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

Zhi-Cong Wang
Chen Wang
Ying Ding
Yuan Ji
Meng-Su Zeng
Sheng-Xiang Rao

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 (VT) were measured in portal venous phase and volume reduction ratios were calculated. Correlations between pre- and post-treatment VT 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 VT, post-treatment VT, and VT reduction ratio were significantly correlated with T stage (r = 0.329, r = 0.546, r = -0.422, respectively). Post-treatment VT and VT reduction ratio were significantly correlated with N stage (r = 0.442 and r = -0.376, respectively). Pretreatment VT, post-treatment VT, and VT 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 VT, P = 0.016 for VT reduction ratio, respectively). The area under the ROC curve (AUC) for identification of T0–2 groups was 0.70 for pretreatment VT, 0.88 for post-treatment VT, and 0.82 for VT reduction ratio, respectively. AUC was 0.78 for post-treatment VT, and 0.74 for VT reduction ratio for identification of N0 groups.

CONCLUSION
CT tumor volumetry, particularly post-treatment measurement of VT, 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). Shiraiishi 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
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 cm³ 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 volumetry (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 Definition 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.

Statistical analysis

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).

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. 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.
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 Vₚ, Vₛ reduction, and Vₛ 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 Vₛ post-treatment Vₛ and Vₛ reduction ratio were significantly correlated with the histopathologic T stage. Correlation was highest for post-treatment Vₛ (Spearman’s correlation coefficient, rₛ=0.546, P<0.001), followed by Vₛ reduction ratio (rₛ=-0.422, P=0.005) and pretreatment Vₛ (rₛ=0.329, P=0.033). However, Vₛ reduction was not significantly correlated with the histopathologic T stage (rₛ=-0.134, P=0.40). Post-treatment Vₛ and Vₛ reduction ratio were significantly correlated with the histopathologic N stage (rₛ=0.442, P=0.003 and rₛ=-0.376, P=0.014, respectively), while pretreatment Vₛ and Vₛ reduction were not (rₛ=0.189, P=0.23 and rₛ=-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 Vₛ post-treatment Vₛ and Vₛ reduction ratio between T₀–2 and T₃,₄ groups are listed in Table 2. Pre- and post-treatment Vₛ values were both significantly smaller in T₀–2 group than in T₃,₄ group (P=0.05 for pretreatment Vₛ and P<0.001 for post-treatment Vₛ, respectively). Vₛ 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 Vₛ (AUC=0.884, followed by Vₛ reduction ratio (AUC =0.818) and the pretreatment Vₛ (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 Vₛ, 72.7% and 90.3% for post-treatment Vₛ, and 72.7% and 83.9% for Vₛ reduction ratio.

Post-treatment Vₛ and Vₛ reduction ratio were significantly different between N₀ and N≥₁ groups (P =0.005 and P =0.016, respectively). However, pretreatment Vₛ 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 Vₛ (AUC=0.78, P<0.001), followed by Vₛ reduction ratio (AUC=0.74, P=0.010) for identification of N₀ groups (Fig. 3). A post-treatment Vₛ of 27.52 mL predicted N₀ stage with 92.31% sensitivity, 58.62% specificity; a 51.39% Vₛ reduction ratio predicted N₀ stage with 61.54% sensitivity.

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

<table>
<thead>
<tr>
<th>T stage</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>rₛ (95% CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Pretreatment Vₛ (mL)</td>
<td>32.5 (14.6–33.3)</td>
<td>23.1 (13.8–44.4)</td>
<td>44.7 (19.9–68.1)</td>
<td>48.9 (14.0–163.5)</td>
<td>57.3 (13.2–184.0)</td>
<td>0.33 (0.03–0.58)</td>
<td>0.033</td>
</tr>
<tr>
<td>Post-treatment Vₛ (mL)</td>
<td>7.4 (0.1–8.1)</td>
<td>9.7 (6.7–12.0)</td>
<td>19.2 (0.1–21.6)</td>
<td>29.6 (11.0–119.4)</td>
<td>30.5 (15.9–212.7)</td>
<td>0.55 (0.29–0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vₛ reduction ratio (%)</td>
<td>77.3 (44.8–99.9)</td>
<td>58.0 (41.8–79.9)</td>
<td>54.3 (21.9–72.3)</td>
<td>37.8 (5.7–64.7)</td>
<td>30.7 (95.8–58.7)</td>
<td>-0.42 (-0.64 to -0.14)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Data are presented as median (range). rₛ, Spearman’s correlation coefficient; 95% CI, 95% confidence interval; Vₛ, tumor volume.

### Table 2. Pre- and post-treatment Vₛ and Vₛ reduction ratio between T₀–2/N₀ groups and T₃,₄/N≥₁ groups

<table>
<thead>
<tr>
<th>Volume (mm³)</th>
<th>T0–2 (n=11)</th>
<th>T₃,₄ (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>32.5 (13.8–68.1)</td>
<td>48.1 (13.2–184)</td>
<td>0.05</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>10.5 (0.01–21.6)</td>
<td>30.5 (8.1–212.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reduction ratio</td>
<td>57.3 (21.9–99.9)</td>
<td>30.8 (95.7–78.8)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are presented as median (range). Vₛ, tumor volume.
Our study showed that CT tumor volumetry of gastric cancer was significantly correlated with T stages (r up to 0.55 for post-treatment Vₜ) and N stages (r up to 0.44 for post-treatment Vₜ) 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 neoadjuvant 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 Vₜ are 72.7% and 90.3% for predicting T0–2 stages and 92.3% and 58.6% 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 local staging; sensitivity and specificity of pre-treatment Vₜ are 72.7% and 90.3% for predicting T0–2 stages and 92.3% and 58.6% 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 information.
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 largest 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 non-measurable. Furthermore, Beer et al. (25) reported that CT volumetry could predict the response to neoadjuvant chemother-apy 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 Vₚ, because post-chemotherapy fibrosis within or around the tumor mimics tumor infiltration and is responsible for post-treatment Vₚ. 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 volumetry analysis of gastric cancer, particularly post-treatment Vₚ and Vₚ 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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