Diagn Interv Radiol 2017; 23:257–262

ABDOMINAL IMAGING

ORIGINAL ARTICLE

CT volumetry can potentially predict the local stage for gastric cancer after chemotherapy

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PURPOSE
We aimed to evaluate the value of CT tumor volumetry for predicting T and N stages of gastric cancer after chemotherapy, with pathologic results as the reference standard.

METHODS
This study retrospectively evaluated 42 patients diagnosed with gastric cancer, who underwent chemotherapy followed by surgery. Pre- and post-treatment CT tumor volumes (V_T) were measured in portal venous phase and volume reduction ratios were calculated. Correlations between pre- and post-treatment V_T, reduction ratio, and pathologic stages were analyzed. Receiver operator characteristic (ROC) analyses were also performed to assess diagnostic performance for prediction of downstaging to T0–2 stage and N0 stage.

RESULTS
Pretreatment V_T, post-treatment V_T, and V_T reduction ratio were significantly correlated with T stage (r_s=0.329, r_s=0.546, r_s= -0.422, respectively). Post-treatment V_T and V_T reduction ratio were significantly correlated with N stage (r_s=0.442 and r_s= -0.376, respectively). Pretreatment V_T, post-treatment V_T, and V_T reduction ratio were significantly different between T0–2 and T3,4 stage tumors ($P = 0.05$, $P < 0.001$, and $P = 0.002$, respectively). The differences between N0 and ≥N1 groups were also statistically significant ($P = 0.005$ for post-treatment V_T, $P = 0.016$ for V_T reduction ratio, respectively). The area under the ROC curve (AUC) for identification of T0–2 groups was 0.70 for pretreatment V_T, 0.88 for post-treatment V_T, and 0.82 for V_T reduction ratio, respectively. AUC was 0.78 for post-treatment V_T and 0.74 for V_T reduction ratio for identification of N0 groups.

CONCLUSION
CT tumor volumetry, particularly post-treatment measurement of V_T, is potentially valuable for predicting histopathologic T and N stages after chemotherapy in patients with gastric cancer.

Gastric cancer is the fifth most common malignancy in the world, and about half of the cases in the world occur in Eastern Asia, mainly in China (1–3). Complete tumor excision of the tumor is the first-line therapy for gastric cancer (4). However, even after potentially curative resection with satisfactory safety margins, the prognosis of patients with locally advanced gastric cancer is still worrying. Consequently, adjuvant and neoadjuvant therapies are now increasingly used in conjunction with surgery for locally advanced gastric cancer, which can significantly downstage the tumor, improve R0 resection rate, progression-free survival, and overall survival (5, 6).

The accurate evaluation of preoperative TNM staging of gastric cancer is essential for selecting the optimal treatment method and predicting prognosis (7). Lu et al. (8) reported that depth of invasion, lymph node metastasis stage, metastatic lymph node ratio, lymphatic invasion, and tumor size were independent predictors of prognosis in gastric cancer patients who underwent radical surgery (R0 resection). Shiraishi et al. (9) demonstrated that serosal invasion, extragastric lymph node metastasis, and liver metastasis were independent prognostic factors in patients with large gastric cancer. Endoscopic ultrasonography (EUS) and CT are currently the main methods of staging gastric cancer. EUS has been in use since the 1980s and is reported to have high T staging accuracy. CT has a great advantage on the evaluation of T stage and is considered the best modality for the staging of gastric cancer, as it can perform

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Received 14 November 2016; revision requested 4 December 2016; last revision received 16 March 2017; accepted 18 March 2017.

