Clinical Radiology 74 (2019) 782–789

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Preoperative N stage evaluation in advanced gastric cancer patients using multidetector CT: can the sum of the diameters of metastatic LNs be used for N stage evaluation?

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ARTICLE INFORMATION

Article history:
Received 28 September 2018
Accepted 28 June 2019

AIM: To compare the diagnostic performance of total counts of metastatic lymph nodes (LN-sum) and conventional multidetector (MD) computed tomography (CT) staging in the nodal evaluation of advanced gastric cancer (AGC) patients.

MATERIALS AND METHODS: In total, 127 consecutive patients who underwent preoperative MDCT and gastrectomy for AGC were identified. Metastatic LNs on MDCT were defined as LNs with a short axis ≥8 mm, marked or heterogeneous enhancement, and morphological features (central necrosis, round shape, clustering). The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the N-stage using LN-sum and conventional MDCT staging were generated and compared. In addition, metastatic LN counts between the MDCT and the histopathological examinations and correlation between LN-sum and histopathological nodal status were analysed.

RESULTS: The total counts of metastatic LNs on MDCT was significantly smaller than those detected in histopathological assessments ($p<0.0001$). LN-sum showed significant correlation with the pathological N stage and the number of metastatic LNs (rho=0.69, 0.73, $p<0.0001$). The areas under the receiver operating characteristic curve were 0.896, and 0.835, for N stage ≥N2 and N3, with cut-off values of 12.5 and 23.5 mm, respectively. LN-sum provided better diagnostic performance than conventional MDCT staging for discriminating N0–2 versus N3; sensitivity, accuracy, PPV and NPV of LN-sum were significantly higher (80.4 versus 52.2%, 81.1 versus 68.5%, 71.2 versus 57.1%, and 88 versus 74.1%).

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https://doi.org/10.1016/j.crad.2019.06.030

CONCLUSION: LN-sum may be sufficiently useful in assessing the N3 stage of AGC and may help to plan appropriate therapy for AGC patients.

Introduction

Although the incidence of gastric cancer and the mortality rates associated with it have declined rapidly over the past few decades, the disease remains a leading cause of cancer-related death in East Asian countries such as Korea, Japan, and China.[1–3] The advent of nationwide screening programmes in high-prevalence areas such as Korea and Japan have resulted in an increase in the detection rate of early gastric cancer, which is defined as a tumour confined to the mucosa and submucosa regardless of lymph node (LN) metastasis. Nevertheless, 30–50% of patients show evidence of advanced disease at the time of initial presentation.[4–6] Although radical surgery is the mainstay of curative treatment for patients with resectable advanced gastric cancer (AGC),[7] the long-term outcome of this approach remains unsatisfactory because more than half of the patients with AGC will develop recurrence, and <40% survive beyond 3 years.[8]

The high rate of relapse after complete gastric resection makes it important to consider adjuvant treatment, and previous studies have clearly demonstrated the therapeutic benefits of adjuvant chemotherapy for patients with AGC.[9–11] Thus, adjuvant chemotherapy has become the standard treatment after gastrectomy with D2 resection for AGC; however, adjuvant chemotherapy may not yield completely satisfactory outcomes in cases of AGC. Therefore, the feasibility of neoadjuvant chemotherapy has also been investigated in recent studies. Several studies have shown that neoadjuvant chemotherapy can facilitate high rates of complete tumour resection and eradication of micrometastatic tumour cells at an earlier stage, thereby offering some advantages over adjuvant chemotherapy.[12–14] In addition, neoadjuvant chemotherapy has been reported to be effective in gastric cancer patients with extensive LN metastasis.[15–17]

