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ABDOMINAL IMAGING

ORIGINAL ARTICLE

pT1-2 gastric cancer with lymph node metastasis predicted by tumor morphologic features on contrast-enhanced computed tomography

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PURPOSE

To investigate the value of tumor morphologic features of pT1-2 gastric cancer (GC) on contrast-enhanced computed tomography (CT) in assessing lymph node metastasis (LNM) with reference to histopathological results.

METHODS

Eighty-six patients seen from October 2017 to April 2019 with pT1-2 GC proven by histopathology were included. Tumor volume and CT densities were measured in the plain scan and the portal-venous phase (PVP), and the percent enhancement was calculated. The correlations between tumor morphologic features and the N stages were analyzed. The diagnostic capability of tumor volume and enhancement features in predicting the LN status of pT1-2 GCs was further investigated using receiver operating characteristic (ROC) analysis.

RESULTS

Tumor volume, CT density in the PVP, and tumor percent enhancement in the PVP correlated significantly with the N stage (rho: 0.307, 0.558, and 0.586, respectively). Tumor volumes were significantly lower in the LNM– group than in the LNM+ group (14.4 mm^3 vs. 22.6 mm^3, $P = 0.004$). The differences between the LNM– and LNM+ groups in the CT density in the PVP and the percent enhancement in the PVP were also statistically significant (68.00 HU vs. 87.50 HU, $P < 0.001$; and 103.06% vs. 179.19%, $P < 0.001$, respectively). The area under the ROC curves for identifying the LNM+ group was 0.69 for tumor volume and 0.88 for percent enhancement in the PVP, respectively. The percent enhancement in the PVP of 145.2% and tumor volume of 17.4 mL achieved good diagnostic performance in determining LNM+ (sensitivity: 71.4%, 82.1%; specificity: 91.4%, 58.6%; and accuracy: 84.9%, 66.3%, respectively).

CONCLUSION

Tumor volume and percent enhancement in the PVP of pT1-2 GC could improve the diagnostic accuracy of LNM and would be helpful in image surveillance of these patients.

KEYWORDS

Computed tomography, contrast enhancement, gastric cancer, lymph node metastasis, tumor volume

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Gastric cancer (GC) is the most common type of malignant tumor in Eastern Asia, the region with the highest incidence and mortality of GC.[1,2] The mortality rate for early gastric cancer (EGC) is still relatively high, and only approximately one-third of these patients survive for more than five years. The five-year survival rate for GC has increased significantly.[3] However, some patients present with metastasis, which is still concerning. Lymph node (LN) staging is based on the number of metastatic LNs and has been shown to help predict patient prognosis and guide treatment. The N stage is classified according to the number of lymph nodes metastatic (LNM) (N0, no metastatic regional lymph nodes; N1, 1–2 metastatic regional lymph nodes; N2, 3–6 metastatic regional lymph nodes; N3, >6 metastatic regional lymph nodes). EGCs in any location are seldom assumed to cause nodal metasta-

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ses. In the literature, however, LNM incidence ranges from 2% to 5% in EGCs confined to the mucosal layer, rising to 10% to 25% when the disease invades the submucosa.[4,5] The incidence of LNM in stage T2 GCs in the right gastroepiploic and para-aortic nodes is 10% and 26%, respectively,[6] which is still considerably high. In Asia, D2 dissection is a conventional surgical approach involving the resection of lymph nodes along the perigastric region, including the left gastric, splenic, celiac, and hepatic arteries. The National Comprehensive Cancer Network recommends D2 dissection as the preferred mode of treatment for these cancers.[7] However, for patients with stage pT1-2 GC, uniform application of this highly invasive surgery may result in overtreatment, increased morbidity and mortality, and a decreased quality of life postoperatively.[8-10]

This aggressive surgical method should be reserved only for patients with pT1-2 GC with a high risk of LNM. Alternatively, minimally invasive surgeries, such as endoscopic submucosal dissection and endoscopic mucosal resection, could be chosen in those patients with LN non-metastatic EGC.[11] Therefore, accurate preoperative diagnoses of LNM are essential in deciding treatment strategies and predicting the prognosis of patients with pT1-2 cancer.

