Depth	
SM	16
MP	2
SS-	3
Extent of lymph node metastasis	
None	13
Pericolic/Perirectal	4
Intermediate	4
Apical	0

ESD, Endoscopic submucosal dissectrion; EMR, endoscopic mucosal resection; TAR, trans-anal resection; SM, submucosa; MP, muclaris propia; SS, deeper than subserosal layer; LN, lymph node; NEC, neuroendocrine carcinoma.

Results

The patients' characteristics are reported in Table I. There were 13 males and 8 females, and the mean age was 58±14.9 years. Most of the tumors were found in the rectum, followed by the colon and appendix, with the distribution in line with a previous report (3). Nine patients underwent an endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR). Moreover, two patients underwent a transanal resection

Table II. *Findings on CT images and LNs metastasis in pericolic/perirectal LNs.*

		Pathologically-proven LNs metastasis		
		LN positive cases (n=8)	LN negative cases (n=13)	
Findings on CT	LNs visible cases (Positive/Negative)	6/2	8/5	n.s.
	No of LNs per case	2.1±0.67	0.84±0.52	n.s. (p=0.075)
	*Maximum Diameter of LNs	6.8±1.4	2.3±1.1	p=0.00124
	*Shape (Round/Ellipse)	6/0	6/2	n.s. (p=0.30)
	*Margin (Regular/Irregular)	3/3	8/0	n. s. (p=0.054)
	*Internal pattern (iso/hetero)	3/3	8/0	n.s. (p=0.054)

*Parameters were evaluated in cases in which the LNs were visible on the CT images (six patients in the LN positive group and eight in the LN negative group). CT, computed tomography; LN, lymph node; n.s.: not significant.

Table III. *Findings on the CT image and LN metastasis in the intermediate LNs.*

		Pathologically-proven LN metastasis		
		LN positive cases (n=4)	LN negative cases (n=17)	
Findings on CT	LN visible cases (Positive/Negative)	4/0	4/13	p=0.012
	No. of LN per case	1.5±0.34	0.29±0.16	p=0.0022
	*Maximum Diameter of LNs	4.3±0.89	0.93±0.43	p=0.0017
	*Shape (Round/Ellipse)	3/1	3/1	n.s.
	*Margin (Regular/Irregular)	3/1	4/0	n.s.
	*Internal pattern (iso/hetero)	4/0	4/0	n.s.

*Parameters were evaluated in the cases in which the LNs were visible on the CT image. LN, lymph node; n.s., not significant.

(TAR) before the colorectal resection. Eleven patients exhibited one or more of the pathological risk factors for lymph node metastasis. The remaining 10 patients had clinical risk factors (*e.g.* tumor size or apparent invasion below submucosal layer), or pathological factors proven by biopsies.

Laparoscopic surgery was performed for most patients. Two patients underwent open surgery during the former period of this study because laparoscopic surgery was not introduced as a common approach during this period. The number of harvested lymph nodes was 16±12, which was large enough to conduct appropriate staging. All specimens were examined using the Ki-67 index using immune-histochemical (IHC) staining along with the mitotic count, and they were categorized into three pathological grades. In total, 15 cases were NET G1, 3 were NET G2 and 3 were NET G3 (neuroendocrine carcinoma; NEC). The depth of tumor invasion was submucosal in 16 cases, confined within the muscularis propia in 2 cases and beyond the muscularis propia in 3 cases.

Following a pathological examination, 13 patients were negative for lymph node metastasis (classified as "LN negative group") and 8 were positive (classified as "LN positive group"). In four cases the extent of the positive lymph nodes was within the pericolic/perirectal region, whereas in the other ones it was extended to an intermediate region. None of the lymph nodes were found in the apical region, so this region was excluded from further analysis.