Thus, accurate preoperative N staging in AGC is very important in establishing therapeutic strategies, especially for neoadjuvant chemotherapy; however, multidetector (MD) computed tomography (CT), which is widely used for preoperative evaluation of gastric cancer in clinical practice, continues to show unsatisfactory ability to detect preoperative LN metastasis. According to Kwee *et al.*,[18] the sensitivity and specificity of MDCT in assessing the N status of gastric cancer varies between 62.5% and 91.9% and 50% and 87.9%, respectively. The number of metastatic LNs detected at MDCT has been reported to be significantly smaller than that detected in histopathological assessments, which may be one of the factors contributing to the limitations of MDCT in the nodal staging of gastric cancer[19–21]; however, several studies have shown that in addition to the size of the largest LN measured at histopathological assessments, the size of the largest LN measured on MDCT also correlated with the number of metastatic LNs in gastric cancer.[22–25] Therefore, the present authors speculated that the sum of the diameters of metastatic LNs on preoperative MDCT (LN-sum) might be more helpful in predicting the N stage of AGC in comparison with conventional MDCT staging. To date, there has been a paucity of data regarding the evaluation of metastatic LNs using LN-sum in gastric cancer patients. Thus, the purpose of the present study was to compare the diagnostic performance of LN-sum and conventional MDCT staging in nodal evaluation of AGC patients.

Materials and methods

Patient selection

The institutional review board approved this retrospective study and the requirement for informed consent was waived. A total of 175 patients with surgically diagnosed advanced gastric adenocarcinoma were identified by a study coordinator, who checked the medical and pathological records between January 2012 and December 2012. The study coordinator did not participate in the MDCT analyses. Patients with a history of gastrectomy and patients with multiple gastric cancers were excluded. In addition, patients who underwent MDCT examinations at outside hospitals were excluded to avoid inhomogeneity of MDCT techniques. Also excluded were cases in which MDCT was not performed appropriately, such as those involving insufficient gastric distension, motion artefacts, or peristaltic motion of the stomach, and cases where the interval between preoperative MDCT and surgery was >6 weeks. Thus, a total of 48 cases were excluded for the following reasons: previously underwent gastrectomy (n=8), multiple gastric cancers (n=6), MDCT undertaken at another hospital (n=21), inappropriate MDCT (insufficient gastric distension, n=7; motion artefacts or peristaltic motion of the stomach, n=3), and an interval >6 weeks between MDCT and resection (n=3). Finally, a total of 127 patients with advanced gastric adenocarcinoma were included in this study. The flow chart for patient selection is summarised in Fig 1. Eighty-two patients were men and 45 were women; their ages ranged from 31 to 86 years (mean ± SD, 63.2 ± 9.6 years).

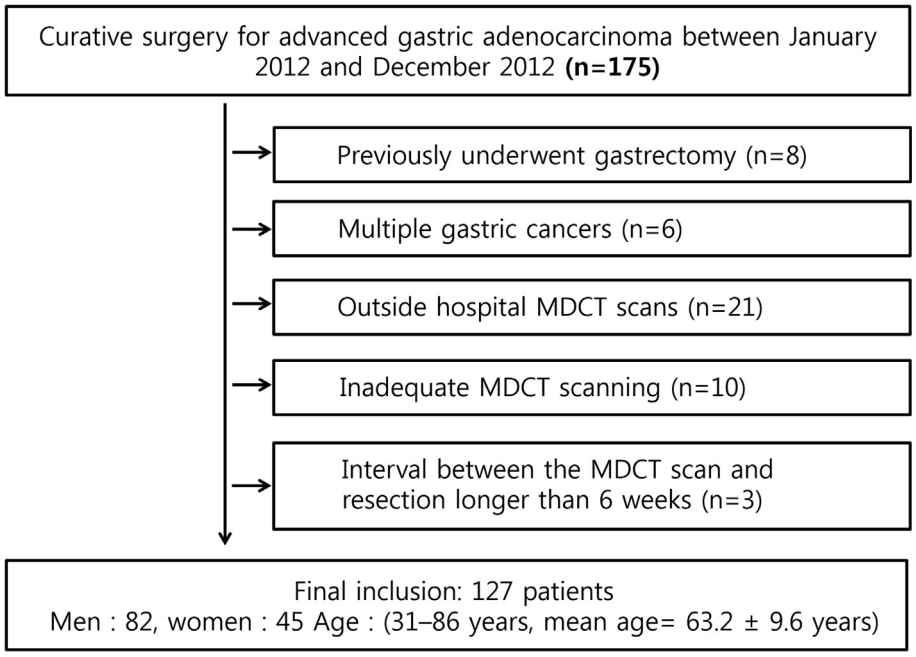

Figure 1 Flow chart of the patient selection process.