DOI 10.5152/dir.2017.16517

You may cite this article as: Wang ZC, Wang C, Ding Y, Ji Y, Zeng MS, Rao SX. CT volumetry can potentially predict the local stage for gastric cancer after chemotherapy. Diagn Interv Radiol 2017; 23:257–262.

noninvasive assessment of local extension of tumor, nodal disease, and metastases. However, studies have shown that EUS and CT demonstrate inaccuracy in identifying T and N stages of gastric cancer after neoadjuvant chemotherapy by visual assessment (10–12). Yoshikawa et al. (12) reported overall accuracy, underdiagnosis, and overdiagnosis rates CT as 42.7%, 10.7%, and 46.7%, respectively, for T-staging of gastric cancer after neoadjuvant chemotherapy. They suggested that T-staging by CT after neoadjuvant chemotherapy should not be considered in clinical decision-making. More recently, studies reported that tumor volume measurement could provide useful information for preoperative staging (13), assessment of response to neoadjuvant chemotherapy (14), and predicting prognosis of gastric cancer (15). Tumor volume reduction rates were significantly correlated with histopathologic grades of tumor regression in gastric cancer patients with a tumor volume reduction rate of 35.6% or higher (14). In primary rectal carcinoma, initial tumor volume (50 cm^3 or smaller) was reported to be helpful in predicting ypT0–2 tumor (confined to the rectal wall) after chemoradiotherapy (16), but little is known concerning gastric cancer.

The aim of our study was to evaluate whether CT volumery (pre- and postchemotherapy tumor volumes and reduction rate of tumor volume) of gastric cancer can aid in assessing T and N stages after chemotherapy, by using histologic results as the reference standard.

Methods

Patients

This study retrospectively evaluated 51 consecutive patients diagnosed with gastric cancer and stratified for preoperative chemotherapy at our institution from January 2009 to March 2014. The research was performed according to the World Medical Association Declaration of Helsinki. Formal consent was not required as this is a retrospective study. The inclusion criteria were as follows: 1) biopsy-confirmed gastric cancer by gastroscopy examination; 2) availability of contrast-enhanced CT scan before and after preoperative chemotherapy followed by surgery; 3) locally advanced gastric cancer (cT3,4 and/or cN[+]) without distant metastasis assessed by prechemotherapy CT scans. Eight of 51 patients were excluded from the study because pretreatment CT was performed in other hospitals, and one patient who did not undergo surgery was excluded because of distant metastasis (liver and lung) after chemotherapy. The final study group comprised 42 patients (age range, 31–75 years; median age, 56.7 years): 31 men (median age, 59.1 years) and 11 women (median age, 49.7 years).

CT acquisition

Contrast-enhanced CT of the stomach was performed as part of the routine abdomen CT protocol. Each patient received 800 mL of water orally approximately 20 min before scanning. An additional 200 mL was given immediately prior to CT scan. CT scans were conducted with a tube voltage of 120 kVp using multislice CT equipment (Siemens Somatom Sensation 16, Somatom Sensation 64, Somatom Defenition AS or Somatom Definition Flash, Siemens Healthcare; GE Lightspeed VCT 64, GE Healthcare). Images were obtained in the arterial phase (30–35 s) and portal-venous phase (80 s) covering the entire stomach after injecting 100 mL nonionic contrast material (300 mgI/mL) at a rate of 3–5 mL/s using a power injector. The portal venous phase CT images at 5 mm thickness were used for volumetric analysis.

CT volumetry

The portal venous phase CT images were evaluated on a picture archiving and communication system and were analyzed by one reader with 3 years of abdominal CT experience (S.X.R) who blinded to the final histologic stage of gastric cancer. The reader measured the whole tumor volume by manually tracing the tumor boundaries for each tumor-containing axial slice shown in Fig. 1. The region of interest (ROI) included the entire tumor or thickness of the gastric wall if there was no clear plane of separation between the gastric cancer and gastric wall. Perigastric lymph nodes, vessels, and adjacent viscera were excluded. Whole-tumor volume was then calculated by multiplying each cross-sectional area by section thickness (5 mm). The pretreatment tumor volume (V_T) and post-treatment V_T were measured independently and in random order. Finally, the reader determined (a) pretreatment V_T; (b) post-treatment V_T; (c) V_T reduction; and (d) V_T reduction ratio, which was calculated as follows: $(V_{Tpre}–V_{Tpost}) \times 100/V_{Tpre}$, where V_{Tpre} is pretreatment V_T and V_{Tpost} is post-treatment V_{Tpost}.

