

# Radiological Cutoff Values for Diagnosis of Lymph Node Metastasis in Colorectal Cancer With Multilevel Analysis

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**Abstract.** *Background/Aim:* A cutoff value for lymph node diameter in colorectal cancer lymph node metastases has not been established. This prospective study aimed to investigate the direct association between swollen lymph nodes identified on preoperative computed tomography (CT) and pathological findings and proposed a cutoff value. *Patients and Methods:* We enrolled patients scheduled to undergo curative surgery with lymph node dissection for colorectal adenocarcinoma who underwent preoperative contrast-enhanced CT and had swollen lymph nodes  $\geq 7$  mm in diameter. Two gastrointestinal surgeons intraoperatively identified the target lymph nodes to assess the association between lymph node diameter and pathological findings. The diagnostic performance for lymph node metastasis was determined using multi-level logistic modelling. *Results:* A total of 109 patients were enrolled, and 225 swollen lymph

nodes were pathologically evaluated. Using a cutoff value of  $\geq 9$  mm for the short diameter, the positive and negative predictive values, sensitivity, and specificity were 100.0% (99.6%-100.0%), 99.9% (99.1%-100.0%), 62.0% (45.6%-76.0%), and 84.9% (67.0%-94.0%), respectively. *Conclusion:* The cutoff value for improving the positive predictive value for the preoperative lymph node metastasis diagnosis in colorectal cancer patients should be at least 9 mm in diameter.

Surgical resection with lymph node dissection is the standard treatment for colorectal cancer (CRC). Previous studies have shown that complete mesocolic excision with central vascular ligation for colon cancer and total mesorectal excision for rectal cancer contribute to an improved prognosis (1-4). In usual clinical practice, we evaluate lymph node metastasis preoperatively by performing contrast-enhanced computed tomography (CT) and measuring the size of the regional lymph nodes. An accurate preoperative diagnosis of lymph node metastases is important not only to help surgeons determine the extent of lymph node dissection but also to predict the prognosis and determine perioperative treatment strategies for CRC.

Swollen lymph nodes are often suspected of having pathologic metastasis. However, the specific cutoff values are not clear. In clinical trials (5-7), cutoff values such as 7 mm in the short diameter and 10 mm in the long diameter are sometimes used, but the basis for these values has not been clarified. Obstruction or obstructive colitis may occur, especially in cases of advanced cancer, which may lead to inflammatory lymph node swelling. Previous studies on the diagnostic accuracy for lymph node metastasis were retrospective analyses at the patient level (8-10), and no prospective study has

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evaluated the association between swollen lymph nodes and pathological metastasis at the lymph node level.

Therefore, we designed a prospective study to enroll patients with swollen lymph nodes scheduled for surgery and to identify and label the swollen lymph nodes intraoperatively. In this study, we investigated the direct association between swollen lymph nodes identified on preoperative CT and pathological findings. These findings will help surgeons determine the surgical and perioperative treatment strategies for CRC.

## Patients and Methods

**Study design and patient enrollment.** This was a single-center prospective observational study. We enrolled patients according to the following criteria: i) patients who were diagnosed with CRC of histologically proven adenocarcinoma from a primary lesion and scheduled to undergo surgical resection with lymph node dissection; ii) patients who underwent contrast-enhanced abdominopelvic CT within 3 weeks before surgery; iii) patients with swollen lymph nodes with a long diameter of  $\geq 7$  mm on CT; and iv) patients with a primary lesion depth of  $\geq cT2$ . Based on our previous study (11), lymph nodes  $< 7$  mm in diameter on contrast-enhanced CT were excluded from the study because these target lymph nodes could often not be correctly identified and labeled in resected specimens. Exclusion criteria included patients who received preoperative chemotherapy or radiotherapy, had other synchronous malignancies, and had previously undergone surgical resection for other colorectal diseases. Patients with bulky or clustered swollen lymph nodes exceeding 30 mm in diameter located near the primary lesion were excluded from this study because metastases could not clearly be measured using CT alone.

The study protocol was conducted in accordance with the Declaration of Helsinki and all applicable local laws and regulations. The protocol was approved by the institutional review board of Southern Tohoku General Hospital. Informed consent was obtained from all participating patients.

**Contrast-enhanced CT.** CT examinations were performed using LightSpeed VCT (GE Healthcare, Milwaukee, WI, USA). Investigators confirmed that helical CT scans included the area from the diaphragm to the symphysis pubis in 5-mm-thick transverse sections at the same intervals. Non-ionic intravenous contrast material was administered. One radiologist and one gastroenterological surgeon evaluated the contrast-enhanced CT images of all patients and measured the long and short diameters in the axial plane. In the event of a disagreement between the two evaluations, a decision was made after consultation with other independent radiologists.