MDCT techniques

All MDCT imaging examinations were performed according to the protocol used at Pusan National University Yangsan Hospital with one of the following MDCT machines: 128-section MDCT (Somatom Definition AS+; Siemens Healthcare) in 35 patients, 64-section MDCT (Discovery CT 750 HD; GE Healthcare) in 82 patients, and 16-section MDCT (Sensation 16; Siemens Healthcare) in 10 patients. The imaging parameters used for these MDCT examinations were as follows: 0.6–1.5 mm detector configuration, 0.8 to 1.35 pitch, 0.5–0.75 seconds rotation time, 120 kVp; and automated dose modulation by using a maximum allowable tube current set at 200 mAs.

In preparation for MDCT, all patients were instructed to fast for >6 hours. They were also advised to drink 500 ml of water as an oral contrast agent 15 minutes before the scan, and an additional 500 ml immediately before the examination. Contrast-enhanced MDCT images were obtained after intravenous injection of 100–150 ml iodinated contrast material with an automated pump at a rate of 3 ml/s via an antecubital vein. The total amount of injected contrast material was adjusted according to the body weight of the patient (2 ml/kg).

Dynamic enhanced images were obtained by scanning the images 60 and 90–110 seconds after the attenuation of the descending thoracic aorta reached 100 HU using the bolus-tracking technique for the portal and delayed phases, respectively. A transverse image was obtained with a section thickness of 3 mm and an interval of 3 mm. All MDCT images were interfaced directly to the picture archiving and communications system (Maroview, Marotech, Seoul, Republic of Korea).

Image analysis

Preoperative MDCT examinations were reviewed retrospectively on a picture archiving and communications system workstation independently by two abdominal radiologists, who were blinded to the pathological findings of the resected LNs. LN size was defined as the short-axis diameter of the LN on transverse MDCT images. Regional LNs with a size of ≥8 mm were considered to indicate metastasis.[26] Regardless of size, LNs showing morphological features such as central necrosis, marked or heterogeneous enhancement (>85 HU in the enhanced scan), nearly round shape (longitudinal/transverse diameter ratio <1.5), and clustering were also considered to indicate metastasis.[27] The LN size (short-axis diameter) was measured when the abovementioned CT findings were observed. When LNs were not well separated from each other, an attempt was made to identify each of LNs where possible. Differences in assessments by the two radiologists were resolved by discussion and consensus.

A third radiologist precisely counted the number of regional LNs considered to be metastatic and recorded N staging according to the 8th edition of the AJCC cancer staging manual (conventional MDCT staging). In addition, the third radiologist also calculated the sum of the short-axis diameters of metastatic LNs (LN-sum) on transverse MDCT images in each patient (Fig 2).

Histopathology

The gross and histopathological features of gastric cancers were reviewed by an experienced gastrointestinal pathologist. All surgical specimens were cut, formalin-fixed, paraffin-embedded, and stained with haematoxylin–eosin.

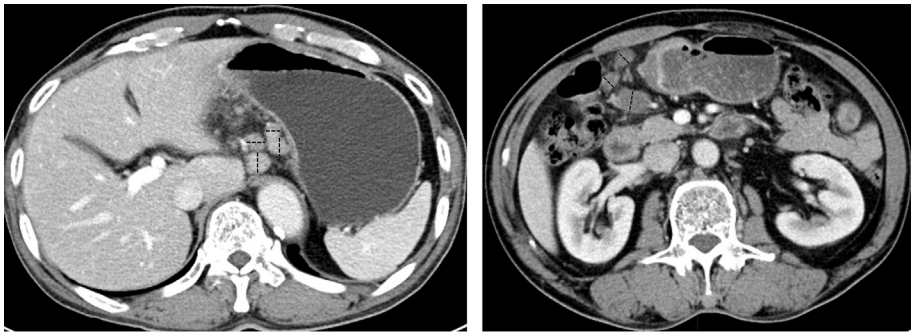

Figure 2 (a) A transverse CT image of a 55-year-old man shows multiple enlarged lymph nodes in the lesser curvature region. (b) A transverse CT image of a 62-year-old man shows multiple enlarged lymph nodes in the subpyloric region. The short diameter (dotted line) of each lymph node were measured and added to obtain the sum (LN-sum), as shown.