Lymph node metastasis in the pericolic/perirectal regions. Table II presents the association between pathologically proven lymph node metastasis and the indicators found in CT images concerning the pericolic/perirectal regions. A large number of visible lymph nodes, a round shape, irregular margin and heterogeneous internal patterns tended to appear in the LN positive group. However, statistical significance was not reached. The largest diameter of the lymph node observed on the CT was an indicator for lymph node metastatic groups (6.8±1.4 in the LN positive group *vs.* 2.3±1.1 in the negative group; p=0.00124). To calculate the accuracy of the prediction, we referred to the ROC as shown in Figure 1. When we detected lymph nodes larger than 5 mm on the CT image, the sensitivity and specificity of lymph node metastasis were 66.7% and 87.5%, respectively. Using this criterion, the area under ROC curve (AUC) reached 0.844.

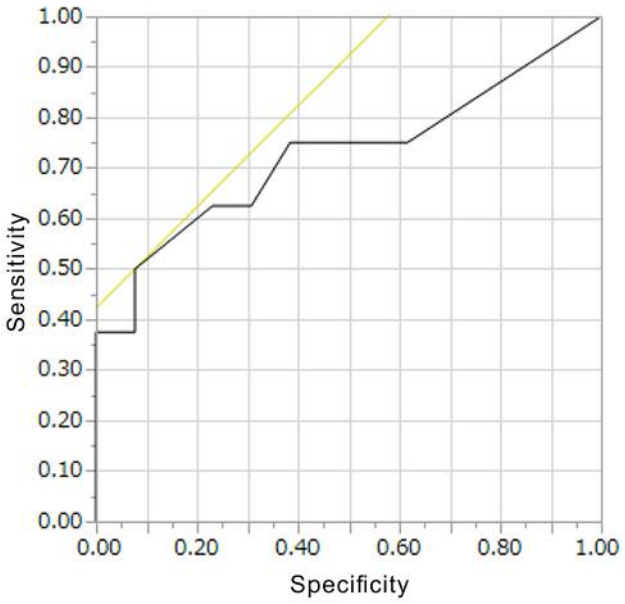

Figure 1. *Number of LNs detected by CT predictive of LN metastasis (AUC=0.844). The sensitivity was 66.7% and specificity was 87.5% for pathologically-positive LNs when LNs larger than 5 mm are detected in the pericolic/perirectal region on the CT images.*

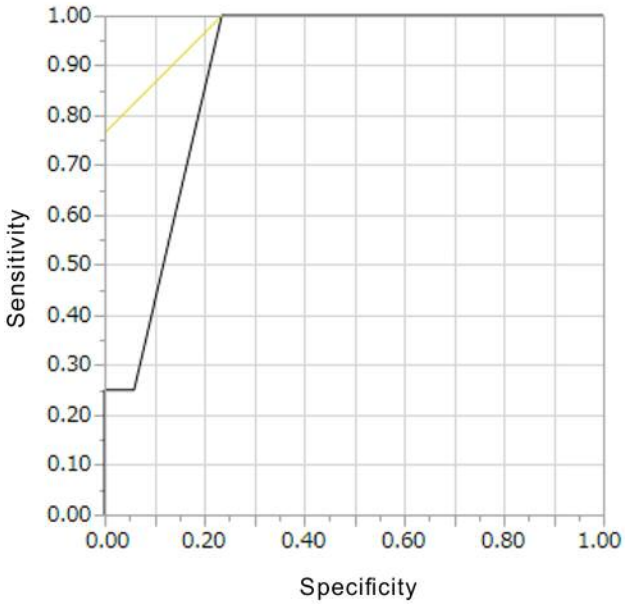

Figure 2. *Number of LNs detected by a CT predictive of LN metastasis (AUC=0.890). The sensitivity was 100% and specificity was 76.5% for pathologically positive LNs when LNs are detected in the intermediate region on the CT image.*

Lymph node metastasis in intermediate regions. Table III demonstrates the association between pathologically proven lymph node metastasis and the indicators detected in the CT images within the intermediate regions. There was a large number of visible lymph node cases in the LN positive group compared to the negative group (p=0.012). The number of visible lymph nodes per case was larger in the LN positive group than in LN negative group (1.5±0.34 *vs*. 0.29±0.16, respectively; p=0.022); similarly, the LN positive group had the larger maximum diameter compared to LN negative group (4.3±0.89 *vs*. 0.93±0.43; p=0.0017). In the intermediate regions, there was no morphological difference among the groups.

