Contrast-enhanced CT imaging for the assessment of lymph node status in patients with colorectal cancer

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Abstract. The aim of the present study was to identify a novel strategy that predicts the metastatic status of lymph nodes (LNs) in patients diagnosed with colorectal cancer, using detailed characteristics of contrast-enhanced CT scan images. A total of 284 preoperative CT scans derived from patients diagnosed with colorectal cancer at Second Affiliated Hospital, Zhejiang University School of Medicine between January 2013 and July 2018 were retrospectively reviewed. A total of 794 LNs were assessed for size, margins, morphology and subtle internal enhancements in the equilibrium phase. Imaging features were analyzed by two abdominal radiologists (Department of Radiology, Second Affiliated Hospital, Zhejiang University School of Medicine and Departments of Radiology; Shaoxing Second Hospital Departments of Radiology, Shaoxing Second Hospital) in a blind manner. If the conclusions were not concordant, the final score was determined by a senior radiologist who specialized in abdominal radiology for ≥30 years. According to the histopathology results, 27.3% (217/794) of LNs were metastatic (LN+). In addition, LNs >10 mm in size demonstrated sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) of 47.0, 80.9, 48.1 and 80.2%, respectively [odds ratio (OR), 3.77; 95% confidence interval (CI), 2.69-5.28]. LNs in the shape of a kidney bean (middle fat depression like kidney) and/or those with an oblong shape were more likely to be metastasis negative LNs (LN-), while lobulated and irregular LNs were more likely to be LN+. In magnified images, internal enhancement characteristics of LN- were defined as homogeneous, spotted, striped and core enhancing. By contrast, rim and heterogeneity enhancement features for LN+ demonstrated sensitivity, specificity, PPVs and NPVs of 46.5, 89.9, 63.5 and 81.7%, respectively (OR, 7.79; 95% CI, 5.33-11.40). The results demonstrated that the internal enhancement features of LNs may be used as a predictor of metastasis. The detailed benign characteristics, such as homogeneity, spotted, striped and core enhancement of LNs may facilitate the identification of LN- in patients with colorectal cancer.

Introduction

Colorectal cancer is one of the most prevalent cancers worldwide, with the third highest global mortality rate (1-3). The incidence and mortality of colorectal cancer varies widely by race and ethnicity (4). The second most common cancer sites were cancers of the colorectal in Europe (1). The World Health Organization estimates that by 2030, the number of newly diagnosed colorectal cancer cases will increase by 77% and the number of colorectal cancer deaths will increase by 80% (2).

Western-style lifestyle-related cancers such as breast and colorectal cancers are rapidly increasing in Chinese cities (5). Studies have identified numerous prognostic markers for colorectal cancer, such as age, T-stage and N-stage (6). An important independent predictor is the number of invaded lymph nodes (LNs) (7-9). The accurate identification of metastatic LNs (LN+) contributes to pre-operative cancer staging and influences treatment selection in clinical practice such as endoscopic resection or surgery, preoperative neoadjuvant chemotherapy (10).

With advances in CT technology, the value of using CT to assess the tumor and node stages of patients with colorectal cancer has been demonstrated (11). However, the accuracy of assessing LN status remains unreliable and quite low; with sensitivity, specificity and accuracy of detecting regional lymph nodes metastases being 71, 41 and 54%, respectively (11,12). To the best of our knowledge, no effective imaging criteria for assessing LN+ in colorectal cancer have currently been identified. At present, LN size is the most common predictor of LN status in the clinical practice (12). A

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Abbreviations: LN, lymph node; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; CI, confidence interval

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threshold size of 10 mm is considered to be strong evidence of LN+ (13-16), and in a previous systematic review and meta-analysis, the sensitivity, specificity and odds ratio (OR) for LN+ were 71.0, 67.0 and 4.8%, respectively (12).

Internal enhancement of CT images is an alternative method to assess the degree of metastasis to LNs (17). Internal heterogeneity is considered a marker of LN+ (17). Subtle changes in internal enhancement features may provide additional valuable information for diagnosing LNs metastasis.