All visible LNs were harvested. The status of each node was classified as benign or metastatic on histopathology. According to the numbers of regional resected metastatic LNs, the N stage of the tumour was classified on the basis of 8th edition of the AJCC N category; N1, 1–2 metastatic LNs; N2, 3–6 metastatic LNs; and N3, ≥7 metastatic LNs.

Statistical analysis

The differences in the metastatic LN counts between the MDCT and the pathological examinations were assessed by the Wilcoxon *t* test. The correlation between LN-sum and pathological N stage and between LN-sum and number of metastatic LNs were analysed using Spearman's rank correlation coefficients. The optimal cut-off values of LN-sum for discrimination of each N staging (N0–1 versus N2–3, N0–2 versus N3) were calculated by using a receiver operating characteristic (ROC) analysis with areas under the curve (AUC) values as indices. Sensitivities, specificities, accuracies, positive predictive values, and negative predictive values using LN-sum were obtained using the calculated cut-off values for each N stage. In addition, the sensitivities, specificities, accuracies, positive predictive values, and negative predictive values were calculated according to conventional MDCT staging. Generalised estimating equation (GEE) analysis was used to compare the diagnostic performance of the two methods. The statistical analyses were performed using SPSS version 21.0 for Windows software (SPSS, Chicago, IL, USA).

Results

Characteristics of patients and tumours

The characteristics of the study patients and gastric cancer are shown in Table 1. The patients were grouped according to the AJCC/UICC staging criteria as follows: 15 patients had stage I disease, 30 had stage II disease, and 82 had stage III disease. With respect to histological types, 46 lesions belonged to the intestinal type, and the other 81 were diffuse-type lesions. The locations of gastric cancer included the fundus (n=30), body (n=42), and antrum (n=55).

More than two-thirds (70%, 89/127) of the patients received subtotal gastrectomy, and all patients received D2 LN dissection. The median number of dissected LNs was 47, and the pathological node-positive rate was 77% (98/127). There were 29, 24, 28, and 46 patients with N0, N1, N2, and N3 stages of gastric cancer. The interval between the MDCT examination and surgical resection was <6 weeks (mean: 18 days, range: 1–40 days) for all the patients.

Comparison of metastatic LN counts between the MDCT and the pathological examinations

The total counts of metastatic LNs detected on preoperative MDCT (N counts on MDCT) were significantly smaller than those detected in pathological assessments (pathological N counts; $p<0.0001$; N counts on MDCT: pathological N counts=3.78 ± 4.4:8.41 ± 12.8 [mean ± SD]).

Correlation between LN-sum and pathological N stages

The LN-sums were 3.4 ± 6.2, 8.5 ± 8.2, 21.1 ± 9.2, and 54.4 ± 46.4 mm for N0, N1, N2, and N3 cases, respectively. LN-sums showed significant correlation with the pathological N stages (rho=0.69, $p<0.0001$; Spearman's rank correlation; Fig 3). The correlation between LN-sum and the number of metastatic LNs in gastric cancer was also significant (rho=0.73, $p<0.0001$; Spearman's rank correlation;

Table 1
The baseline characteristics of the gastric cancer patients.

Characteristics		*n*
Sex	Male/female	82/45
Age (years)	Median (range)	63 (31–86)
Location	Fundus/body/antrum	30/42/55
Gastrectomy	Total/subtotal	38/89
No. of dissected lymph nodes	Median (range)	47 (13–95)
No. of lymph nodes with metastasis	Median (range)	4 (0–73)
pT	T2/T3/T4	23/32/72
pN	N0/N1/N2/N3	29/24/28/46
pStage	I/II/III	15/30/82
Histology	Intestinal/diffuse	46/81