**Fluorodeoxyglucose positron emission tomography (FDG PET)/CT.** FDG PET/CT examinations were performed using a Discovery LS8 (GE Healthcare). The patients fasted for over six hours. Under calm conditions, they were intravenously injected with FDG after their glucose levels had been routinely evaluated and confirmed to be  $< 180$  mg/dl. The dose of FDG was 370 MBq, and scanning was started 60 min after FDG administration. The patients laid calmly in a dark room for approximately one hour; after urination, they underwent PET-CT. The examinations included CT and PET, with whole-body PET performed from the base of the skull to the femur immediately after the completion of CT. The images were

Table I. Patient characteristics.

|                                     | Patients<br>(n=109) |
|-------------------------------------|---------------------|
| Age, median (IQR)                   | 71 (64-80)          |
| Sex, n (%)                          |                     |
| Male                                | 61 (56.0)           |
| Female                              | 48 (44.0)           |
| Primary site, n (%)                 |                     |
| Cecum                               | 20 (18.4)           |
| Ascending                           | 31 (28.4)           |
| Transverse                          | 11 (10.1)           |
| Descending                          | 9 (8.3)             |
| Sigmoid                             | 20 (18.4)           |
| Rectosigmoid/rectum                 | 18 (16.4)           |
| Histology, n (%)                    |                     |
| Well                                | 33 (30.3)           |
| Moderately                          | 60 (55.0)           |
| Poorly/mucinous                     | 15 (13.8)           |
| Obstruction, n (%)                  |                     |
| Presence                            | 43 (39.4)           |
| Absence                             | 66 (60.6)           |
| Harvested Lymph nodes, median (IQR) | 19 (13-26)          |
| pT-stage, n (%)                     |                     |
| T1                                  | 3 (2.8)             |
| T2                                  | 11 (10.1)           |
| T3                                  | 60 (55.1)           |
| T4a/T4b                             | 34 (31.2)           |
| pN-stage, n (%)                     |                     |
| N0                                  | 45 (41.3)           |
| N1a                                 | 21 (19.3)           |
| N1b                                 | 17 (15.6)           |
| N2a                                 | 15 (13.8)           |
| N2b                                 | 5 (4.6)             |
| N3                                  | 6 (5.5)             |

IQR: Interquartile range.

transmitted to a workstation, and cross-sectional reconstruction was performed with a slice thickness of 7.0 mm. One radiologist and one gastroenterologist evaluated the FDG uptake and measured the standardized uptake value (SUV) and metabolic volume (MV) to diagnose metastasis in cases with lymph nodes  $\geq 7$  mm in the long diameter on contrast-enhanced CT.

**Surgical procedure and the pathological diagnosis.** All surgical procedures were performed by board-certified surgeons from the Japanese Society of Gastroenterological Surgery. In accordance with the Japanese Society for Cancer of the Colon and Rectum guidelines (12), we performed radical resection for CRC, leaving a 10-cm margin from the oral and anal side of the tumor for colon cancer, a 3-cm margin from the lower edge for rectosigmoid or upper rectal cancer, and a 2-cm margin for lower rectal cancer with D3 lymph node dissection as standard procedures. Total mesorectal excision was performed for rectal cancer.

Two gastrointestinal surgeons identified the target lymph nodes (those larger than 7 mm in length found on preoperative CT images) immediately after resection of the specimen. All harvested lymph nodes were selected from the specimens and fixed in formalin for 48 h, after which each lymph node was sliced at 4-mm intervals and

Table II. Number and proportion of metastatic lymph nodes per lymph node diameter.

