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ORIGINAL RESEARCH

The Correlation Between Computed Tomography Volumetry and Prognosis of Advanced Gastric Cancer Treated with Neoadjuvant Chemotherapy

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Purpose: To investigate the feasibility and utility of computer tomography (CT) volumetry in evaluating the tumor response to neoadjuvant chemotherapy (NAC) in advanced gastric cancer (AGC) patients.

Patients and Methods: One hundred and seventeen Patients with AGC who received NAC followed by R0 resection between January 2006 and December 2012 were included. Tumor volumes were quantified using OsiriX software. The volume reduction rate (VRR) was calculated as follows: VRR = [(pre-chemotherapy total volume) − (post-chemotherapy total volume)]/(pre-chemotherapy total volume) × 100%. The optimal cut-off VRR for differentiating favorable from unfavorable prognosis was determined by receiver operating characteristic (ROC) analysis. Overall survival was calculated using Kaplan-Meier analysis and values were compared using the Log-rank test. Multivariate analysis was determined by the Cox proportional regression model.

Results: The optimal cut-off VRR was 31.95% according to ROC analysis, with a sensitivity of 70.4% and a specificity of 71.7%. Based on the cut-off VRR, patients were divided into the VRR-High (VRR ≥ 31.95%, n = 63) and VRR-Low (VRR < 31.95%, n = 54) groups. The VRR-Low group exhibited a worse prognosis than that of the VRR-High group (HR, 2.85; 95% CI, 1.69–4.82, P < 0.001), with 3-year survival rates of 40.7% and 79.4%, and 5-year survival rates of 31.5% and 63.5%, respectively.

Conclusion: CT volumetry is a feasible and reliable method for assessing the tumor response to NAC in patients with AGC.

Keywords: advanced gastric cancer, neoadjuvant chemotherapy, computed tomography volumetry

Introduction

Gastric cancer is the third-leading cause of cancer-related mortality worldwide, accounting for about 754,000 deaths annually.[1] Although the 5-year overall survival (OS) rate of advanced gastric cancer (AGC) has improved from 23% to 40%, the prognosis of AGC remains unsatisfactory.[2–4] Neoadjuvant chemotherapy (NAC) is widely regarded as an effective multidisciplinary approach to AGC therapy, with evidence of improved survival of patients with AGC compared with surgery alone.[4–6] Furthermore, the adverse events associated with NAC in AGC were found to be tolerable and manageable, with a low perioperative morbidity.[5,7] However, the methods used in these studies to evaluate the tumor response to NAC were not well established and remain controversial.

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Computed tomography (CT) is a common procedure for assessing the clinical stage of gastric cancer due to its convenient and non-invasive nature. The Response Evaluation Criteria in Solid Tumors (RECIST) are one of the most widely used methods for evaluating the response to chemotherapy in various tumors.[8,9] According to the RECIST for gastric cancer, only lymph nodes with a short-axis diameter greater than 15 mm or other metastatic lesions (such as hepatic lesions) are considered target lesions;[9] primary gastric cancer lesions are deemed unsuitable targets because of their irregular shape, although the sensitivity and specificity of CT for detecting lymph node metastases vary in gastric cancer. One study reported a specificity of 99.8% and a positive predictive value of 98.6% for lymph nodes with a short-axis diameter greater than 15 mm; however, the sensitivity of this test was only 22.5%.[10] Accordingly, the utility of the RECIST for evaluating the tumor response to NAC in patients with AGC might be limited. The Japanese Classification of Gastric Carcinoma–Response Assessment of Chemotherapy for Gastric Cancer (JCGC criteria) is based on morphological changes in the primary lesions, as determined using barium X-ray or endoscopic examinations,[11] but it does not evaluate metastatic lesions such as lymph nodes. Furthermore, patients find the procedure inconvenient and are generally unwilling to undergo repeated endoscopic examinations.