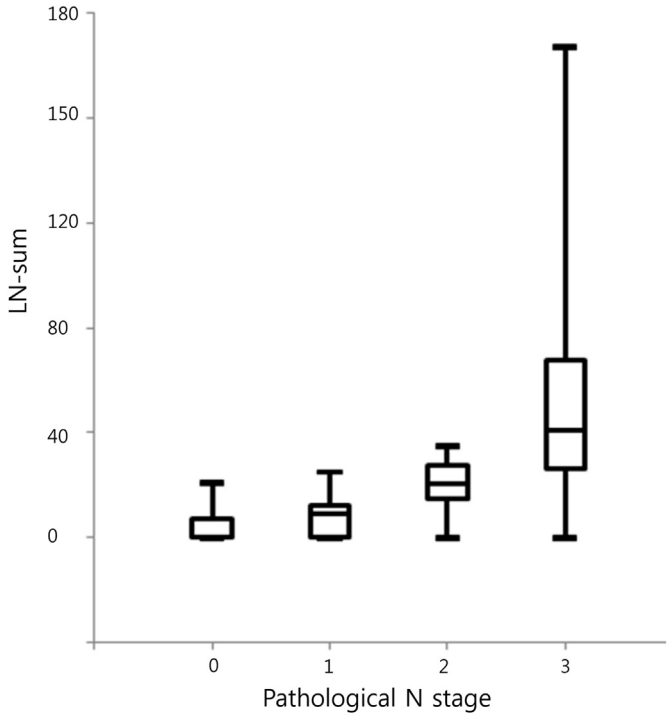

Figure 3 Box plots of LN-sum according to pathological N stage (N0–3). LN-sum showed significant correlation with the pathological N stage in patients with AGC (rho=0.69, $p<0.0001$, Spearman's rank correlation).

Fig 4). The cut-off values and AUC calculated from ROC analysis were 12.5 mm and 0.896 (95% confidence interval [CI] 0.836–0.956, $p<0.001$; Fig 5a) for N0–1 versus N2–3. For N0–2 versus N3, the cut-off values and AUC calculated from ROC analysis were 23.5 mm and 0.835 (95% CI: 0.761–0.908, $p<0.001$; Fig 5b). Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for discriminating N0–1 versus N2–3 were 83.8%, 84.9%, 84.3%, 88.6%, and 78.9%, while those for discriminating N0–2 versus N3 were 80.4%, 81.5%, 81.1%, 71.2%, and 88%, respectively (Table 2).

Correlation between conventional MDCT staging and pathological N stages

For conventional MDCT staging, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for discriminating N0–1 versus N2-3 were 85.1%, 83%, 84.3%, 87.5%, and 80%, respectively. Those for discriminating N0–2 versus N3 were 52.2%, 78.8%, 68.5%, 57.1%, and 74.1%, respectively (Table 2).

Comparison of LN-sum and conventional MDCT staging in discriminating pathological N stages

The sensitivity, accuracy, positive predictive value, and negative predictive value of LN-sum for discriminating N0–2 versus N3 were significantly higher than those of the

