Tumor size measured by multidetector CT in resectable colon cancer: Correlation with regional lymph node metastasis

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Abstract

Background : The aim of our study was to determine whether tumor size measured by multidetector computed tomography (MDCT) could be used to evaluate lymph node metastasis (LNM) in patients with resectable colon cancer.

Methods: This retrospective study consisted of 106 consecutive patients with colon cancer who underwent radical surgery within 1 week after contrast enhanced-CT scan. Tumor size including tumor length (Tlen), tumor maximum diameter (Tdia), tumor maximum cross-sectional area (Tare) and tumor volume (Tvol) were measured on contrast enhanced-CT images and correlated with pathologic LNM and N stages using univariate analysis, logistic regression analysis and receiver operating characteristic (ROC) curve analysis.

Results: The inter - (intraclass correlation coefficient [ICC]=0.94, 0.81, 0.97, 0.99) and intraobserver (ICC=0.95, 0.93, 0.91 and 0.99) reproducibility of Tlen, Tdia, Tare and Tvol parameters measurement is excellent. Univariate analysis showed Tlen, Tdia, Tare, and Tvol could predict LNM (all $P < 0.05$), whereas Tvol was an independent risk factor for LNM (odds ratio =1.09; 95% confidence interval, 1.02-1.17; $P = 0.017$) by logistic regression analysis. Tlen, Tdia, Tare and Tvol could distinguish between N0 and N1, N0 and N2, N0 and N1-2, and N0-1 and N2 disease (all $P < 0.05$). The area under the ROC (AUC) was higher for Tvol than for Tlen, Tdia and Tare in identifying LNM (AUC =0.83, 0.82, 0.69, 0.79, respectively) and distinguishing N0 from N1 (AUC =0.79, 0.78, 0.63, 0.74, respectively), N0 from N2 (AUC =0.92, 0.89, 0.80, 0.89, respectively), and N0-1 from N2 (AUC =0.84, 0.79, 0.76, 0.83, respectively).

Conclusion: Tlen , Tdia, Tare and Tvol measured with MDCT correlated with regional LNM in resectable colon cancer. In particular, Tvol showed the most potential for noninvasive preoperative evaluation of regional LNM.

Background

Colorectal cancer ranks third, with an estimated 1.8 million new cases, among common cancers worldwide. It is the second most common cause of cancer death, with an estimated 881,000 deaths from colorectal cancer in 2018, accounting for approximately 1/10 of cancer cases and deaths (1,2). Lymph node metastasis (LNM) is nearly always associated with poor long-term outcomes. Patients who have more positive lymph node involvement have lower 5-year survival rates compared to those with less lymph node involvement (3). The 5-year overall survival rates were 83%, 76% and 54%, respectively, for patients with N0, N1, and N2 disease (4). Moreover, according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for colon cancers, all patients with cT1N0M0 disease can directly receive transanal endoscopic microsurgery, while those with cT2N0M0 or cT3N0M0 disease can be recommended to undergo radical resection of colon cancer. Patients with LNM, including those with cT1-3N1M0 disease, are strongly recommended for preoperative chemoradiation therapy (5,6). Accurate

noninvasive assessment of LNM and N stage preoperatively is crucial for effective treatment plans and predicting survival in patients with colon cancer (6).

Endorectal ultrasound and magnetic resonance imaging are widely used in the staging of rectal cancer. However, they are limited in colon cancer because of low sensitivity (7,8). In contrast, computed tomography (CT) is the most common method to preoperatively stage colon cancer because it can describe primary tumor shape, size, location, relationship with surrounding tissues, and the presence of distant metastasis due to its advantages of high tissue resolution, rapid scanning, and convenient follow-up (9–12). Currently, evaluation of preoperative lymph node status based on morphological features shows poor performance, with a sensitivity of 71% and specificity of 67% because lymph node enlargement might be caused by inflammation and because microscopic metastases in small lymph nodes are difficult for radiologists to characterize (12). The accuracy of CT for detecting LNM is 61%-67% (13). Lymph node size and shape are not reliable indicators for LNM (14). To address these issues, one quantitative method, tumor volumetry measured on CT, has been studied as a tool for the prediction of LNM and tumor response to therapy in rectal cancer, esophageal squamous cell and gastric carcinoma (ESCC) (15–20). Therefore, the purpose of this study was to determine whether tumor size measured by multidetector CT could be used to evaluate LNM and N-staging in patients with colon cancer.

Methods

Ethical approval for this retrospective study was granted by the institutional review board, and the requirement for patient consent was waived because of the retrospective nature of the study.