TNM staging

All patients underwent surgical resection. All resected gastric tumors were analyzed by one pathology expert (Y.J. with 18 years of experience), who was blinded to CT information. The pathologic stage of gastric cancer was determined according to TNM staging criteria by the AJCC guidelines, 7th edition (17).

Statistical analysis

All statistical analyses were performed using the MedCalc version 12.1.4 (MedCalc software). V_T, V_T reduction, and V_T reduction ratio were correlated with different T-stages

Main points

- Accurate restaging of gastric cancer after chemotherapy by imaging is important for determining appropriate treatment.
- CT tumor volumetry correlated well with the histopathologic T and N stages of gastric cancer after chemotherapy.
- CT tumor volumetry could potentially identify T0–2 stage and ≥N1 stage following chemotherapy.
- CT tumor volumetry provided useful adjunct information for gastric cancer restaging.

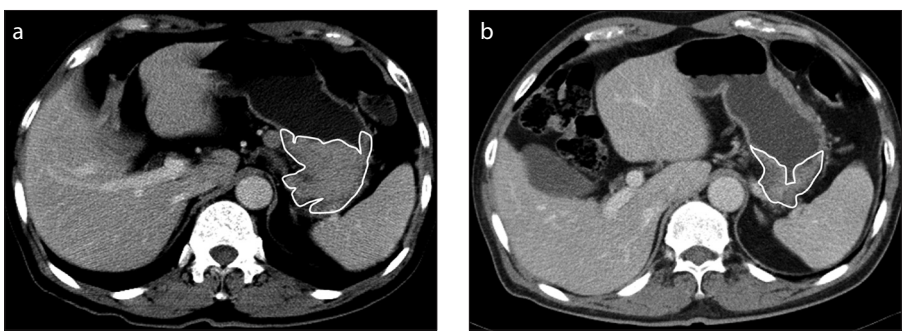

Figure 1. a, b. Contrast-enhanced axial CT images of portal venous phase before treatment **(a)** and after treatment **(b)** show examples of manual tracing of free-hand ROIs *(white outline)* for determination of the sectional area of gastric cancer. Sectional areas were multiplied by section thickness to calculate the whole tumor volume.

Table 1. Median tumor volumes and correlations between CT volumetry and post-chemotherapy pathologic stages

	T stage						
	T0	T1	T2	T3	T4	r_s (95% CI)	*P*
Pretreatment V_T (mL)	32.5 (14.6–33.3)	23.1 (13.8–44.4)	44.7 (19.9–68.1)	48.9 (14.0–163.5)	57.3 (13.2–184.0)	0.33 (0.03–0.58)	0.033
Post-treatment V_T (mL)	7.4 (0.1–8.1)	9.7 (6.7–12.0)	19.2 (0.1–21.6)	29.6 (11.0–119.4)	30.5 (15.9–212.7)	0.55 (0.29–0.73)	<0.001
V_T reduction ratio (%)	77.3 (44.8–99.9)	58.0 (41.8–79.9)	54.3 (21.9–72.3)	37.8 (5.7–64.7)	30.7 (-95.8–58.7)	-0.42 (-0.64 to -0.14)	0.005
	N stage						
	N0	N1	N2	N3	r_s (95% CI)	*P*	
Pretreatment V_T (mL)	33.3 (13.7–75.3)	24.2 (17.9–163.4)	89.9 (28.1–184.1)	46.2 (13.2–139.7)	0.19 (-0.12 to 0.47)	0.23	
Post-treatment V_T (mL)	12.0 (0.1–62.4)	21.6 (8.1–76.9)	30.3 (10.4–119.4)	39.2 (9.9–212.7)	0.44 (0.16–0.66)	0.003	
V_T reduction ratio (%)	59.3 (17.1–99.9)	56.9 (24.9–78.7)	41.8 (-95.7 to 56.3)	29.7 (-52.2 to 60.1)	-0.38 (-0.61 to -0.08)	0.014	

Data are presented as median (range).
r_s, Spearman's correlation coefficient; 95% CI, 95% confidence interval; V_T, tumor volume.