| Short diameter | Harvested LN | Metastatic LN | %     | Long diameter | Harvested LN | Metastatic LN | %     |
|----------------|--------------|---------------|-------|---------------|--------------|---------------|-------|
| 4              | 10           | 5             | 50.0  |               |              |               |       |
| 5              | 10           | 2             | 20.0  |               |              |               |       |
| 6              | 25           | 7             | 28.0  |               |              |               |       |
| 7              | 34           | 8             | 23.5  | 7             | 18           | 8             | 44.4  |
| 8              | 46           | 13            | 28.3  | 8             | 38           | 6             | 15.8  |
| 9              | 22           | 8             | 36.4  | 9             | 22           | 8             | 36.4  |
| 10             | 22           | 12            | 54.5  | 10            | 28           | 6             | 21.4  |
| 11             | 14           | 9             | 64.3  | 11            | 16           | 7             | 43.8  |
| 12             | 5            | 4             | 80.0  | 12            | 23           | 13            | 56.5  |
| 13             | 11           | 9             | 81.8  | 13            | 14           | 7             | 50.0  |
| 14             | 4            | 3             | 75.0  | 14            | 15           | 6             | 40.0  |
| 15             | 5            | 5             | 100.0 | 15            | 9            | 7             | 77.8  |
| 16             | 3            | 2             | 66.7  | 16            | 6            | 3             | 50.0  |
| 17             | 4            | 4             | 100.0 | 17            | 2            | 2             | 100.0 |
| 18             | 3            | 2             | 66.7  | 18            | 5            | 2             | 40.0  |
| 19             | 2            | 2             | 100.0 | 19            | 3            | 3             | 100.0 |
| 20             | 5            | 3             | 60.0  | 20            | 26           | 20            | 76.9  |

LN: Lymph nodes.

prepared in paraffin blocks. A pathologist diagnosed the lymph nodes using hematoxylin-eosin staining.

**Outcomes and statistical analyses.** The main outcome was the proportion of positive pathological metastases per lymph node diameter. The diagnostic performance [*i.e.*, positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity] of each lymph node diameter was determined. Based on these results, we determined the cutoff value for positive metastasis in the CT diagnosis.

As each lymph node belongs to a certain patient, clustering should be considered in the analysis. To this end, we used multilevel logistic modeling to estimate diagnostic performance. For sensitivity and specificity, we constructed a model with the correct classification by contrast-enhanced CT [*i.e.*, positive CT findings (lymph node diameter  $\geq$  cutoff value)=pathologically metastatic lymph nodes, negative findings=pathologically non-metastatic lymph nodes] as the outcome and the results of the pathological assessment as the covariate. Owing to non-convergence issues associated with multilevel logistic models, we used univariate random effects modeling. Sensitivity was estimated as the probability of positive CT findings for metastatic lymph nodes (MLNs), whereas specificity was estimated as the probability of negative CT findings for non-MLNs. For the PPV, we constructed a model with correct classification by contrast-enhanced CT as a covariate and the results of the pathological assessment as the outcome. The PPV was then estimated as the probability of MLNs when the CT findings were positive, whereas the NPV was estimated as the probability of non-MLNs when CT findings were negative. For all diagnostic performance measures, 95% confidence intervals (CIs) and 95% prediction intervals (PIs) were calculated. The CI indicates the average of each performance measure across all patients included in the analyses, whereas the PI indicates the expected performance when contrast-enhanced CT is performed in a new individual.

We defined an inflammatory lymph node (ILN) as a lymph node  $\geq 7$  mm in diameter with accumulation of inflammatory cells without evidence of metastases or other lesions. As a secondary outcome, we evaluated the clinical factors between ILN and MLNs; the presence of bowel obstruction, the location of the primary tumor (right or left side), the ratio of long to short diameter and irregular margins on CT, the location of lymph nodes (pericolic or intermediate/main lymph nodes), the maximum SUV (SUVmax) and MV on FDG PET/CT were compared between the two groups.

Patient characteristics are reported as descriptive statistics, with continuous variables expressed as medians and interquartile ranges and categorical variables expressed as counts and percentages. Categorical variables were compared using the chi-squared test, and continuous variables were compared using Student's *t*-test. All tests were two-sided, and a *p*-value of 0.05 was considered to indicate statistical significance. All analyses were conducted by a medical statistician (TT) trained in diagnostic studies.

## Results

**Enrolled patients and evaluated lymph nodes.** A total of 109 patients were enrolled, and 225 swollen lymph nodes with a long diameter  $\geq 7$  mm were pathologically evaluated. Table I shows the patient characteristics. Pathological metastases were found in 64 patients (58.7%) and 98 lymph nodes (43.6%).