Patients

Between December 2017 and June 2019, one hundred and six patients diagnosed with colon cancer in our hospital were enrolled in this retrospective analysis. The inclusion criteria for this study were as follows: 1) immunohistochemical testing and biopsy-proven colon cancer; 2) patient did not receive any tumor-related treatment (e.g., radiation therapy or chemotherapy) before CT; 3) tumor was considered resectable and there were no contraindications to surgery; 4) patient was subjected to contrast CT and visible colon cancer was detected on CT images. Exclusion criteria were as follows: patient did not receive preoperative enhancement CT scan; the quality of the CT images was poor, or no tumor was visible on CT images; preoperative chemotherapy or radiotherapy. The remaining 106 patients (mean age of 62.93 years old; range from 18–83 years old) constituted the study population. According to the 7th AJCC criteria, patients were classified as having stage N0 disease if there were no metastatic lymph nodes. Stage N1a is defined as one metastatic lymph node, N1b includes two to three metastatic lymph nodes, and N1c is defined with a tumor deposited under the serosa, in the mesentery, or in the pericolonic/rectal tissues without peritoneal coverage. N2a is defined by four to six metastatic lymph nodes, and N2b includes more than seven metastatic lymph nodes (5). Ultimately, there were 52 patients with LNM, defined as positive LNM (N+); of these 52 patients, 35 patients had N1 disease, including 13 patients with N1a, 15 with N1b and 7 with N1c. 17 patients had N2 disease, including 11 with N2a and 6

with N2b. There were 54 patients without lymph node involvement, defined as negative lymph node involvement (N0).

CT technique

All study patients underwent contrast CT on a 64-section multidetector CT system. All patients were asked to adhere to a liquid or semiliquid diet and not to eat after eight o'clock PM the day before. Before CT image acquisition, 1000 mL of water was given orally every hour to distend the colon and increase the intestinal contrast. In order to minimize the peristaltic bowel movement, all patients received 10 mg of butylscopolamine bromide (Buscopan; Boehringer Ingelheim, Ingelheim, Germany) before the CT examination. Patients were performed in the supine position. The CT scanning variables were 120 kVp, 200–380 mA, section thickness of 8 mm, and reconstruction interval of 1–2 mm. CT scanning was performed during the arterial phase (25–30 s) and portal venous phase (60–70 s) after initiation of the contrast material injection (Ultravist 300, Iopamidol; Bayer Healthcare, Berlin, Germany), and anatomic coverage was from the thorax to the pelvic cavity covering the entire colon.

Tumor geometry parameters measurement

All data were reviewed and measured on Workstation 4.4 (Advantage Workstation version 4.4; General Electric Healthcare). Coronal and sagittal views were re-established. The tumor margin was delineated by different enhancement of abnormal wall thickening and normal adjacent colon wall on the contrast CT images and corresponding noncontrast CT images. Parameters were measured on 2D images manually, as follows: 1) Tumor length (Tlen): the longest diameter of the tumor in any plane; 2) Tumor maximum diameter (Tdia): the maximum diameter of the tumor in the axial plane; 3) Tumor maximum cross-sectional area (Tare): regions of interest (ROIs) of tumor area were drawn by tracing the lesion boundary in the axial view; 4) Tumor volume (Tvol) = sum of axial area of ROIs of tumor × slice thickness. Pericolic lymph nodes, vessels, adjacent viscera and lumen were carefully excluded (Fig. 1).

To estimate the accuracy of the measurement in colon cancer, patients were randomly selected to be analyzed blindly by an experienced radiologist with 9 years of experience in abdominal radiology (H.L.) and a radiologist with 5 years of experience in radiology measurement (A.M.) for testing Interobserver repeatability. The patient measurements were repeated two months later by a radiology (A.M.) in order to verify the intraobserver repeatability.

Statistical Analysis

All statistical analyses were performed by SPSS software (version 22.0 for Windows; SPSS, Chicago). Interobserver and intraobserver measurement agreement were analyzed by calculating the intraclass correlation coefficient (ICC) (0–0.20, poor correlation; 0.21–0.40, fair correlation; 0.41–0.60, moderate correlation; 0.61–0.80, good correlation; and 0.81–1.00, excellent correlation). The differentiation of clinicopathologic factors including age, sex, differentiation status, tumor location, vascular carcinoma embolus invasion, neural infiltration and T stage were performed by univariate analysis. On the basis of the univariate analysis, potentially risk factors were tested for the ability to differentiate LNM with

multiple logistic regression analysis. Mann-Whitney U test and receiver-operating curve (ROC) characteristic analysis were performed to determine whether Tlen, Tdia, Tarea and Tvol could predict LNM and differentiate N stages. $P < 0.05$ was considered a significant difference.