Predicting LNM in pT1-2 GCs is still an arduous task. Fluorodeoxyglucose positron emission tomography (FDG-PET), endoscopic ultrasonography, and computed tomography (CT) are available methods for diagnosing LNM. However, FDG-PET is unreliable in predicting LNM due to its low sensitivity.[12,13] Endoscopic ultrasonography defines LN status depending on LN size, morphology, and echogenicity, but its accuracy is only 64% for predicting LN presence.[14] CT is another anatomical imaging method to define metastasis in clinical practice, mainly based on LN size. Although CT, in combination with multiplanar reformation, can show the location and size of LNs, differentiating between hyperplastic, metastatic, and inflammatory LNs is still unreliable since it depends solely on LN size as a criterion.[15,16] Thus, other parameters are needed to improve the accuracy of CT for diagnosing LNM. Tumor volume and enhancement features can be used to identify LNM. Tumor size has been reported to correlate significantly with the likelihood of LNM in EGC;[17,18] however, tumor volume may be a better preoperative parameter than size. Size cannot be defined on axial images as GC always involves the gastric wall circumferentially. Tumor percent enhancement has also helped determine LN status in rectal cancer.[19] In light of these considerations, this study aims to investigate the diagnostic value of CT tumor volume and enhancement in predicting LNM in stage pT1-2 GC.

Main points

- Accurate prediction of lymph node metastasis (LNM) of pT1-2 gastric cancer (GC) through imaging is crucial in deciding treatment strategies.
- The pathologic N stage of pT1-2 GC significantly correlated with computed tomography (CT) tumor volume, density, and tumor percent enhancement.
- CT tumor volumetry and enhancement features of pT1-2 GC provided useful adjunct information for predicting LNM.
- Percent enhancement of portal-venous phase achieved better diagnostic performance than tumor volume in determining LNM.

Methods

Patients

Our institutional review board approved this retrospective study and waived the requirement for informed consent (approval ID: KY027-01). This study enrolled consecutive patients from October 2017 to April 2019 with pathologically proven stage T1-2 GC confined to the mucosa or submucosa and the muscularis propria. The inclusion criteria were as follows: (1) patients with histopathological confirmation of T1-2 GC, regardless of N and M stage; (2) those who underwent multislice CT scanning before surgery; (3) those who had no radiotherapy or chemotherapy before surgery; and (4) those who underwent surgical resection with extensive LN excision. For further confirmation of LNM, surgically excised LNs were fixed and stained with hematoxylin and eosin. LNM was defined as the presence of tumor cells or tissue in LNs at magnifications of 10× and 40×. Eleven patients were excluded because the filling state of the stomach was unsatisfactory or they lacked a contrast-enhanced CT. Finally, a total of 86 patients were enrolled, including 28 patients with LNM+ and 58 patients without LNM– (Figure 1).

Computed tomography acquisition

All patients underwent CT with multislice equipment (Siemens Somatom Sensation 64), with a tube voltage of 120 kV, a tube current of 200 mAs, a collimator width of 16 × 0.75 mm, a screw pitch of 0.750, a slice thickness of 5 mm, and a slice interval of 5 mm. Each patient who completed breathing exercises was requested to fast for at least eight hours and received 800 mL of water orally and an intramuscular injection of 10 mg of anisodamine to achieve gastric distension approximately 20 minutes before the examination. The CT scan covered the upper or entire abdomen. The iodinated contrast material was administered at a dose of 1.5 to 2.0 mL/kg (Omnipaque 350 mg I/mL) and an injection flow rate of 3.0 mL/s using a high-pressure syringe. Images were obtained in the arterial phase (30 s) and portal-venous phase (80 s) after initiation of contrast material injection.