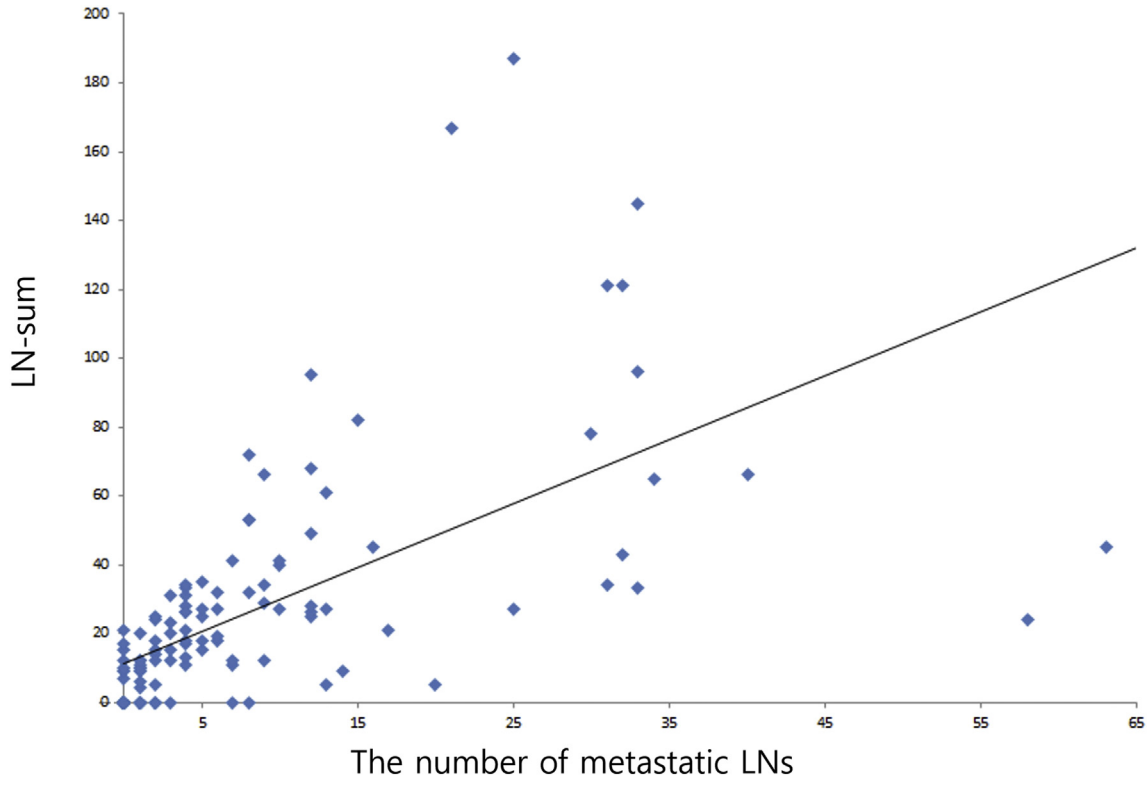

Figure 4 Scatter plot demonstrate relationship between LN-sum and the number of metastatic LNs; data indicate a strong correlation ($p<0.0001$, $r=0.73$; Spearman's rank coefficient).

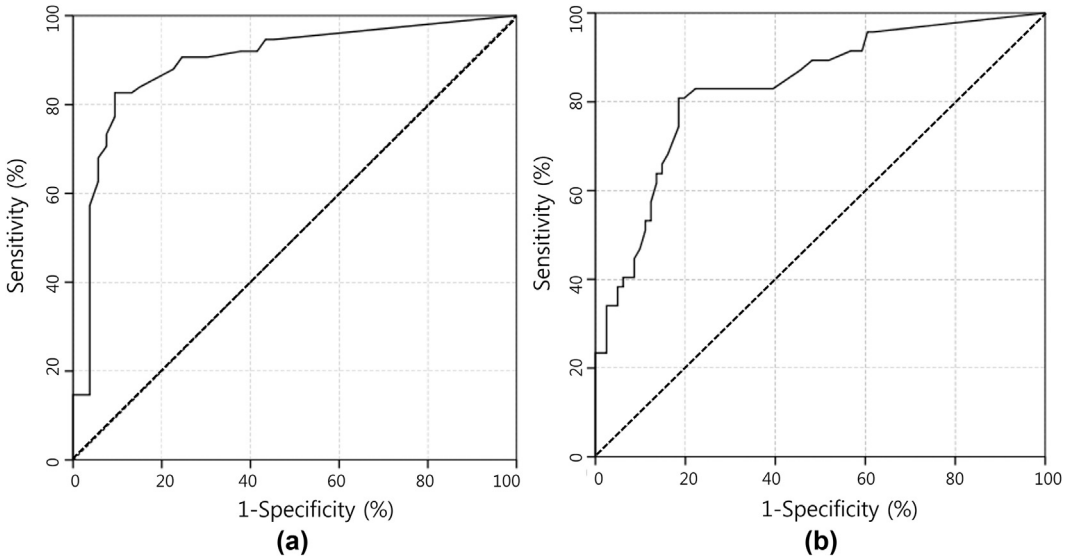

Figure 5 ROC analysis to determine cut-off values in discriminating pathological N stages. (a) N0–1 versus N2–3: AUC (Az value) was 0.896 with a cut-off value of 12.5 mm. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 83.8%, 84.9%, 84.3%, 88.6%, and 78.9%, respectively. (b) N0–2 versus N3: Az value was 0.835 with a cut-off value of 23.5 mm. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 80.4%, 81.5%, 81.1%, 71.2%, and 88%, respectively.

Table 2
Comparison of diagnostic performance between conventional MDCT staging and LN-sum for N staging in the gastric cancer.