Results

Inter- and intraobserver variability of Tlen, Tdia, Tare and Tvol measurements

The ICC of Interobserver measurement for Tlen, Tdia, Tare and Tvol is 0.94, 0.81, 0.97, and 0.99, respectively. The ICC of the intraobserver measurement by one observer is 0.95, 0.93, 0.91 and 0.99 for Tlen, Tdia, Tare and Tvol, respectively.

Clinicopathologic factors associated with LNM

The correlation between clinicopathologic factors and LNM is shown in Table 1. Age, sex, location of colon cancer, vascular carcinoma embolus invasion and neural infiltration exhibited no significant differences between positive and negative LNM ($P = 0.711, 0.123, 0.415, 0.426$ and 0.712 , respectively). There were significant differences in differentiation, T staging, Tlen, Tdia, Tare and Tvol between negative and positive LNM ($P = 0.028, 0.005, < 0.001, 0.001, < 0.001, < 0.001$, respectively) (Table 1). According to multivariate analysis, Tvol (odds ratio = 1.09; 95% confidence interval, 1.02–1.17; $P = 0.017$) was independent risk factors for predicting LNM. Tlen, Tdia and Tare was not risk for LNM ($P = 0.56, 0.15, 0.66$, respectively).

Table 1
Clinical pathologic factors associated with lymph node metastasis in colon cancer

parameter	Positive lymph nodes(N = 52)	Negative lymph nodes(N = 54)	P value
Age(years)	62.46 ± 11.68	63.39 ± 12.93	0.711
Sex			0.123
M	24(46.15%)	33(61.11%)	
F	28(53.85%)	21(38.89%)	
Differentiation			0.028
Well differentiated	2 (3.85%)	5(9.26%)	
Modernately differentiated	31 (59.61%)	41 (75.93%)	
Poorly differentiated	19 (36.54%)	8 (14.81%)	
Location			0.415
Left colon cancer	20 (38.46%)	25(46.30%)	
Right colon cancer	32 (61.54%)	29 (53.70%)	
Vascular carcinoma embolus invasion			0.426
positive	10(19.23%)	7 (12.96%)	
negative	42 (80.77%)	45 (83.34%)	
Neural infiltration			0.712
positive	7 (6.38%)	6 (8.51%)	
negative	45 (93.62%)	48 (91.49%)	
T staging			0.005
T1	0	4 (7.4%)	
T2	1 (1.92%)	10(18.52%)	
T3	47 (90.38%)	37 (68.52%)	
T4a	4 (7.70%)	3 (5.56%)	
Tumor size			
Tlen (cm)	6.42 ± 2.17	4.25 ± 1.61	< 0.001

data are medians ± standard deviations

parameter	Positive lymph nodes(N = 52)	Negative lymph nodes(N = 54)	P value
Tdia (cm)	2.29 ± 1.09	1.67 ± 0.76	0.001
Tare (cm ²)	15.73 ± 6.44	8.76 ± 4.84	< 0.001
Tvol (cm ³)	65.70 ± 56.67	23.96 ± 16.44	< 0.001
data are medians ± standard deviations			

Analysis of Tlen, Tdia, Tare and Tvol in the determination of N stage

Tlen, Tdia, Tare and Tvol could distinguish between N0 and N1 stage, N0 and N2, N0 and N1-N2, and N0-N1 and N2 disease (all $P < 0.05$). AUC, sensitivity, specificity, accuracy and predictive values of Tlen, Tlen, Tare and Tvol in the differentiation of N stage in colon cancer are summarized in Table 2, Fig. 2. From ROC analysis, we found that Tlen cutoff of 5.20 cm, Tdia cutoff of 1.56 cm, Tare cutoff of 9.47 cm² and Tvol cutoff of 38.00 cm³ could identify LNM. The AUC was higher for Tvol than for Tlen, Tdia and Tare in identifying LNM (AUC = 0.83, 0.82, 0.69, 0.79, respectively), distinguishing N0 from N1 stage (AUC = 0.79, 0.78, 0.63, 0.74, respectively), distinguishing N0 from N2 stage (AUC = 0.92, 0.89, 0.80, 0.89, respectively) and distinguishing N0-1 from N2 (AUC = 0.84, 0.79, 0.76, 0.83, respectively).