Tumor analyses

The CT images of the PVP were sent to the workstation, and the GC lesions were determined by two radiologists (with at least eight years of experience in abdominal imaging) who were blind to the clinicopathological stage. They analyzed the images together to determine the outline of the tumor. Disagreement was resolved by discussion, and a consensus was reached, ensuring the accuracy of the tumor volume measurement. The tumors were manually drawn by tracing the lesion edge (Figure 2). Focal thickening of the gastric wall by 6 mm or greater with noticeable enhancement was included in the region of interest (ROI) if it was difficult to differentiate tumor tissue from the adjacent normal gastric wall;[20,21] the gastric lumen and artifacts were excluded. The radiologists then calculated the tumor volume by multiplying the area of each ROI by the slice thickness (5 mm). Percent enhancement in the PVP was calculated according to the following equation: (Val-p – Val-0)/Val-0×100%, where Val-0 and Val-p represented the CT density in Hounsfield units (HU) of the ROI of the lesion on the largest slice before contrast enhancement and in the PVP, respectively.

Statistical analysis

Spearman's rank correlation test was applied to analyze the correlation between tumor morphologic features and different N stages (0.00–0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; and 0.81–1.00, excellent). The differences between tumor volume, CT density in the PVP, and tumor percent enhancement in the PVP of different N stage groups (LNM+ vs. LNM–) were compared using the Mann–Whitney U test. The diagnostic efficacy of significant features predicting LNM in T1-2 GC was evaluated using receiver operating characteristic

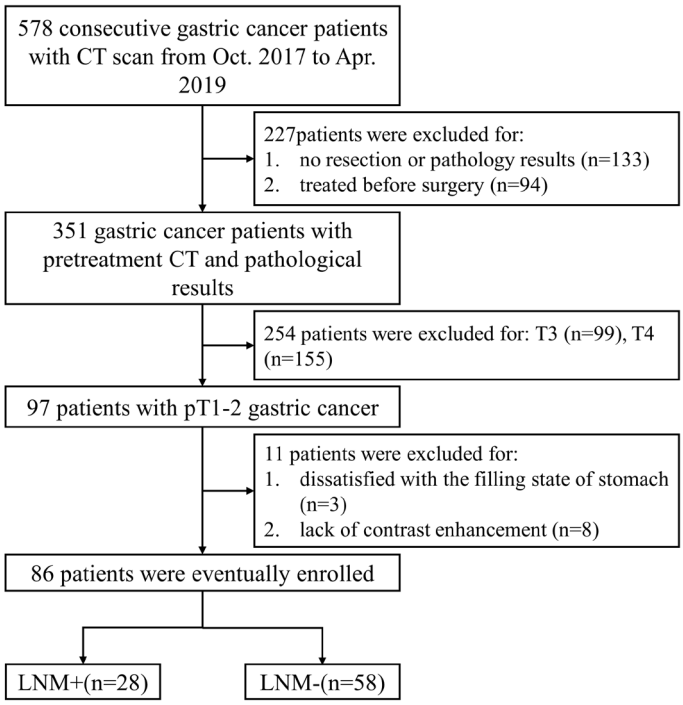

Figure 1. Patient selection flowchart. CT, computed tomography, LNM, lymph node metastasis.

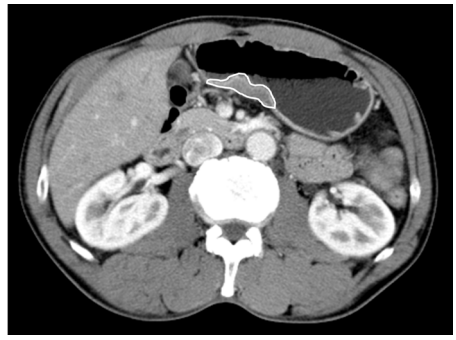

Figure 2. Shows the computed tomography (CT) images of a 56-year-old man with poorly differentiated adenocarcinoma and signet ring cell carcinoma, the lesion infiltrating the submucosa. The CT image of the portal-venous phase shows a thickened wall with heterogeneous enhancement in the stomach. The region of interest was manually drawn along the margin of the lesion (white line).

(ROC) analysis. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

The study group comprised 86 patients ranging in age from 27–80 years (median age, 59 years); 56 of the 86 patients were men (median age, 61 years), and 30 were women (median age, 56 years). Regarding the T stage, 57 patients (57/86, 66.3%) were T1, and 29 patients (29/86, 33.7%) were T2; and regarding the N stage, 58 patients (58/86, 67.4%) were N0, 12 patients (12/86, 14.0%) were N1, seven patients (7/86, 8.1%) were N2, and nine patients (9/86, 10.5%) were N3. Regarding the number of lymph nodes available for histopathological examination in resection specimens, 15 patients had 15–20 lymph nodes (15/86, 17.4%), 50 patients had 21–40 lymph nodes (50/86, 58.1%), and 21 patients had 41–63 lymph nodes (21/86, 24.4%) (Table 1).