Recent studies have suggested CT volumetry as a useful technique for tumor assessment in gastric cancer,[12,13] yielding significantly greater accuracy in predicting T and N_3 stages compared with conventional CT,[14] with post-chemotherapy tumor volumes significantly correlated with tumor stage in patients with gastric cancer.[13] Moreover, two small studies showed a significant association between CT volume reduction in primary gastric lesions after NAC and clinical outcomes.[15,16] Here, we sought to investigate the feasibility and utility of CT volumetry for evaluating the tumor response to NAC.

Patients and Methods

Ethics

Ethics approval for this study was obtained from the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. Patient consent was not required as this is a retrospective study. Patient data confidentiality was guaranteed. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Patient Selection

Patients with AGC who received NAC followed by R0 resection between January 2006 and December 2012 were considered for this study (Figure 1). The inclusion criteria were as follows: (1) pathologically confirmed gastric adenocarcinoma, (2) a primary tumor invading the serosa (T4a) or adjacent structures (T4b) with or without metastatic lymph nodes according to CT, (3) ambulatory males or females aged 18–80 years, (4) Eastern Cooperative Oncology Group score of 0–2, (5) life expectancy greater than 3 months, (6) and normal cardiac, hepatic, renal, and bone marrow function. The exclusion criteria included (1) distant metastasis (such as lymph nodes 13 and 16, liver, lung, brain, bone, and peritoneal metastases), (2) previous major stomach surgery, (3) previous cytotoxic chemotherapy, radiotherapy, target therapy, or immunotherapy for any tumor, (4) history of another malignancy except cured basal cell carcinoma of the skin and cured carcinoma in-situ of the uterine cervix, (5) and women who were pregnant, breastfeeding, or contemplating pregnancy.

NAC Regimen and Surgery

Chemotherapy regimens included XELOX (130 mg/m^2 oxaliplatin as a 2-hrs infusion on day 1, followed by 1000 mg/m^2 capecitabine twice daily for 14 consecutive days), FOLFOX (130 mg/m^2 oxaliplatin as a 2-hrs infusion, 400 mg/m^2 leucovorin, and a bolus of 400 mg/m^2 5-fluorouracil on day 1, followed by a 46-hrs infusion of 2400 mg/m^2 5-fluorouracil), and SOX (130 mg/m^2 oxaliplatin as a 2-hrs infusion on day 1, followed by S-1 given orally twice daily for 2 weeks). The dose of S-1 was 80 mg/day for a body surface area (BSA) <1.25 m^2, 100 mg/day for a BSA ≥ 1.25 to < 1.5 m^2, and 120 mg/day for a BSA ≥ 1.5 m^2. Chemotherapy was repeated every 3 weeks.

Surgery was performed after at least two cycles of chemotherapy. Distal, total gastrectomy, or combined resection was performed within 2 weeks after completion of the last cycle of NAC, depending on the location and extent of the primary tumor. D2 lymphadenectomy was conducted according to the criteria established by the Japanese Gastric Cancer Association.[17] Postoperative chemotherapy was initiated at 4–6 weeks after surgery. The yield pathological (yp) TNM stage was assessed according to the criteria of the AJCC TNM staging system, 7th edition.[18]