The aim of the present study was to use contrast-enhanced CT to improve the identification of LN+ in patients diagnosed with colorectal cancer.

Materials and methods

Patients. The present retrospective study was performed at the Departments of Surgery and Radiology of the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) and was approved by the Local Ethics committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. The requirement for written informed consent from patients was waived due to the retrospective design of the study.

CT images from 284 patients diagnosed with colorectal cancer that had undergone radical surgery between January 2013 and July 2018 were collected. The inclusion criteria for the present study were as follows: i) Pathological diagnosis of colorectal cancer; ii) pre-operative CT scan; iii) resection of colorectal cancer, loco-regional LN-bearing mesentery and 12-15 recruited LNs. Exclusion criteria: i) Patients that had previously received treatment, including preoperative neoadjuvant radiotherapy or chemotherapy; ii) presented with metastasis to other organs; iii) had malignant disease of any abdominal or pelvic organ. Patient medical records were used to collect additional information, including age, sex and body mass index.

Image acquisition. For all patients, a multidetector-row helical CT scan (Somatom Definition AS 40-row; Siemens Healthineers) was performed, which ranged from the cartilago ensiformis and the anal verge, with 3 mm axial sections and no intersection gap. Non-ionic contrast agent (Omnipaque 300 g/l; GE Healthcare Sciences) was intravenously injected at a rate of 3 ml/sec following a non-enhanced CT scan. The arterial phase (25 sec delay), portal venous phase (60 sec delay) and equilibrium phase (100 sec delay) were obtained. Coronal reconstructions were performed in order to observe the lesions. The following scan parameters were used: Voltage, 120 kV; tube current, 160 mA/sec; slice collimation, 0.6 mm; slice thickness, 3 mm; pitch, 1.2; overlap, 50%; field of view, 32 cm.

Pathology. All patients underwent radical surgical resection of the colorectal carcinoma and the loco-regional LNs and mesentery in the drainage area of the mass (17). In the Tumor-Node-Metastasis (6) staging criteria for colorectal cancer, LNs that can be removed by radical surgery were defined as loco-regional LNs (18,19). A light microscope was used at 100 x magnification. Histopathological analysis of the LNs was performed by two experienced pathologists (written by a junior pathologist, Shi Dan, attending physician, Department of Pathology, Shaoxing Second Hospital and reviewed by a senior pathologist, Liu Qing-Meng, chief physician, Department of Pathology, Shaoxing Second Hospital) in a blind manner. LNs were sectioned (thickness, 4-5 μm), fixed in 10% formalin at room temperature for 24-36 h, embedded in paraffin and stained with hematoxylin and eosin at room temperature for ~55 min (cat. no. CG008, Ningbo Tongsheng Biotechnology Co., Ltd). For the LN metastasis negative (LN-) group, no metastasis was observed in all 12-15 loco-regional LNs, nor in the LNs at the origin of the inferior mesenteric artery (0/1). For the LN+ group, according to pathological results, cases with a metastatic LN ratio of ≥0.8 were included, which meant metastatic LNs/harvested LNs ≥0.8. The area located ≤5 cm from the distal edge of the tumor, which had a higher incidence of metastatic LNs (20). According to the surgical records, the area of the corresponding LNs was determined.

Image analysis. The CT images were analyzed by two radiologists specialized in gastrointestinal imaging (Second Affiliated Hospital, Zhejiang University School of Medicine and Shaoxing Second Hospital) and were blinded to the experimental groups. If the radiologists disagreed, a third radiologist with >30 years of experience was consulted and provided the final decision. LN size, margin, morphology and internal characteristics in the equilibrium phase were recorded.

Round-shaped LNs were considered as those with a short/long axis ratio of ≥0.7 (21). In magnified images, detailed internal enhancement characteristics were classified into the following 6 types: Homogeneous, spotted (Fig. 1), striped (Fig. 2), core (Fig. 3), rim and heterogeneous. The spotted characteristic manifested as the appearance of small low intensity circles, which were similar in size (≤3 mm), with clear boundaries. The striped characteristic was defined as regular arrangements of linear belts of low enhancement. The core characteristic appeared as a central bright spot. Heterogeneous characteristics were defined as LNs with spots ≥3 mm in size and with irregular boundaries. The rim characteristic appeared as a central low intensity and high intensity rim peripherally.