Relationship between morphologic features and N stage

Tumor volume, CT density in the PVP, and percent enhancement in the PVP correlated significantly with the pathologic N stage. The correlation factor (rho) was highest for the percent enhancement in the PVP (rho= 0.586, $P < 0.001$), followed by CT density in the PVP (rho= 0.558, $P < 0.001$) and tumor volume (rho= 0.307, $P = 0.004$). However, CT density on non-contrast images did not correlate with the N stage (rho= –0.076, $P = 0.49$) (Table 2).

Lymph node metastasis plus versus lymph node metastasis minus groups

The LNM+ group had twenty-eight patients (28/86, 32.6%) with stage N1, N2, or N3 disease, while the LNM– group had 58 patients (58/86, 67.4%) with stage N0 disease. The median tumor volumes in the LNM+ and LNM– groups were 22.6 mm^3 and 14.4 mm^3, respectively. Tumor volume was significantly less in the LNM– group than in the LNM+ group ($P = 0.004$). The median percent enhancement in the PVP in the LNM+ and LNM– groups was 179.19% and 103.06%, respectively. Differences between the two groups in CT density in the PVP and percent enhancement in the PVP were also statistically significant ($P < 0.001$). However, there was no statistically significant difference between pre-contrast CT density and nodal involvement ($P = 0.40$). Table 3 shows the tumor volume, CT density, and percent enhancement in the PVP in the LNM+ and LNM– groups.

Receiver operating characteristic analysis

The diagnostic efficacy of tumor volume, CT density in the PVP, and percent enhancement in the PVP for differentiating between the LNM+ and LNM– groups were further evaluated using ROC analysis. The area under the ROC curve (AUC) for determining LNM+ in stage T1-2 GC was highest for the percent enhancement in the PVP (AUC= 0.883, $P = 0.001$), followed by CT density in the PVP (AUC= 0.865, $P < 0.001$) and tumor volume (AUC= 0.693, $P < 0.001$) (Figure 3). The percent enhancement in the PVP of 145.2% achieved good diagnostic performance in determining LNM+ (sensitivity: 71.43%, specificity: 91.38%, and accuracy: 84.88%). The CT density of 76 HU in the PVP predicted LNM+ with 89.29% sensitivity and 75.86% specificity, while a tumor volume of 17.35 mm^3 predicted LNM+ with 82.14% sensitivity and 58.62% specificity. Table 4 shows the

Table 1. Clinicopathological characteristics of patients

	LNM–	LNM+			Total
		N1	N2	N3	
Patient, n (%)	58 (67.4%)	12 (14.0%)	7 (8.1%)	9 (10.5%)	86 (100%)
Age, y*	59 ± 11	62 ± 6	60 ± 9	56 ± 13	59 ± 10
Male/female, n	37/21	8/4	7/0	4/5	56/30
T1/T2, n	44/14	5/7	4/3	4/5	57/29

*Data are presented as mean ± SD. SD, standard deviation; LNM+, lymph node metastasis present; LNM–, no lymph node metastasis.

Table 2. Median values and correlation between morphologic features and N stage

	N stage				Rho	*P*
	N0	N1	N2	N3	(95% CI)	
Tumor volume median mm³	14.4	22.4	24.7	22.8	0.307	0.004
Range	(1.9–63.0)	(10.7–102.2)	(7.6–65.0)	(12.8–94.6)	(0.102–0.487)	
CT density on non-contrast images: median	34.0	31.5	31.0	34.0	-0.076	0.49
Range (HU)	(15.0–56.0)	(25.0–43.0)	(24.0–39.0)	(22.0–42.0)	(-0.283–0.139)	
CT density in PVP: median	68.0	95.0	90.0	81.0	0.558	< 0.001
Range (HU)	(23.0–97.0)	(65.0–120.0)	(78.0–105.0)	(71.0–149.0)	(0.393–0.689)	
Percent enhancement %	103.1	202.9	190.3	150.0	0.586	< 0.001
Median (range)	(14.3–304.3)	(116.7–314.3)	(135.9–258.3)	(91.9–304.5)	(0.427–0.710)	

Rho, correlation coefficient; CI, confidence interval; PVP, portal-venous phase; HU, Hounsfield units.