**Primary outcome.** Table II shows the number and proportion of lymph nodes with pathological metastases per lymph node diameter. Table III shows the PPV, NPV, sensitivity, and specificity for each lymph node diameter as cutoff values. Figure 1 shows the PPV and sensitivity for each cutoff value. The PPV and sensitivity crossed at a point 8 mm in short diameter. The diagnosis of lymph node metastasis is highly

Table III. The diagnostic performance of each cutoff value.

| Cutoff value | PPV   | 95%CI      | PI        | NPV   | 95%CI      | PI        | Sensitivity | 95%CI      | PI        | Specificity | 95%CI     | PI        |
|--------------|-------|------------|-----------|-------|------------|-----------|-------------|------------|-----------|-------------|-----------|-----------|
| 4            | 35.6  | 19.3-56.0  | 0.1-99.5  | 33.3  | 3.4-87.6   | 3.3-88.0  | 100.0       | 99.6-100.0 | 0.0-100.0 | 0.0         | 0.0-0.4   | 0.0-100.0 |
| 5            | 33.2  | 16.6-55.3  | 0.1-99.6  | 50.0  | 24.4-75.6  | 24.1-75.9 | 100.0       | 97.3-100.0 | 0.0-100.0 | 0.0         | 0.0-94.3  | 0.0-100.0 |
| 6            | 37.2  | 17.9-61.6  | 0.1-99.8  | 100.0 | 97.6-100.0 | 0.0-100.0 | 100.0       | 99.8-100.0 | 0.0-100.0 | 12.2        | 5.0-26.7  | 1.0-64.7  |
| 7            | 32.0  | 10.7-64.8  | 0.0-99.9  | 83.1  | 32.4-98.1  | 2.5-99.9  | 100.0       | 99.9-100.0 | 0.0-100.0 | 18.9        | 7.9-38.8  | 0.9-85.5  |
| 8            | 66.7  | 36.3-87.6  | 0.2-99.9  | 78.5  | 60.6-89.7  | 13.9-98.8 | 73.7        | 58.6-84.7  | 19.6-97.0 | 63.8        | 48.8-76.5 | 8.5-97.1  |
| 9            | 100.0 | 99.6-100.0 | 0.0-100.0 | 99.9  | 99.1-100.0 | 0.0-100.0 | 62.0        | 45.6-76.0  | 7.9-96.9  | 84.9        | 67.0-94.0 | 17.5-99.3 |
| 10           | 100.0 | 99.9-100.0 | 0.0-100.0 | 99.9  | 99.0-100.0 | 0.0-100.0 | 46.4        | 30.7-62.9  | 4.7-93.8  | 92.8        | 67.7-98.7 | 27.5-99.8 |
| 11           | 100.0 | 99.6-100.0 | 0.0-100.0 | 71.3  | 54.9-83.6  | 3.4-99.4  | 35.0        | 23.9-48.1  | 10.2-71.9 | 92.1        | 86.0-95.7 | 85.9-95.7 |
| 12           | 100.0 | 99.8-100.0 | 0.0-100.0 | 69.2  | 51.7-82.5  | 2.0-99.6  | 28.0        | 17.9-41.1  | 8.6-61.8  | 93.7        | 87.9-96.8 | 87.8-96.8 |
| 13           | 100.0 | 99.0-100.0 | 0.0-100.0 | 68.0  | 50.6-81.5  | 1.7-99.6  | 23.7        | 15.7-34.0  | 7.1-55.8  | 100.0       | 7.7-100.0 | 0.0-100.0 |
| 14           | 100.0 | 98.9-100.0 | 0.0-100.0 | 65.0  | 47.7-79.1  | 1.4-99.6  | 14.7        | 6.7-29.4   | 2.4-55.1  | 96.9        | 91.9-98.8 | 91.8-98.8 |
| 15           | 100.0 | 97.8-100.0 | 0.0-100.0 | 64.0  | 46.1-78.7  | 1.0-99.7  | 12.5        | 5.4-26.3   | 2.4-45.6  | 96.9        | 91.9-98.8 | 91.8-98.8 |
| 16           | 100.0 | 80.6-100.0 | 0.0-100.0 | 64.1  | 45.2-79.4  | 0.8-99.8  | 9.4         | 2.7-27.6   | 1.6-39.2  | 100.0       | 99.9-100. | 0.0-100.0 |

PPV: Positive predictive value; NPV: negative predictive value; CI: confidence interval; PI: prediction interval.

sensitive if the cutoff value is  $\geq 7$  mm for the short diameter; it is possible to prevent overlooked pathologically metastasis-positive lymph nodes. However, a cutoff value of  $\geq 9$  mm for the short diameter would improve the PPV and increase the accuracy of the lymph node diagnosis while maintaining a certain level of sensitivity.