Statistical analysis. Data analysis was performed using SPSS software (version 23.0; IBM Corp.). Descriptive statistics (Table I, median and range, percentage; Table II/III, percentage) were calculated for the LN characteristics, including the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and ORs. The following formula was used to analyze data: Diagnostic accuracy = (true positive + true negative)/totality. The χ^2 test (Tables II and III) was performed to ascertain significant predictors of LN+. For χ^2 test the group lacking the characteristic A (reference to the characteristics involved in the present study) was used as the baseline to calculate the risk of characteristic A. In Table III, using first columns as criteria for predicting LNs status, LNs were classified into the two groups to form a crosstab, and finally the χ^2 test was used to calculate the P-value. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients and histopathology. A total of 284 patients diagnosed with colorectal cancer (confirmed by histopathological

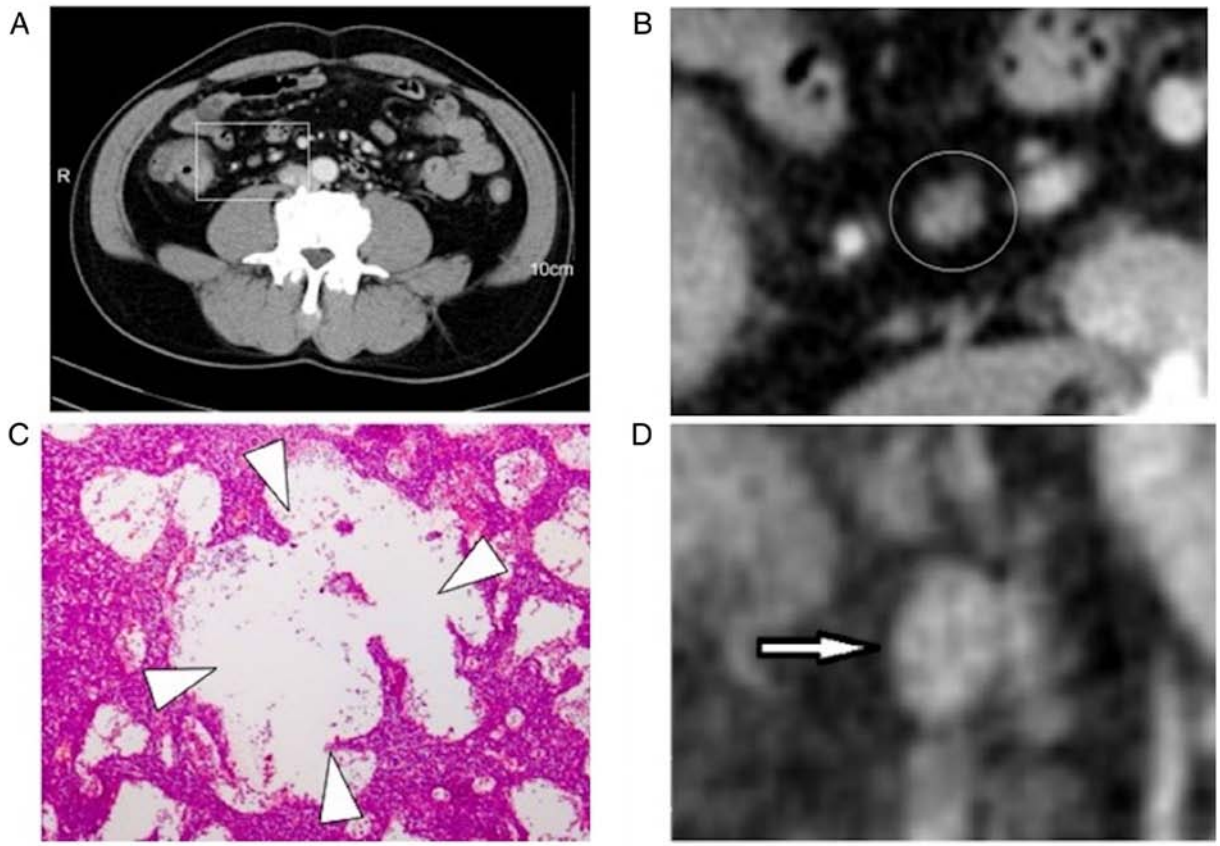

Figure 1. Spotted characteristics (A) Colon cancer in the ascending cancer. (B) Transverse contrast-enhanced CT scan images showing a tumor located in the ascending colon, and a lymph node showing spotted characteristics (magnification 5x). (C) The region of the pathological section indicated with a white arrow, exhibited several dilated subcapsular sinuses (magnification, 100x). (D) An additional lymph node (white arrow) with spotted characteristics.

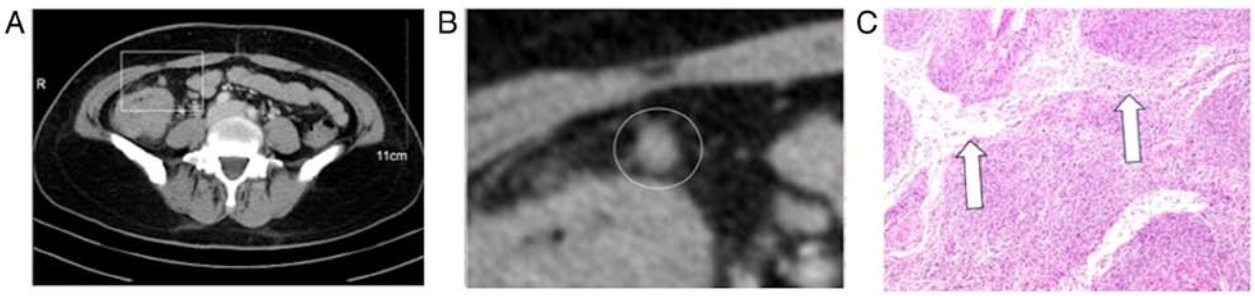