Table 2. Pre- and post-treatment V_T and V_T reduction ratio between T0–2/N0 groups and T3,4/≥N1 groups

	T stage			N stage		
Volume (mm^3)	T0–2 (n=11)	T3,4 (n=31)	*P*	N0 (n=13)	≥N1 (n=29)	*P*
Pretreatment	32.5 (13.8–68.1)	48.1 (13.2–184)	0.05	33.3 (13.8–75.3)	48.1 (13.21–184)	0.23
Post-treatment	10.5 (0.01–21.6)	30.5 (8.1–212.7)	<0.001	12.0 (0.01–62.4)	30.5 (8.1–212.7)	0.005
Reduction ratio	57.3 (21.9–99.9)	30.8 (-95.7 to 78.8)	0.002	57.3 (17.1–99.9)	33.0 (-95.7 to 78.8)	0.016

Data are presented as median (range).
V_T, tumor volume.

and N-stages using the Spearman's rank correlation test (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). Mann-Whitney U test was performed to assess differences between V_T, V_T reduction, and V_T reduction ratio of different T-stages (T0–2 vs. T3,4) and N-stages (N0 vs. N≥1). Receiver-operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of significant parameters for prediction of T stage and N stage.

Results

The tumors were located on the fundus/cardia in 8 patients (19.1%), corpus including the lesser curvature and the greater curvature in 16 patients (38.1%), antrum in 15 patients (35.7%), and pylorus in 3 patients (7.1%). Three patients (7.2%) were diagnosed with T0 stage, 4 patients (9.5%) with T1 stage, 4 patients (9.5%) with T2 stage, 8 patients (19%) with T3 stage, and 23 patients (54.8%) with T4 stage; as for N stage, 13 patients (31%) were diagnosed with N0 stage, 5 patients (11.9%) with N1 stage, 4 patients (9.5%) with N2 stage, and 20 patients (47.6%) with N3 stage.

Pretreatment V_T, post-treatment V_T, and V_T reduction ratio were significantly correlated with the histopathologic T stage. Correlation was highest for post-treatment V_T (spearman's correlation coefficient, r_s=0.546, $P < 0.001$), followed by V_T reduction ratio (r_s= -0.422, P = 0.005) and pretreatment V_T (r_s=0.329, P = 0.033). However, V_T reduction was not significantly correlated with the histopathologic T stage (r_s= -0.134, P = 0.40). Post-treatment V_T and V_T reduction ratio were significantly correlated with the histopathologic N stage (r_s=0.442, P = 0.003 and r_s= -0.376, P = 0.014, respectively), while pretreatment V_T and V_T reduction were not (r_s=0.189, P = 0.23 and r_s=-0.164, P = 0.30, respectively). Details of the results are presented in Table 1.

Eleven patients were classified as T0–2 group and 31 were classified as T3,4 group. Pretreatment V_T, post-treatment V_T, V_T reduction, and V_T reduction ratio between T0–2 and T3,4 groups are listed in Table 2. Pre- and post-treatment V_T values were both significantly smaller in T0–2 group than in T3,4 group (P = 0.05 for pretreatment V_T and $P < 0.001$ for post-treatment V_T, respectively). V_T reduction ratio was also significantly different between the two groups (P = 0.002). In addition, ROC curve analyses were performed to determine the predictive performance of volumetric parameters for differentiating T0–2 from T3,4 groups. The area under the ROC curve (AUC) value was largest in post-treatment V_T (AUC= 0.884), followed by V_T reduction ratio (AUC = 0.818) and the pretreatment V_T (AUC = 0.701) for identification of T0–2 (Fig. 2). For assessment of T0–2 stage, sensitivity and specificity were 63.6% and 67.7% for pretreatment V_T, 72.7% and 90.3% for post-treatment V_T, and 72.7% and 83.9% for V_T reduction ratio.