Table 2
ROC analysis of Tlen, Tare and Tvol in the differentiation of N staging

	Cutoff	AUC	P value	Sensitivity	Specificity	Accuracy
N0 VS N1-2						
Tlen (cm)	5.20	0.82	0.000	71.2%	81.5%	76.4%
Tdia (cm)	1.56	0.69	0.001	71.2%	51.9%	61.3%
Tare (cm ²)	9.47	0.79	0.000	84.6%	61.1%	72.6%
Tvol (cm ³)	38.00	0.83	0.000	69.2%	83.3%	77.4%
N0 VS N1						
Tlen (cm)	4.25	0.78	0.000	82.9%	61.1%	69.7%
Tdia (cm)	1.49	0.63	0.041	74.3%	48.1%	58.4%
Tare (cm ²)	9.47	0.74	0.048	80.0%	61.1%	69.7%
Tvol (cm ³)	23.22	0.79	0.006	88.6%	57.4%	69.7%
N0 VS N2						
Tlen (cm)	5.20	0.89	0.000	94.1%	81.5%	84.51%
Tdia (cm)	1.99	0.80	0.000	82.4%	70.4%	74.6%
Tare (cm ²)	13.41	0.89	0.000	82.4%	83.3%	81.7%
Tvol (cm ³)	38.40	0.92	0.000	94.1%	83.3%	88.7%
N0-1 VS N2						
Tlen (cm)	5.20	0.79	0.000	94.1%	65.2%	70.6%
Tdia (cm)	2.00	0.76	0.001	82.4%	67.4%	78.3%
Tare (cm ²)	13.41	0.83	0.000	82.4%	75.3%	76.4%
Tvol (cm ³)	38.63	0.84	0.000	94.1%	68.5%	83.0%
AUC = area under the ROC curve						

Discussion

In our study, we evaluated the effectiveness of tumor size on MDCT as a tool for the initial prediction of LNM in colon cancer. Our preliminary results showed that Tvol was an independent risk factor for LNM. Tumor size including Tlen, Tdia, Tare, and Tvol could distinguish between N0 and N1 stage, N0 and N2,

N0 and N1-2, and N0-1 and N2 disease. Tvol had the best diagnostic efficacy in identifying LNM and differentiating N stage.

Previous study reported that tumor length is an independent predictor of mortality in patients with esophageal carcinoma and a risk factor for LNM to predict survival in patients with ESCC (21–22). In this study, we indicated that tumor length could predict LNM in patients with colon cancer. This was because increasing longitudinal growth in the lymphatic-rich submucosa was a predictor of regional LNM. The longer the tumor length, the deeper the tumor invading the colonic wall and the more frequent the incidence of LNM. Tumor thickness was an independent adverse factor for LNM in oral carcinoma (23) and could be associated with LNM in ESCC (21). The larger the tumor diameter, the deeper tumor invading the colon wall, more likely invading adjacent structures, and the higher risk of LNM. In our study, Tdia could help identify LNM but the diagnostic efficacy of Tdia is the worst in colon cancer. We thought that the inflatable dilatation of the colon and blur margin caused by tumor inflammation and invasion could affect tumor diameter measurement. For Tare, we found that Tare could predict LNM. Tare is the maximum cross-sectional area of colon cancer and is used for delineating the whole circumference of the tumor. Compared with Tdia, it contains a much broader margin and could reflect tumor geometry and growth.

Although a recent article showed that CT tumor volumetry indicated no significant differences according to N stage, it serves as a useful prediction of prognosis in pT4b and M1b stages using CT colonography (24). Our result was different from that study. In this study, we confirmed that tumor volume had the best repeatability measurement, it could predict LNM and was the only risk factor for LNM in the patients with colon cancer by multivariate analysis compared with Tlen, Tdia and Tare. We demonstrated that Tvol could help differentiate N0 from N1-2, N0 from N1, N0 from N2, and N0-1 from N2 with moderately sensitivity (69.2%, 88.6%, 94.1%, 94.1%), specificity (83.3%, 57.4%, 83.3%, 68.5%) and accuracy (77.4%, 69.7%, 88.7%, 83.0%). CT tumor volumetry for discriminating N staging and is an independent risk factor for LNM had been confirmed by most of the previous articles (19–21). Tumor volume was moderately accurate in predicting N1, N2 and N3 stage in gastric carcinoma (19). Li et al. showed that tumor volume could predict regional LNM and differentiate various N stages with an accuracy of 70% in adenocarcinoma of the esophagogastric Junction (20). Tumor volume measured on MDCT could differentiate N0 and N1-3 stages, N0-1 and N2-3, and N0-2 and N3 with sensitivity values of 76%, 63% and 75% and specificity values of 75%, 61% and 81%, respectively, in resectable esophageal squamous cell carcinoma (21). Chen et al reported that tumor volume data had better correlation with LNM than tumor length and tumor diameters (25). We also demonstrated that Tvol had the highest AUC than Tlen, Tdia and Tare in distinguishing N stage. This may be because that Tvol contains more morphology information to reflect tumor growth pattern and infiltration based on Tlen, Tdia and Tare. The larger the tumor volume, the deeper the tumor invading the colonic wall and the more frequent the incidence of LNM. We can conclude that Tvol may be the best predictor to predict N stage in colon cancer.