Figure 2. Stripe enhancement characteristics. (A) Contrast-enhanced CT scan images in the equilibrium phase with colon cancer in the ileocecum. (B) A lymph node with stripe enhancement characteristics. (C) The white arrow indicates the interlinked capsular sinus of the lymph node.

analysis) that had undergone radical surgical resection were analyzed in the present study and 794 LNs were obtained. Among these patients, 132 were male and 152 were female (median age, 61.71 years; range, 17-91 years; median body mass index, 22.76; range, 15.67-38.50). Out of the 794 LNs obtained, 217 were LN+ and 577 were LN-, with a median size of 7.95 mm (range, 4.60-30.00 mm). The tumor location, and T and N stages of tumors are presented in Table I. No significant association between body mass index, age, sex and the size of LNs was observed (P=0.492, P=0.950 and P=0.555, respectively; data not shown).

Internal enhancement and morphology of LNs. According to the ORs (Table II), kidney bean and oblong shapes were most likely to be LN-, while rounded, lobulated and irregular shapes were most likely to predict LN+, with sensitivity, specificity, PPVs and NPVs of 70.50% (153/217), 45.10% (260/577), 32.60% (153/470) and 80.20% (260/324), respectively (OR, 1.96; 95% CI, 1.40-2.70; Table III).

According to the ORs (Table II), homogeneous, spotted, striped and core internal enhancement characteristics were indicators of LN-, while rim and heterogeneous characteristics indicated LN+, with sensitivity, specificity, PPVs and NPVs of 46.50% (101/217), 89.90% (519/577), 63.50% (101/159) and 81.70% (519/635), respectively (OR, 7.79; 95% CI, 5.33-11.40; Table III). Statistical analysis of the results demonstrated that a rounded shape (P=0.425) and internal homogeneity (P=0.26) on their own were not significantly different between LN- and LN+.