Post-treatment V_T and V_T reduction ratio were significantly different between N0 and N≥1 groups (P = 0.005 and P = 0.016, respectively). However, pretreatment V_T was not significantly different between the two groups (P = 0.23). Comparison of volumetric parameters between N0 and N≥1 groups are shown in Table 2. AUC value was largest in post-treatment V_T (AUC=0.78, $P < 0.001$), followed by V_T reduction ratio (AUC=0.74, P = 0.010) for identification of N0 groups (Fig. 3). A post-treatment V_T of 27.52 mL predicted N0 stage with 92.31% sensitivity, 58.62% specificity; a 51.39% V_T reduction ratio predicted N0 stage with 61.54% sensitivity,

Table 3. Diagnostic performance of whole tumor CT volumetry in predicting ≤T2 stage and N0 stage by ROC analysis

	AUC (95% CI)	Cutoff values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
≤T2 stage							
Pretreatment V_T	0.70 (0.54–0.83)	≤33.3 mm^3	63.6 (7/11)	67.7 (21/31)	41.2 (7/17)	84.0 (21/25)	66.7 (28/42)
Post-treatment V_T	0.88 (0.75–0.96)	≤12.0 mm^3	72.7 (8/11)	90.3 (28/31)	72.7 (8/11)	90.3 (28/31)	85.7 (36/42)
V_T reduction ratio	0.82 (0.67–0.92)	>51.4%	72.7 (8/11)	83.9 (26/31)	61.5 (8/13)	89.7 (26/29)	81.0 (34/42)
N0 stage							
Pretreatment V_T	0.62 (0.46–0.76)	≤33.3 mm^3	53.9 (7/13)	65.5 (19/29)	41.2 (7/17)	76 (19/25)	61.9 (26/42)
Post-treatment V_T	0.78 (0.62–0.89)	≤27.5 mm^3	92.3 (12/13)	58.6 (17/29)	50 (12/24)	94.4 (17/18)	69.1 (29/42)
V_T reduction ratio	0.74 (0.58–0.86)	>51.4%	61.5 (8/13)	82.8 (24/29)	61.5 (8/13)	83.7 (24/29)	76.2 (32/42)

Cutoff values were chosen according to the point nearest to the upper left corner in the ROC curves.
ROC, receiver operating characteristic; AUC, area under the ROC curve; V_T, whole tumor volume; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value.