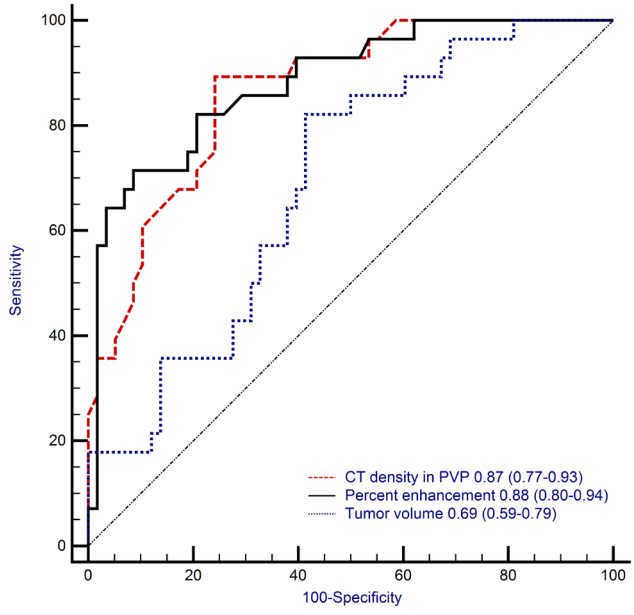

Figure 3. Shows the receiver operating characteristic (ROC) curves of tumor volume, computed tomography density in the portal venous phase, and percent enhancement for identification of lymph node metastases in pT1-2 gastric cancers. The area under the curve and 95% confidence interval are shown in the lower right corner of the figure. PVP, portal-venous phase; CT, computed tomograhy.

Table 3. Median values and interquartile ranges between the LNM+ and LNM– groups

	LNM+ (n = 28)	LNM– (n = 58)	Z	*P*
Tumor volume in mm³	22.6	14.4	2.894	0.004
Interquartile range	18.3–38.6	8.8–26.2		
CT density on non-contrast images in HU	33.0	34.0	0.844	0.40
Interquartile range	29.0–37.0	30.0–37.0		
CT density in the PVP in HU	87.5	68.0	5.461	< 0.001
Interquartile range	79.5–101.0	59.0–76.0		
Percent enhancement %	179.2	103.1	5.737	< 0.001
Interquartile range	134.1–232.3	83.3–123.5	-	-

LNM+, lymph node metastasis; LNM–, lymph node non-metastasis; PVP, portal-venous phase; HU, Hounsfield units.

sensitivities, specificities, negative and positive predictive values, and accuracy.

Discussion

Individualized treatment is set to become the cornerstone for more effective cancer therapy. Patients with early-stage GC are frequently overtreated because of a lack of available detection methods that are robust and accurate in identifying LN metastasis before surgery. Our study indicated that tumor volume, CT density in the PVP, and percent enhancement in the PVP significantly correlated with the pathologic N stage in pT1-2 GC. These variables were useful for accurate preoperative diagnosis of LN metastasis and may improve the prognosis of patients with GC.

Previously published studies have shown that tumor volume measured using CT was reproducible and valuable as an additional parameter for TNM staging in GC.[22,23] They showed that tumor volume significantly correlated with the N stage in GC with an AUC of 0.75 for stage ≥ N1. Our study also showed similar results. Our study found that gastric tumors with larger volumes are related to an increased likelihood of invasion and LNM, i.e., higher T and N stages.