We calculated the ROC concerning the number of lymph nodes and lymph node metastasis (Figure 2). The cut-off value of the number of lymph nodes to maximize the accuracy was 1. Therefore, when we detected any visible lymph nodes via CT, it predicted lymph node metastasis with a sensitivity and specificity of 100% and 76.5%, respectively with an AUC of 0.890. We also referred to the ROC concerning the maximum diameter of the nodes in association with metastasis and found that a diameter larger than 3 mm was the predictive indicator of lymph node metastasis with a sensitivity and specificity of 100% and 82.4%, respectively, with an AUC of 0.8971 (Figure 3).

Discussion

When planning the therapeutic strategy for neoplasia, it is crucial to detect the extent of the primary tumor, grade of lymph node involvement and existence of distant metastasis. From this point of view, we conducted this study to determine the prediction rate of lymph node involvement estimated by contrast-enhanced CT. The regions of the lymph nodes were categorized into three fields based on their location along the branching of the feeding artery: i) pericolic/perirectal, ii) intermediate, and iii) apical lymph node. We typically perform a lymph node dissection conscious of this geographical category. That is the reason why in the present study, we examined the prediction rate of lymph node metastasis in each region. As far as we know, this is the first report to describe the prediction rate of colorectal NET, and the prediction rate in each geographical field.

A diameter larger than 1 cm has been commonly accepted as a predictor of adjacent lymph node involvement in colorectal cancer (9, 13). In contrast, our study found that smaller lymph nodes detected by CT were positive for lymph node metastasis compared to colorectal cancer. Kim *et al*. published a similar result using formaldehyde-fixed, paraffin-embedded blocks and measured the diameter of the dissected lymph node in 200 μm sections of colorectal NET. They revealed that 24.5% of lymph nodes smaller than 5 mm were

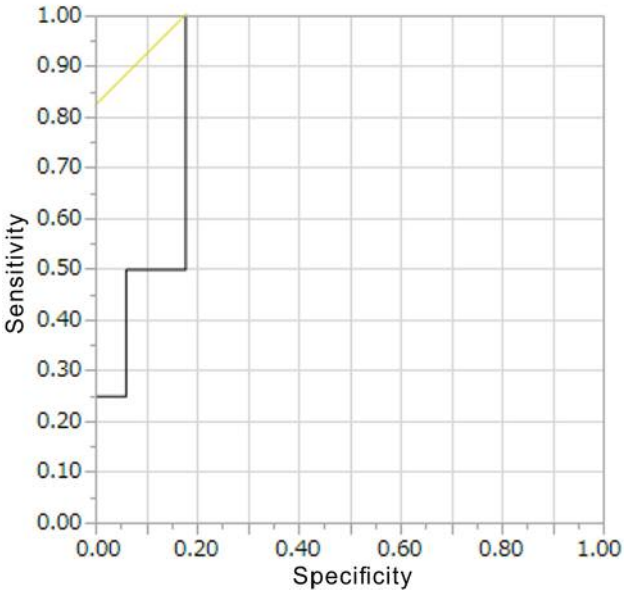

Figure 3. *Diameter of intermediate LNs measured by CT to predict LN metastasis (AUC=0.8971). The sensitivity was 100% and specificity was 82.4% for pathologically positive LNs when LNs larger than 3 mm in diameter are found on the CT image.*

positive for metastasis along with the fact that a higher rate of involvement was observed as the diameter is increased (6.14 *vs*. 2.91 mm, in positive *vs*. negative LNs, respectively) (21). As they used formaldehyde fixed specimens, it might show a different morphology compared to fresh specimens or those measured in the CT images. However, we should set new criteria for lymph node metastasis from NETs considering the results from both studies.

Another morphological predictor of lymph node metastasis was its shape. Kanamoto *et al*. reported that the point of 0.8 or greater in the short/long axis diameter ratio was the index for lymph node involvement in colorectal cancer (22), and this criterion has also been commonly accepted in colorectal cancer. In reference to their results, we also examined this ratio in our cases; however, there was no correlation between lymph node metastasis and its shape. We consider that this result may be influenced by the fact that the dissected lymph node in NETs are smaller compared to those in colorectal cancer (21).