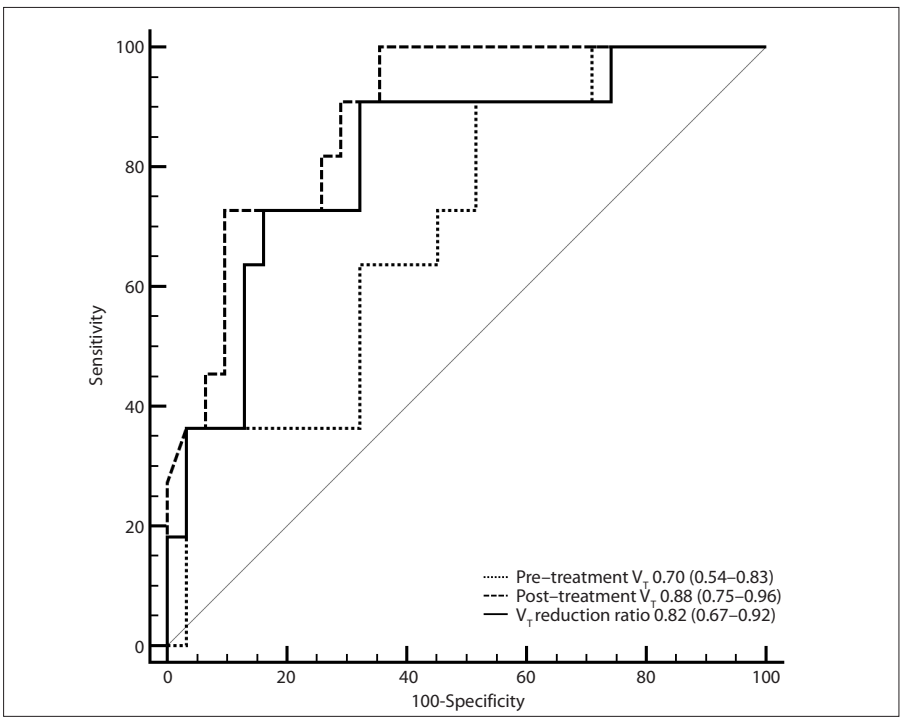

Figure 2. Graph displaying receiver operating characteristic (ROC) curves and area under the curve (AUC) of pretreatment tumor volume (V_T), post-treatment V_T, and V_T reduction ratio for identification of T0–2 tumors. Data are presented as AUC (95% confidence interval).

82.76% specificity. Corresponding sensitivity, specificity, NPV, PPV, and accuracy data are provided in Table 3.

Discussion

Our study showed that CT tumor volumetry of gastric cancer was significantly correlated with T stages (r_s up to 0.55 for post-treatment V_T) and N stages (r_s up to 0.44 for post-treatment V_T) using pathologic findings as reference standard. We showed that volumetry was useful for prediction of T0–2 stage (AUC, 0.70–0.88) and N0 stage (AUC, 0.62–0.78).

In order to improve the imaging assessment of local stage of gastric cancer after chemotherapy, we need to have an additional quantifiable measurement that can be combined with morphologic criteria. Kikuchi et al. (18) suggested that staging system based on tumor volume measured from continuous tissue sections by the surface rendering method after surgery may have advantages over conventional staging systems for gastric cancer. Previously published data showed that tumor volume measured by CT is also feasible and reproducible, which could provide useful adjunct information for TNM staging of gastric cancer (13). They demonstrated that CT volumetry correlated well with T and N stages for gastric cancer without preoperative treatment with an AUC of 0.89 for ≥T2 stage and 0.75 for ≥N1 stage. Lee et al. (14) reported that diagnostic accuracy of post-chemotherapy CT by visual assessment was only 33.3% (11/33) for T staging and 51.5% (17/33) for N staging. However, the percentage CT volume reduction rate correlated well with the histopathologic grades of regression after neoadjvant chemotherapy. Optimal cutoff value for volume reduction rate was determined as 35.6%, yielding a sensitivity of 100% (16/16) and a specificity of 58.8% (10/17).

In theory, after chemotherapy, viable tumor decreases and fibrotic tissue develops within the tumor. Differentiating fibrotic tissue from tumor on CT remains difficult. Chemotherapy-associated fibrosis around the tumor may mimic tumor infiltration. So T0–2 tumor with peritumoral fibrosis after chemotherapy is sometimes overstaged as T3,4 tumor on CT. Our findings show that CT volumetry, mainly post-treatment volume of tumor, has potential value for local staging; sensitivity and specificity of post-treatment V_T are 72.7% and 90.3% for predicting T0–2 stages and 92.31% and 58.62% for predicting N0 stage. A possible explanation could be that gastric tumors with larger volume have an increased likelihood of tumor invasion. We also found that prechemotherapy tumor volume has potential value for prediction of T0–2 tumors, which requires further study. Prediction of treatment response before chemotherapy would be beneficial as it may allow for further treatment optimization.Accurate determination of T0–2 tumor (depth of invasion into the gastric wall) provides prognostic informa-