N staging	Methods for N staging in MDCT	Sensitivity	Specificity	Accuracy	PPV	NPV
≤N1 vs ≥N2	Conventional MDCT staging	85.1 (75–92.3)	83 (70.2–91.9)	84.3 (76.7–90.1)	87.5 (79.3–92.8)	80 (69.6–87.5)
		63/74	44/53	107/127	63/72	44/55
	LN-sum	83.8 (73.4–91.3)	84.9 (72.4–93.3)	84.3 (76.7–90.1)	88.6 (80.2–93.7)	78.9 (68.8–86.4)
		62/74	45/53	107/127	62/70	45/57
p-Value (conventional vs LN-sum)		0.654	0.313	1	0.543	0.45
≤N2 vs ≥N3	Conventional MDCT staging	52.2 (37–67.1)	77.8 (67.2–86.3)	68.5 (59.7–76.5)	57.1 (44.9–68.6)	74.1 (67.5–79.8)
		24/46	63/81	87/127	24/42	63/85
	LN-sum	80.4 (66.1–90.6)	81.5 (71.3–89.3)	81.1 (73.2–87.5)	71.2 (60.5–79.9)	88 (80.2–93)
		37/46	66/81	103/127	37/52	66/75
p-Value (conventional vs LN-sum)		<0.001	0.491	<0.001	<0.001	<0.001

Data are expressed as percentages (95% confidence intervals) or as the number of patients.
PPV, positive predictive value; NPV, negative predictive value.

conventional MDCT staging ($p<0.001$), but the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for discriminating N0–1 versus N2–3 and the specificity for discriminating N0–2 versus N3 did not differ significantly ($p=0.654$, 0.313, 1, 0.543, 0.45, and 0.491, respectively; Table 2).

Discussion

The present study evaluated LN-sum values on MDCT in comparison with conventional MDCT staging for the prediction of N stage in gastric cancer patients. The present results showed that LN-sum was more effective than conventional MDCT staging in indicating the nodal stage of gastric cancer for discriminating N0–2 versus N3, although there was no statistically significant difference for discriminating N0–1 versus N2–3. The present study revealed significantly enhanced diagnostic sensitivity, accuracy, positive predictive value, and negative predictive value when LN-sum was applied using the cut-off value for discriminating N0–2 versus N3. In other words, LN-sum shows better diagnostic performance than conventional MDCT staging for the diagnosis of extensive LN metastasis in gastric cancer.

Recent advancements in diagnostic techniques, such as endoscopic ultrasonography and 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-positron-emission tomography (PET) have improved the accuracy of T and M staging in gastric cancer, but precise N staging is still difficult.[28] MDCT has been reported to show diagnostic accuracies ranging from 46% to 83% for N staging of gastric cancer.[18,26,29] This low and variable diagnostic performance may be attributed to the current criteria for LN metastasis, which are usually based on the size, shape, margin, density, and enhancement of LN. These findings cannot be considered completely satisfactory to differentiate benign and metastatic LNs.

Currently, the absolute number of metastatic LNs is used for nodal staging of gastric cancer in the UICC/AJCC TNM classification. Furthermore, it is now generally accepted that in addition to the presence of LN metastases, the number of metastatic LNs might be a predictor of survival in gastric

cancer.[30–32] Therefore, accurate assessment of nodal status is crucial for treatment planning and predicting the patient prognosis; however, it is difficult to distinguish the accurate number of involved LNs in preoperative N staging using MDCT. The results of the present study revealed that the number of positive LNs detected on MDCT was significantly smaller than that on pathological LNs. This might be one of the reasons why the accuracy of MDCT N staging was low. The present results correspond well with those of previous studies regarding the differences between metastatic nodal counts in MDCT and pathological assessments in gastric cancer.[19–21] Kawaguchi *et al.*,[19] derived the following special equation from Spearman's correlation analysis: pathological N counts=1.63 × (N counts on MDCT) + 2.5. In another study by Yan *et al.*,[23] the sensitivity of MDCT for predicting stage pN2–3 gastric cancer was especially low, because the discrepancy in nodal counts between MDCT and pathological assessments increases with N stage, thereby unavoidably leading to understaging N stage for gastric cancer. The present findings were in concordance with this result, as conventional MDCT staging had low sensitivity (52.2%) in N3 staging of gastric cancer. This phenomenon may be attributable to the presence of metastatic foci in normal-sized LN.[33]

Conversely, several previous studies have reported that the size of the largest metastatic LN measured on MDCT is associated with the number of metastatic LNs in gastric cancer.[22–25] One possible explanation for this is that rows of metastatic LNs or clustered LNs may hinder accurate determination of the number of metastatic LNs in MDCT, and thus result in significant underestimation of N stage.[34] In the same context, several recent studies have reported that the size of the largest metastatic LN was an important factor in the prognosis of gastric cancer patients.[35,36] Therefore, it was anticipated that LN-sum complements the shortcomings of conventional MDCT staging, and the present results were in concordance with expectations.