Our results showed that lymph nodes with an irregular margin or a heterogeneous internal pattern tended to present with lymph node metastasis, although this did not reach statistical significance. These factors are accepted as predictors of lymph node involvement in colorectal cancer (8-18). Therefore, we should conduct further analyses with a larger number of patients.

Regarding the different results observed among the fields, both the size and number of lymph nodes were found to be predictors in the intermediate field, whereas only the diameter was a predictor in the pericolon/perirectum. The reason for this difference is unclear. However, in the lymph node negative group (Tables II and III), the lymph node was more visible in the pericolic/perirectal field compared to the intermediate field (8 out of 13 *vs*. 4 out of 17, respectively; p=0.042). The higher rate of benign lymph node swelling in the pericolic/perirectal field might have caused the different results concerning the predictive indicators.

2-Deoxy-2-[fluorine-18]fluoro- D-glucose integrated with CT (FDG-PET/CT) represents another modality to detect lymph node metastasis in colorectal cancer. A meta-analysis revealed an estimated sensitivity and specificity of ^{18}F-FDG PET/CT for the detection of pre-therapeutic lymph node involvement to be 42.9% and 87.9%, respectively (23). Concerning NET, the performance of FDG-PET/CT in the diagnosis of mediastinal lymph node metastasis was reported in pulmonary carcinoid tumors, with a sensitivity of 33% and a specificity of 94% (24). However, no reports have been published concerning colorectal NET to date. Another problem with ^{18}F-FDG-PET in NET is that the sensitivity is influenced by the pathological grade. It is reported that 92% of the tumors with a Ki-67 index greater than 15% (corresponding to NEC) present with an accumulation in the primary tumor, whereas only 41% of those cases with a Ki-67 index less than 2% (corresponding to NET G1) present with an accumulation (25). Considering that NET G1 is the most commonly observed NET, FDG-PET is not a recommended modality to detect lymph node metastasis in clinical practice.

Octreotide analogue scintigraphy is a new modality applied to gastrointestinal NETs. It presented with a high accumulation rate of 87% in NET G1 primary tumors (25). Concerning lymph node metastasis, the diagnostic accuracy of the octreotide scan was proven to be lower than the FDG-PET (76% *vs*. 85%, respectively) for a pulmonary carcinoid (26). In consideration of this result, a high accuracy is not expected in an octreotide scan when an evaluating lymph node metastasis in colorectal NET. In addition, cost-effectiveness should be considered in actual clinical practice. Therefore, we consider scintigraphy to be inferior to contrast-enhanced CT for tumor staging.

This study has several limitations: i) the number of patients is small. Because NET is a rare manifestation of colorectal tumors, we should conduct a multi-intuitional or population-based survey to obtain more reliable findings; ii) our findings suggest a prediction rate in each field not a node-by-node comparison, which would provide further novel findings and iii) we cannot eliminate the bias of patient selection. All of the patients in this study presented with pathological or clinical risk factors for lymph node

involvement during the preoperative examination (6, 7). We did not evaluate the CT and lymph node status of the patients who were excluded from the colorectal resection because of the lack of risk factors. Despite these limitations, our findings indicate the importance of completing a lymph node dissection even if it presented with a small size.

Conclusion

Lymph nodes larger than 5 mm on the CT images were predictive indicators for lymph node metastasis in the pericolic/perirectal field. The sensitivity and specificity for this criterion were 66.7% and 87.5%, respectively with an AUC of 0.844. In addition, in the intermediate field, lymph node involvement was predicted when any lymph node is detected in the CT images, with a sensitivity and specificity of 100% and 76.4%, respectively, with an AUC of 0.890. When we set the cut-off value as 3 mm for lymph node involvement, the specificity improved to 82.4% for intermediate nodes. Our results should be taken under consideration for the prediction of colorectal neuroendocrine tumor metastasis, as they reveal the importance of dissecting lymph nodes even with smaller size than it is suggested in literature.

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