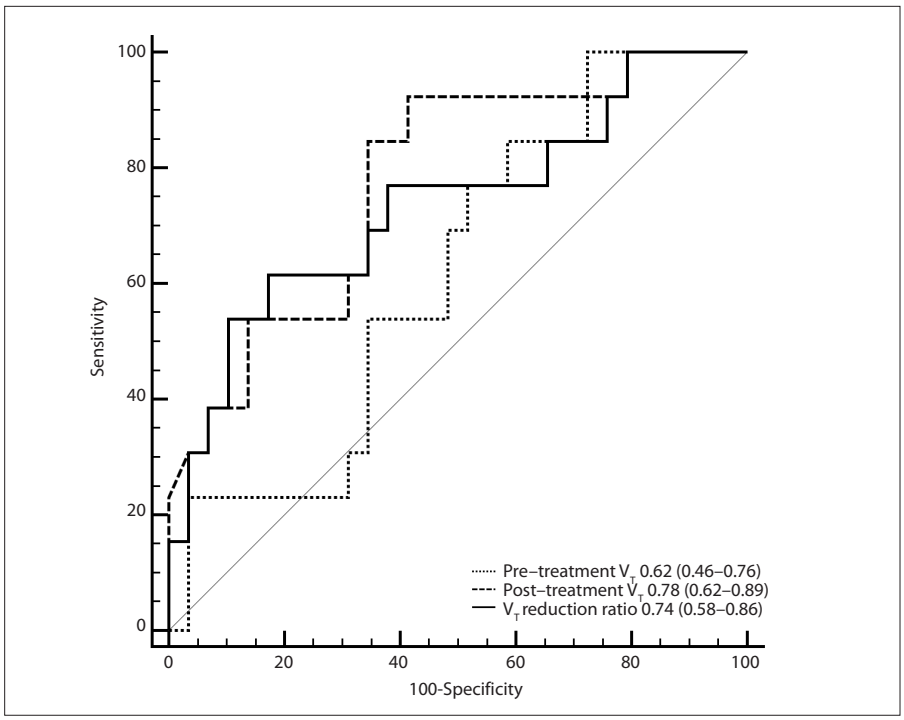

Figure 3. Graph displaying ROC curves and AUC of pretreatment tumor volume (V_T), post-treatment V_T and V_T reduction ratio for determination of N0 stage. Data are presented as AUC (95% confidence interval).

tion, as it shows better survival compared with T3,4 tumor (19). However, accurate prediction of T0–2 tumors is not enough, as it is also crucial to be able to accurately predict N0 lesions in these patients. Studies reported that tumor volume from pathology had potential value for predicting metastasis of lymph node both for early and advanced gastric cancer (20–22). However, our study showed relatively low accuracy for differentiating malignant lymph nodes and no relationship was found between prechemotherapy volumetry and metastasis to lymph nodes. This might be due to small sample size and low rate of complete response of metastatic lymph nodes. Li et al. (23) demonstrated that tumor volume of resectable adenocarcinoma of the esophagogastric junction measured by CT was associated with regional lymph node metastasis and N stage.

In clinical practice, response is typically mainly assessed using response evaluation criteria in solid tumors (RECIST 1.1), which measures changes in the longest axial tumor diameter (24). However, infiltrative gastric cancer always shows a tumor circumferentially involving the gastric wall, whose longest diameter cannot be defined on axial images, making it nonmeasurable. Furthermore, Beer et al. (25) reported that CT volumetry could predict the response to neoadjuvant chemotherapy in patients with adenocarcinoma of the esophagogastric junction, while the classic approach of tumor diameter measurement could not.

There are several limitations in our study. First, the number of our patients was small and there was a relatively lower proportion of T0–2, N1, and N2 stage tumors in the study group with a predominance of T4 and N3 stage tumors. Second, technical factors such as some patients' poor demarcation between gastric tumor and tissue, may affect the slice choice; manual tracing for the calculation of volume of gastric tumor might be subjective and confusing, particularly for post-treatment V_T, because post-chemotherapy fibrosis within or around the tumor mimics tumor infiltration and is responsible for post-treatment V_T. Third, CT volumetry is time-consuming, requiring an additional 10–20 minutes per patient to manually trace the tumor boundaries on the axial images. Finally, we performed CT using 5 mm slice thickness in our routine clinical practice, which might affect volume calculations of small tumors (26).

In conclusion, we have identified that CT tumor volumetry analysis of gastric cancer, particularly post-treatment V_T and V_T reduction ratio, yields moderate correlation with the histopathologic T stage and N stage, and could be used to predict histopathologic stage by obtaining appropriate cutoff values. Further studies with a larger number of patients are needed to confirm our findings.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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