To the authors' knowledge, only one study has evaluated the value of LN-sum in gastric cancer; however, this study focused on the association of prognosis with LN-sum and did not compare the diagnostic performance of LN-sum and conventional MDCT staging.[37] Therefore, the present study is the first to demonstrate significant correlations between LN-sum and the N stage of gastric cancer and show the better diagnostic performance of this approach than conventional MDCT N staging. Additionally, it is worth verifying whether it can be applied to the nodal stage of other primary tumours.

The standard care of adjuvant treatment for potentially curable gastric cancer in Asia involves postoperative adjuvant chemotherapy after D2 surgery; however, the survival benefits from radical gastrectomy with or without postoperative adjuvant chemotherapy are still limited and unsatisfactory, particularly in gastric cancer patients with stage III disease.[38] Thus, several clinical trials are in progress even in East Asia to show the superiority of neoadjuvant chemotherapy over postoperative adjuvant chemotherapy for gastric cancer patients with clinical stage III disease.[39] In particular, in many European centres, perioperative chemotherapy for high-risk gastric cancer is regarded the standard treatment for high-risk gastric cancer based primarily on the results of three large, randomised trials: the UK-MAGICAL Trial,[40] the French FNCLCC/FFCD phase III trial,[41] and the European Organization for Research and Treatment of Cancer Randomized Trial 4095442.[42] Thus, it is necessary to identify gastric cancer patients who are at a high risk of recurrence and provide neoadjuvant or perioperative chemotherapy to these patients. In addition, results of recent clinical trials on neoadjuvant chemotherapy followed by gastrectomy were shown to be effective in the gastric cancer patients with extensive lymph node metastasis.[15–17] In this regard, the use of LN-sum may be of value to oncologists and surgeons by providing more accurate information, thereby allowing selection of the appropriate treatment.

This study has several limitations. First, due to the retrospective study design, there may have been a potential risk of selection bias. Second, even though the cut-off LN-sum of 23.5 mm for diagnosing N3 stage was internally validated, the study results need to be validated in a larger patient population and prospective design.

Third, the positive LNs recognised on MDCT could not be matched one-by-one with the surgically removed LNs. Fourth, the reproducibility of lymph node size measurement between reviewers was not evaluated. Therefore, future studies of reproducibility are needed to establish the usefulness of LN-sum in gastric cancer patients. Fifth, the present study only included patients with gastric cancers that were T2 or higher stages. Thus, the observations made might not be directly applicable to early gastric cancer; however, preoperative diagnosis of N stage may be more appropriate for T2 or higher than T1 because the "NCCN Guidelines for Gastric Cancer" in 2013 recommended preoperative treatment for gastric cancer of T2 or higher.[43] Sixth, inclusion of preoperative CT imaging acquired with three different scanners may have an impact on the measurement of the diameter of the LN. Seventh, LN-sum was not statistically different from conventional MDCT staging for discriminating N0–1 versus N2–3. Although, as mentioned earlier, neoadjuvant therapy has been reported to be an useful treatment for extensive LN metastasis, neoadjuvant therapy can be more effectively targeted and unnecessary neoadjuvant therapy can be avoided, allowing appropriate surgical treatment If LN-sum is more successful in accurately differentiating early N stage (N0–1) versus advanced N stage (N2–3) than conventional MDCT. This is a shortcoming considering implications regarding treatment selection and further studies will be needed. Finally, the correlation between LN-sum and prognosis was not assessed in the present study. The finding that LN-sum indirectly represents the pathological nodal status of gastric cancer means that it is closely related with prognosis, although it would be better to prove a direct correlation between LN-sum and survival rates. Therefore, further studies will be required to investigate the correlation between LN-sum and prognosis in AGC patients.

In conclusion, LN-sum may show better diagnostic accuracy for N3 gastric cancer in comparison with

conventional MDCT staging, which may then facilitate identification of high-risk patients and selection of appropriate candidates for alternative treatments such as neoadjuvant chemotherapy.

Conflict of interest

The authors declare no conflict of interest.

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