**Secondary outcome.** Using this cutoff value ( $\geq 7$  mm short diameter), the number of ILNs was 96 (53.3%). Table IV shows the clinical and imaging factors of ILNs and MLNs. The SUVmax (5.9 vs. 1.9 min,  $p < 0.001$ ) and MV (2.4 vs. 0.7,  $p = 0.002$ ) were both higher in the MLN group than in the ILN group.

## Discussion

In this prospective lymph node-level study, we successfully investigated the direct association between the lymph node diameter and pathologic metastasis by intraoperative identification and labeling of swollen lymph nodes identified on preoperative contrast-enhanced CT. Diagnostic performance (*i.e.*, PPV, NPV, sensitivity, and specificity) was calculated using a multilevel analysis considering the clustering of lymph nodes, and we demonstrated the relationship between each cutoff value and diagnostic performance. The lymph node morphology on CT, preoperative patient clinical symptoms, and location of the primary tumor and lymph nodes did not affect the diagnostic accuracy. The degree of the FDG uptake on FDG-PET/CT may differentiate metastasis from inflammatory lymph node swelling.

Based on the present findings, we make the following recommendations: If surgeons intend to avoid overlooking pathologically metastasis-positive lymph nodes, they should

use a cutoff value of  $\geq 7$  mm for the short diameter for lymph nodes on CT. However, the PPV is also a relevant indicator for clinicians to ensure an accurate preoperative diagnosis. In the present study, the PPV reached 100% at a short diameter of 9 mm. Therefore, we believe that this cutoff value is clinically appropriate. In clinical trials (5-7), cutoff values such as 7 mm for the short diameter and 10 mm for the long diameter are sometimes used, but the basis for these values has not been established. A limitation of previous studies concerning the diagnostic accuracy of the lymph node diameter was that they were all patient-level retrospective analyses (8-10). Since there was no assurance that the swollen lymph nodes were truly associated with pathological findings, it was not possible to determine a cutoff value for lymph node diameter. This is the first prospective study to analyze the direct association between pathological findings and swollen lymph nodes on a node-by-node basis. The data from this study will help clinicians predict patient prognoses preoperatively. Furthermore, the proposed cutoff values are important for planning future clinical trials on the preoperative treatment of CRC.

A high FDG uptake was observed more frequently in MLNs than in ILNs, so a high FDG uptake was considered suggestive of metastasis. Our previous study reported that FDG PET/CT, in addition to contrast-enhanced CT, was useful for the diagnosis of lymph node metastasis (11), and the results were consistent in the present study. However, there was no marked difference in the location of the primary tumor or lymph nodes and the presence of obstruction between the MLN and ILN groups. Previous studies have suggested that regional lymph nodes of right-sided colon cancer or obstructive colitis and pericolic lymph nodes may swell even if they are negative for metastasis (1, 13, 14). However, these

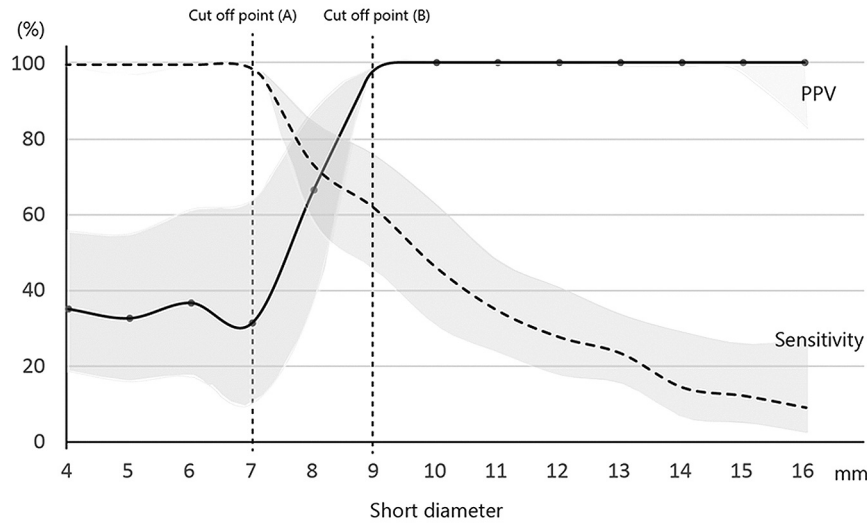


Figure 1. The positive predictive value and sensitivity for each cutoff value. The cutoff point (A) was  $\geq 7$  mm in the short diameter and showed high sensitivity. The cutoff point (B) was  $\geq 9$  mm in the short diameter and showed a high positive predictive value.