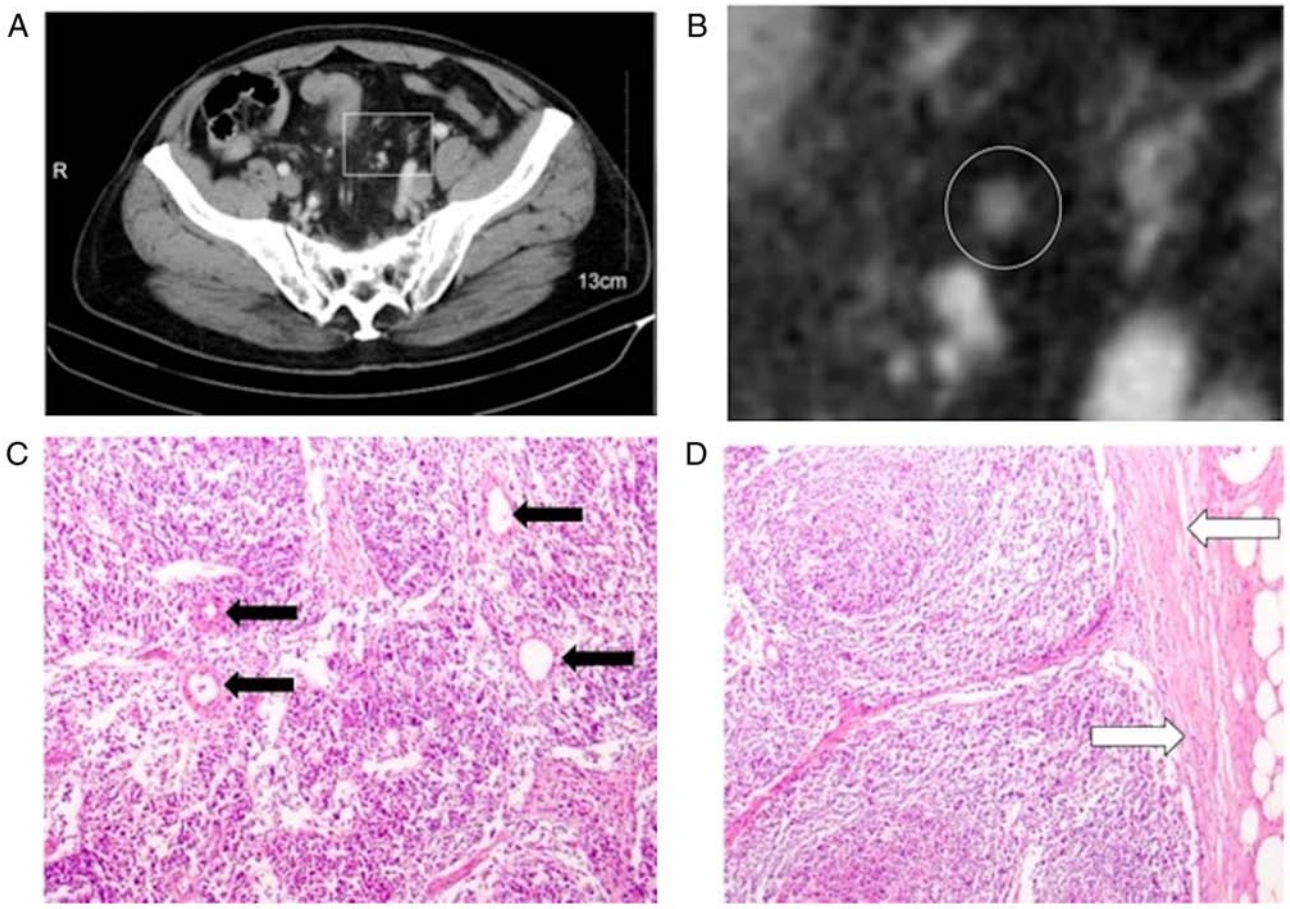

Figure 3. (A) Contrast-enhanced, equilibrium phase CT scan images of a lymph node with colon cancer of the rectum. (B) A lymph node exhibiting core enhancement features. (C) The black arrow indicates a small blood vessel in the central region of the lymph node. (D) The white arrow indicates the capsule of the lymph node and blood vessels in this region were rare.