Various studies have reported that tumor percent enhancement could help in evaluating the prognosis of hepatocellular carcinoma,[24] distinguishing the histological type of GC,[25] predicting synchronous and metachronous hepatic metastasis in GC,[26] and determining LNM of rectal cancer.[19,27] These studies revealed that enhancement features of tumors play an essential role in assessing tumor prognosis and clinical stage. Our study also showed that tumor CT den-

Table 4. Diagnostic performance of whole tumor volume and enhancement features in predicting lymph node metastasis in pT1-2 stage gastric cancers by receiver operating characteristic curve analyses

	AUC (95% CI)	Cut-off values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Tumor volume	0.69 (0.59–0.79)	17.4 mm^3	82.1 (23/28)	58.6 (34/58)	48.9 (23/47)	87.2 (34/39)	66.3 (57/86)
CT density in the PVP	0.87 (0.77–0.93)	76 HU	89.3 (25/28)	75.9 (44/58)	64.1 (25/39)	93.6 (44/47)	80.2 (69/86)
Percent enhancement	0.88 (0.80–0.94)	145.2%	71.4 (20/28)	91.4 (53/58)	80.0 (20/25)	86.9 (53/61)	84.9 (73/86)

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; PVP, portal-venous phase; CT, computed tomography.

sity in the PVP and percent enhancement in the PVP could help assess LNMs in pT1-2 GC by obtaining appropriate cut-off values. The growth of solid tumors depends heavily on surrounding angiogenesis, which accelerates tumor growth and increases the likelihood of tumor metastasis. Moreover, in the progression of malignant tumors, increased leakage of arteriovenous shunts and neovascularization often occur, leading to early enhancement of tumors on CT/magnetic resonance imaging (MRI). In addition, compared with normal vessels, the endothelial cells of tumor capillaries have a wider gap, and the basement membrane is discontinuous, making it easier for tumor cells to penetrate.[28] Our research also indicated that tumors with higher percent enhancement were more likely to metastasize to LNs, which might attract the attention of radiologists and gastric surgeons. Notably, CT density in the PVP and percent enhancement in N1 was higher than in N2 and N3. We speculated that once tumor cells have metastasized to sentinel lymph nodes, the increase in metastatic LNs no longer depends on the tumor itself but on metastasis from one LN to another.

In clinical practice, the abnormalities of LNs on CT/MRI are generally evaluated using the Response Evaluation Criteria in Solid Tumors, which has adopted the short-axis diameter (SAD) of LNs as a criterion.[29] However, the definition of LNM varies, and different cut-off values have been used in various studies.[30-34] Ahn et al.[34] determined LNM as an SAD ≥8 mm, while Tokunaga et al.[31] suggested an SAD cut-off of ≥15 mm. Saito et al.[35] showed that the accuracy of individual SAD cut-off values in diagnosing LNM was 71.1% based on pathological type. More recently, however, Kim and Kim[16] reported that the largest LN was the metastatic LN in only a small percentage of patients with EGC. In other words, the largest diameter LN may only be an inflamed lymph node. Relying solely on the size of the LN to diagnose metastatic LN would lead to a lack of optimal disease treatment. Long and short diameter values were also used to assess LNM; nevertheless, there is still no defined size standard.[36] In addition to size, other CT features of the LN can also be used to evaluate the nodal status, such as morphology (long/short diameter ratio <1.5), uneven enhancement, and clustered nodes.[33,34,37]

In this study, we only enrolled pT1-2 patients because the lymph nodal status of these patients is crucial in deciding treatment strategies. To the best of our knowledge, there are currently no defined reliable criteria for nodal involvement based on CT features. To obtain multiple additional quantifiable indicators, we combined the morphologic parameters of gastric tumors to determine the LNM status - an innovative aspect of our research.

This study has several limitations. First, it was based in a single center, had a relatively small sample size (especially when considering patients with LNM), and had an inevitable selection bias. Second, the reproducibility of data measurement between reviewers was not evaluated. Finally, manual measurement of gastric tumor volume might be subjective. With the development of artificial intelligence, graphics-processing capabilities have become more powerful. We believe that an automatized tool will take the place of manual tracing and be a better option to circumvent this limitation. Tumor volume could then be more readily and precisely assessed.

In conclusion, we have established that tumor volume, CT density in the PVP, and percent enhancement in the PVP, could be used to determine LNMs in pT1-2 GC, with percent enhancement in the PVP achieving better diagnostic performance than tumor volume. Identifying an appropriate cut-off value for percent enhancement and tumor volume can improve the diagnostic accuracy for LNM.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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