Table IV. Clinical symptoms and imaging features of inflammatory or metastatic lymph nodes.

|                                            | ILN (n=96)  | MLN (n=84)  | p-Value |
|--------------------------------------------|-------------|-------------|---------|
| Primary site, n (%)                        |             |             |         |
| Right side                                 | 59 (61.5)   | 57 (67.9)   | 0.37    |
| Left side                                  | 37 (38.5)   | 27 (32.1)   |         |
| Pericolic                                  | 68 (70.8)   | 68 (80.9)   | 0.29    |
| Intermediate                               | 24 (25.0)   | 14 (16.7)   |         |
| Main                                       | 4 (4.2)     | 2 (2.4)     |         |
| Ratio of long to short diameter, mean (SD) | 1.32 (0.24) | 1.33 (0.23) | 0.88    |
| Irregular margins, n (%)                   |             |             |         |
| Presence                                   | 29 (30.2)   | 32 (38.1)   | 0.27    |
| Absence                                    | 67 (69.8)   | 52 (61.9)   |         |
| Obstruction, n (%)                         |             |             |         |
| Presence                                   | 42 (43.8)   | 34 (40.5)   | 0.66    |
| Absence                                    | 54 (56.2)   | 50 (59.5)   |         |
| SUVmax, mean (SD)                          | 1.9 (4.2)   | 5.9 (6.2)   | <0.001  |
| Metabolic volume, mean (SD)                | 0.7 (1.8)   | 2.4 (3.7)   | 0.002   |

ILN: Inflammatory lymph nodes; MLN: metastatic lymph nodes; SD: standard deviation; SUVmax: maximum standardized uptake value.

findings did not affect the diagnostic accuracy in this study. Similarly, the imaging morphology of the lymph nodes, such as the long-to-short-diameter ratio and irregular margins, did not affect the diagnostic accuracy. These results suggest that it is difficult to differentiate metastasis from inflammatory lymph node swelling based solely on the morphological characteristics of the lymph nodes.

Several limitations associated with the present study warrant mention. First, we could not determine whether or not the target lymph node had been correctly identified and selected from the resected specimens. Based on the results of

our previous study (11), we considered lymph nodes  $\geq 7$  mm in diameter to be identifiable. Therefore, we enrolled patients with lymph nodes  $\geq 7$  mm in diameter on preoperative contrast-enhanced CT in this study. During surgery, two gastrointestinal surgeons determined the location of the swollen lymph nodes identified by preoperative CT and promptly picked up the target lymph nodes from the resected specimens. Most lymph nodes were identifiable, and we believe that the results are reliable. However, we cannot confirm whether these links are truly correct. Second, we could not evaluate the diagnosis of lateral lymph nodes or



distant lymph node metastases, such as para-aortic lymph nodes. In the diagnosis of lymph node metastasis, a preoperative diagnosis of lymph node metastases in the lateral and para-aortic lymph nodes is relevant because it greatly influences the treatment plan, regardless of whether or not lymph node dissection is performed. As these lymph nodes were not included in this study, we could not validate whether the results of this study could be extrapolated. We plan to conduct future studies using the cutoff values obtained in this study for the lateral or para-aortic lymph nodes.

## Conclusion

We propose that the cutoff value for the lymph node diameter to improve the PPV for the preoperative lymph node metastasis diagnosis in patients with CRC should be at least 9 mm.

## Conflicts of Interest

Drs. Todate, Takada, Honda, Miyakawa, Yamamoto, Toshiyama, Nakao, Mashiko, Kakinuma, Kawamura, Yamaguchi, Takagawa, and Kono have no conflicts of interest or financial ties to disclose in relation to this study.

## Authors' Contributions

Yukitoshi Todate: Conceptualization, Data curation, Writing – original draft; Toshihiko Takada: Formal analysis, Methodology; Michitaka Honda: Conceptualization, Project administration, Writing – review & editing; Teppei Miyakawa: Data curation, Formal analysis, Supervision; Ryuya Yamamoto: Data curation, Investigation; Satoshi Toshiyama: Investigation, Methodology, Project administration; Eiichi Nakao: Data curation, Methodology, Writing – original draft; Ryutaro Mashiko: Data curation, Formal analysis, Investigation; Hirohito Kakinuma: Data curation, Writing – review & editing; Hidetaka Kawamura: Conceptualization, Data curation, Methodology; Hisashi Yamaguchi: Data curation, Investigation, Methodology, Writing – review & editing; Yoshiaki Takagawa: Methodology, Supervision, Writing – review & editing; Koji Kono: Conceptualization, Project administration, Writing – review & editing.

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