Evaluation of LN size. As presented in Table III, LNs ≥10 mm in size demonstrated sensitivity, specificity, PPV and NPVs of 47.00% (102/217), 80.90% (467/577), 48.10% (102/212) and 80.20% (467/582), respectively [OR, 3.77; 95% confidence interval (CI), 2.69-5.28). LNs ≥8 mm in size demonstrated sensitivity, specificity, PPVs and NPVs of 71.40% (155/217), 58.10% (335/577), 39.00% (155/397) and 84.40% (335/397), respectively (OR, 3.46; 95% CI, 2.47-4.85). A significant association was observed between the size of LNs and tumor stage (P=0.001).

Combining size and internal enhancement characteristics. By combining LN size and internal enhancement characteristics, the metastatic status of LNs was subsequently estimated in the present study. The results revealed that LNs <10 mm or ≥10 mm in size with benign internal enhancement characteristics predicted LN-. These features demonstrated sensitivity, specificity, PPVs, NPVs and a diagnostic accuracy of 32.30% (70/217), 96.40% (556/577), 76.90% (70/91), 79.00% (556/704) and 79.10% (628/794), respectively (Table III). In addition, LNs <8 or ≥8 mm in size with benign internal enhancement features predicted LN-, with sensitivity, specificity, PPVs, NPVs and a diagnostic accuracy of 38.70% (84/217), 93.40% (539/577), 68.90% (84/122), 80.2% (539/672) and 78.5% (623/794), respectively (Table III). For LNs ≥10 mm in size (n=212), using the internal enhancement criteria would prevent 42.0% (n=89) of LNs from being wrongly diagnosed as LN+ and neglect 9.9% (n=21) of metastatic LNs. For LNs ≥8 mm in size (n=397), using the internal enhancement criteria would prevent 51.4% (n=204) of LNs from being wrongly diagnosed as LN+ and neglect 9.6% (n=38) of metastatic LNs.

Discussion

Metastasis to regional LNs is an independent risk factor for the prognosis of colorectal cancer (22). According to the American Joint Committee on Cancer (AJCC; 8th Edition) (6), node stage represents the number of positive LNs (22,23). However, the criteria for predicting LN+ based on CT images varies (17,24). The most common criteria for LN+ is the presence of regional LNs >10 mm in size and/or clusters of ≥3 LNs (10,25-28). In addition, LNs ≥8 mm in size also predicts LN+ (29). Rodriguez-Bigas *et al* (30) reported that LN size did not affect whether the tumor became metastatic, and the majority of metastatic LNs were <5 mm in size. Using CT scan images, de Vries *et al* (12) demonstrated that the diagnostic accuracy of using LNs in patients diagnosed with colon cancer was only 54%. At present, the major disadvantage of using CT scan images is the poor efficiency in differentiating malignant and benign LNs (12). Relying on LN size to predict LN+ may be problematic, as the size of LN- may be falsely diagnosed as LN+, due to inflammation (21). Despite this, larger LNs are more likely to be LN+, with increasing specificity, but decreasing

Table I. Patient characteristics including CT scan variables of 284 patients and 794 lymph nodes.

Variable	Value
Age, years, median (range)	61.71 (17-91)
BMI (median, range)	22.76 (15.67-38.50)
Size, mm, median (range)	7.95 (4.60-30.00)
Sex, male/female, n (%)	132 (46.5)/152 (53.5)
Lymph node status, positive/negative (%)	217 (27.3)/577 (72.7)
Tumor T stage, n (%)	
T1	10 (3.5)
T2	25 (8.8)
T3	148 (52.1)
T4	101 (35.6)
Tumor N stage, n (%)	
N0	217 (76.4)
N2	67 (23.6)
Tumor localization, n (%)	
Ascending colon	113 (39.8)
Transverse colon	19 (6.7)
Descending colon	22 (7.7)
Sigmoid colon	51 (18.0)
Rectum	79 (27.8)
Shape, n (%)	
Round	355 (44.7)
Kidney-bean	176 (22.2)
Oblong	148 (18.6)
Lobulated	42 (5.3)
Irregular	73 (9.2)
Inner enhancement, n (%)	
Homogeneity	30 (3.8)
Spotted	311 (39.2)
Stripe	267 (33.6)
Core	26 (3.3)
Rim	91 (11.5)
Heterogeneity	69 (8.7)

BMI, body mass index.