Previous studies have applied different criteria based on either size and/or morphology for identifying LNM (26). Audrey et al. used the radiographic criteria of lymph node diameter (> 1.0 cm) or round shape,

heterogeneity, eccentricity, hilar thinning, calcification, central necrosis, and perinodal infiltration to evaluate lymph node involvement with sensitivity of 54%-88%, specificity of 55%-66%, accuracy of 61%-70%, positive predictive value of 52%-59% and negative predictive value of 68%-88% (13). Sibilleau et al. reported a method for identifying LNM using a long-axis diameter of 5 mm or more, clustering of three or more lymph nodes regardless of size, and a density of 100 HU or more, with high sensitivity (91%) and low specificity (68%) (27). However, metastatic lymph node smaller than 2 mm are difficult to depict with MR imaging and CT imaging and can easily be misinterpreted as small blood vessels and, most important, that some of nodes larger than 1 cm seen on CT images may be the benign. Therefore, the node seen on CT images that could not be matched with histopathologic findings all were judged to be benign on CT images. This limitation made morphological method not accurate to assess lymph node status. It is hard to ensure the metastatic lymph node we diagnosed on CT images is the one confirmed by pathology eventually. In our study, Tvol showed good diagnostic efficacy for differentiating N0 from N1-2 with sensitivity values of 69.2%, specificity values of 83.3%, and accuracy values of 77.4%.

Our study had several limitations. First, the collected sample number for LNM is too small compared with a previous study (19, 20). Lymphovascular invasion and perineural invasion have a high risk for LNM and a poor prognostic factor in colon diseases (25, 28, 29). In our study, we did not find these correlations because of small sample size of positive lymphovascular or perineural invasion. Second, Tumor volume measurements on CT images can be time-consuming. However, in this study, the time required for well-trained radiologists to draw the whole tumor area was controlled to 10 minutes. In future study, semiautomatic measurement method may be used to reduce the time of measurement. Third, the measurement of Tlen, Tdia and Tare might be affected by the distention of the contents in the intestinal canal. To minimize this effect, all patients were asked to perform bowel preparation with butylscopolamine bromide and drink 1000 mL of water before CT scanning.

Conclusion

Tlen, Tdia and Tare and Tvol measured on MDCT in patients with colon cancer has good repeatability. Tvol had higher diagnostic efficacy in identifying LNM and differentiating N0 from N1, N0-1 from N2, and N0 from N2 disease. Tvol could be helpful in quantitatively predicting LNM for the appropriate choice of treatment approach for this tumor.

Abbreviations

MDCT

multidetector computed tomography

LNM

lymph node metastasis

Tlen

tumor length

Tdia

tumor maximum diameter
Tare
tumor maximum cross-sectional area
Tvol
tumor volume
ROC
receiver operating characteristic
AUC
area under the ROC curve
ICC
intraclass correlation coefficient
ESCC
esophageal squamous cell carcinoma
AJCC
American Joint Committee on Cancer
NCCN
National Comprehensive Cancer Network

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of Sichuan Provincial People's Hospital, and the requirement for patient consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Competing interests

There is no conflict of interest among all authors.

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Authors' Contributions

HL and XC designed the overall study. AM and HL collected, analyzed the data and edited the manuscript. FF, HP and XC provide some advice to supervise this manuscript. All authors approved the final version of the manuscript.

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Figures

Figure 1

Tumor size measurement using enhanced CT in a 70-80 year old patient with colon cancer. a, tumor maximum diameter (Tdia). b, reconstructed coronal image to measure tumor length (Tlen). c, manually drawn area along the margin of the tumor and the value of this area (383 mm²) automatically derived from software together with minimal, maximal, and average CT attenuation (in Hounsfield units).

Figure 2

Receiver-operating curve analysis of tumor length (Tlen) (blue line), tumor maximum diameter (Tdia) (green line), tumor maximum cross-sectional area (Tare) (purple line) and tumor volume (Tvol) (red line) for distinguishing N0 from N1-2 (A), N0 from N1(B), N0 from N2 (C), N0-1 form N2 stage (D) in patients with colon cancer.