Table II. χ^2 test to detect metastatic lymph nodes of different characteristics.

	Risk			
		95% confidence interval		
Variables	Odds ratio	Lower	Upper	P-value
Margin	1.59	1.12	2.24	0.009
Size, ≥10 mm	3.77	2.69	5.28	<0.001
Size, ≥8 mm	3.46	2.47	4.85	<0.001
Shape				
Round	1.14	0.83	1.55	0.425
Kidney-bean	0.65	0.43	0.97	0.033
Oblong	0.56	0.36	0.87	0.009
Lobulated	2.21	1.19	4.12	0.020
Irregular	2.41	1.47	3.93	<0.001
Shape criteria	1.96	1.4	2.7	<0.001
Inner enhancement				
Homogeneity	0.52	0.2	1.38	0.260
Spotted	0.43	0.3	0.6	<0.001
Striped	0.59	0.41	0.83	0.002
Core	0.1	0.01	0.76	0.012
Rim	9.06	5.56	14.78	<0.001
Heterogeneity	3.28	1.99	5.41	<0.001

sensitivity (11). Consistent with these results, the present study demonstrated that LNs ≥8 mm in size exhibited sensitivity and specificity values of 71.40 and 58.10%, respectively, while LNs ≥10 mm in size demonstrated sensitivity and specificity values of 47.00 and 80.90%, respectively. However, regardless of size (8 or 10 mm), false positive rates are high, which is the major disadvantage of using these criteria.

Internal enhancement characteristics of LNs may be helpful in estimating LNs status (17). Previous studies have indicated that heterogeneity and rim enhancement features on CT images may be characteristics of LN+ (21). This may be explained by the invasion of tumor cells into the sub capsular sinus via afferent lymphatic vessels (31), leading to infiltration and damage of lymphoid tissue, which is then replaced by tumor cells (32). A lack of blood supply and subsequent central necrosis may then occur in the medulla (32). In the present study, spotted enhancement features in pathological sections revealed several dilated subcapsular sinuses, which may coincide with the low enhancement and small circle area (Fig. 1). The low enhancement and striped area of the striped characteristic may correspond to the interlinked capsular sinus (Fig. 2). Compared with the size criteria, internal enhancement criteria demonstrated improved PPV and diagnostic accuracy, while other parameters remained stable. Among the internal enhancement characteristics, core enhancement demonstrated excellent efficiency in estimating LN-. The spotted and striped characteristics were also able to differentiate between LN+ and LN-. These results may lead to changes in cancer staging according to the AJCC criteria (6), particularly for patients diagnosed with T3-4 stage. During pre-operative assessment of these patients, LN+ is a criterion for upgrading the lesion from stage II to stage III (22).

The present study identified internal enhancement characteristics and classified them into several groups. A previous study suggested that internal heterogeneity may be a feature of LN+ (17). The present study demonstrated that internal enhancement features of LNs varied upon magnification of the images, even though they may appear similar in normal unmagnified CT images. Therefore, to the best of our knowledge, the present study is the first to classify the detailed internal enhancement features of LN CT images to differentiate between LN- and LN+. The results revealed that detailed internal enhancement characteristics were superior to LN size when assessing LN status.

Table III. Sensitivity, specificity, PPV, NPV, diagnostic accuracy and distributions of the different computed-tomography characteristics of lymph nodes.

Variable	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Diagnostic accuracy, %	OR	P-value
Margin	31.30	77.60	34.50	75.00	65.00	1.59	0.009
Size ≥10 mm	47.00	80.90	48.10	80.20	71.70	3.77	<0.001
Size ≥8 mm	71.40	58.10	39.00	84.40	56.70	3.46	<0.001
Shape criteria	70.40	45.10	32.60	80.20	52.00	1.96	<0.001
Internal enhancement criteria	46.50	89.90	63.50	81.70	78.10	7.79	<0.001
Size ≥10 mm + internal enhancement	32.30	96.40	76.90	79.00	79.10	12.01	<0.001
Size ≥8 mm + internal enhancement	38.70	93.40	68.90	80.20	78.50	8.71	<0.001

Shape criteria: Kidney bean and oblong shapes were evidence of LN^-; rounded, lobulated and irregular shapes were evidence to predict LN^+. Internal enhancement criteria: Homogeneous, spotted, striped and core internal enhancement characteristics were evidence of LN^-, while rim and heterogeneous characteristics indicated LN^+. PPV, positive predictive value; NPV, negative predictive value; OR, odds radio; LN, lymph node.

The present study attempted to combine internal enhancement characteristics with LN size to increase the diagnostic accuracy, in order to resolve problems with using LN size alone as an objective criterion. For LNs ≥10 mm in size (n=212), using the internal enhancement criteria would prevent 42.0% (n=89) of LNs from being wrongly diagnosed as LN+; however, it would neglect 9.9% (n=21) of metastatic LNs. For LNs ≥8 mm in size (n=397), using the internal enhancement criteria would prevent 51.4% (n=204) of LNs from being wrongly diagnosed as LN+ and neglect 9.6% (n=38) of metastatic LNs. Therefore, the present study suggests that combining LN size with internal enhancement criteria may decrease false positive results and decrease false negative results.

LN morphology is an additional variable used to assess the metastatic status of LNs (17,21). LN- are generally kidney bean-shaped (33) and oblong (21,34,35), whereas LN+ are irregularly-shaped and lobulated (17). McMahon *et al* (21) revealed that a short-to-long axis ratio of >0.7 was able to effectively differentiate LN- from LN+. However, according to the results of the present study, the rounded shape of LNs was not observed to be a significant predictor of LN+. The underlying reasons for these inconsistencies are currently unclear and require further investigation.

Previous studies have assessed the value of MRI and positron emission tomography in predicting the metastatic status of LNs (10,36,37). Doyon *et al* (38) and Gagliardi *et al* (39) demonstrated that a threshold value of >5 mm could be used to identify LN+. Margin characteristics and the signal intensity of LNs were also significant variables for the assessment of LN metastatic status in patients with colon cancer (24). However, the use of MRI to assess LN status may lead to overdiagnosis (36), and therefore may be an unreliable tool (40,41). The performance of positron emission tomography combined with fluorine-18 fluorodeoxyglucose for predicting LN+ may also be insufficient to assess LN status (42,43).

The present study has several limitations. First, it was a retrospective study involving the analysis of loco-regional LNs from patients with colorectal cancer, thereby introducing bias when interpreting the results. Secondly, the imaging and histopathological analysis of LNs in the present study were not matched one by one. However, for the LN metastasis negative (LN-) group, no metastasis was observed in all 12-15 loco-regional LNs, nor in the LNs at the origin of the inferior mesenteric artery (0/1). For the LN+ group, cases with a metastatic LN ratio of ≥0.8 were included. Third, LNs with a diameter of ≤4.5 mm were difficult to identify from the internal enhancement of CT images, as the diameters of harvested LNs ranged from 4.60-30.00 mm. Finally, the number of LNs analyzed was insufficient, and a larger sample size is required in order to confirm the results.

In conclusion, the present study identified novel internal enhancement characteristics, including the spotted, striped and core enhancement features on magnified CT images that may facilitate the identification of LN- in patients with colorectal cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SM and YL analyzed and interpreted the patient data regarding colorectal cancers. SM, YL and HC wrote the manuscript. HC made substantial contributions to analysis and interpretation

of data. QL performed the histological examination of the lesions. JC and YP contributed to acquisition of data for the work. RY conceived the concept and designed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the local Ethics committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China). The requirement for written informed consent from patients was waived due to the retrospective design of the study.

Patient consent for publication

The patient(s) referred to in this study provided consent for the publication of their information.

Competing interests

The authors declare that they have no competing interests.

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