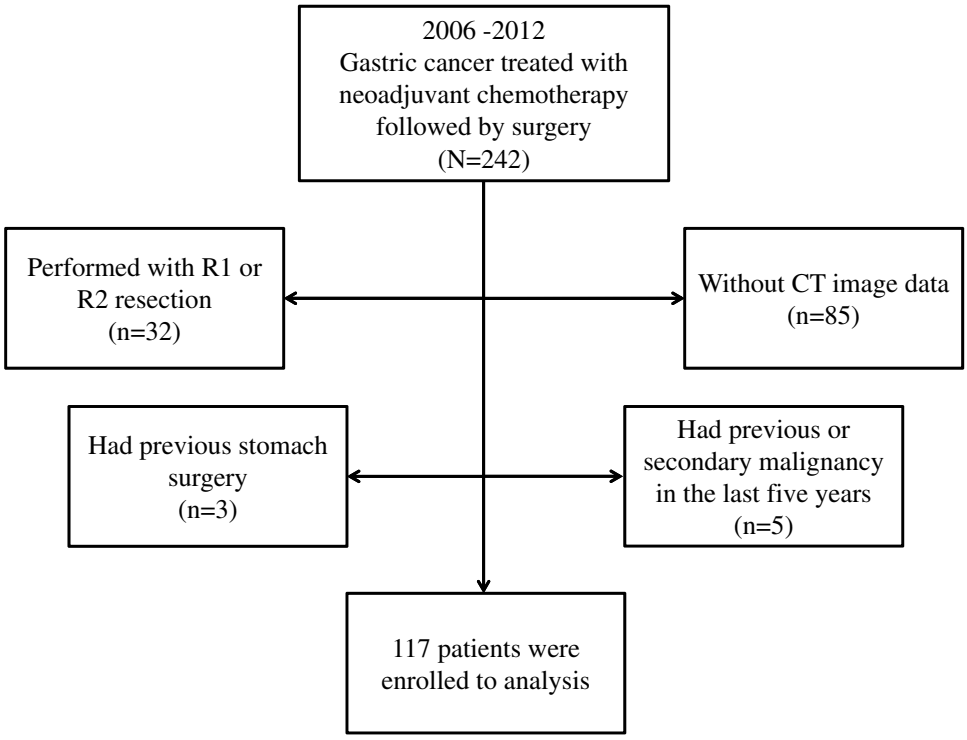

Figure 1 Flowchart shows the study enrollment. Of the 242 initial patients, 117 were finally included.

CT Acquisition and Analysis

A baseline CT workup was obtained up to 2 weeks prior to the initiation of NAC. For response evaluation, CT was also performed after completing at least two cycles of NAC.

Patient preparation included oral administration of 1000 mL water before CT. Patients were placed in the supine position and examined on a 16-row multi-slice spiral computed tomography (MDCT) scanner (Toshiba-MEC CT3; HiSpeed, GE Medical Systems) or a 64-row MDCT scanner (Brilliance 64, Philips Medical Systems). The scanning parameters used for 16-, and 64-row MDCT scanners were detector configuration of 16 × 0.75 mm and 64 × 0.625 mm, respectively, slice thickness of 5 mm, table speed of 15 and 40 mm/rotation, respectively, rotation time of 0.5 s, effective mAs of 200, tube voltage of 120 kVp, and matrix size of 512 × 512. The images of the portal venous phase were used for volume measurements. Volume measurement was performed using the CT image post-processing software OsiriX v7.5.1 (Pixmeo, Switzerland).

Measurable lesions were defined using the following criteria: primary lesion covering at least four consecutive CT scanning layers and measurable lymph nodes covering at least four CT scanning layers or those greater than 15 mm in the short-axis diameter at the maximum cross-section.

In the portal venous phase, the enclosed area along the edge of the primary tumor or lymph node was considered a region of interest (ROI, Figure 2). The ROI area was calculated automatically using OsiriX software. The volume of the target lesion was calculated by multiplying the slice thickness of the CT scan by the sum of each ROI area using the following formula:

$$V = \sum_{n=1}^{N} S_n \cdot D$$

(The layers of the target lesions covered in the CT scan were defined as N, the ROI area for each layer was defined as Sn, slice thickness was defined as D, and target lesion volume was defined as V).

The number of measurable lesions was limited to a maximum of total five. The total volume was calculated by summing the volumes of the primary lesion and target lymph nodes. The percentage volume reduction rate (VRR) was calculated using the following equation:

$$VRR = \left[\begin{pmatrix}\text{pre} - \text{chemotherapy total}\\ \text{volume}\end{pmatrix} - \begin{pmatrix}\text{post} - \text{chemotherapy total}\\ \text{volume}\end{pmatrix}\right] / (\text{pre} - \text{chemotherapy total volume}) \times 100\%$$

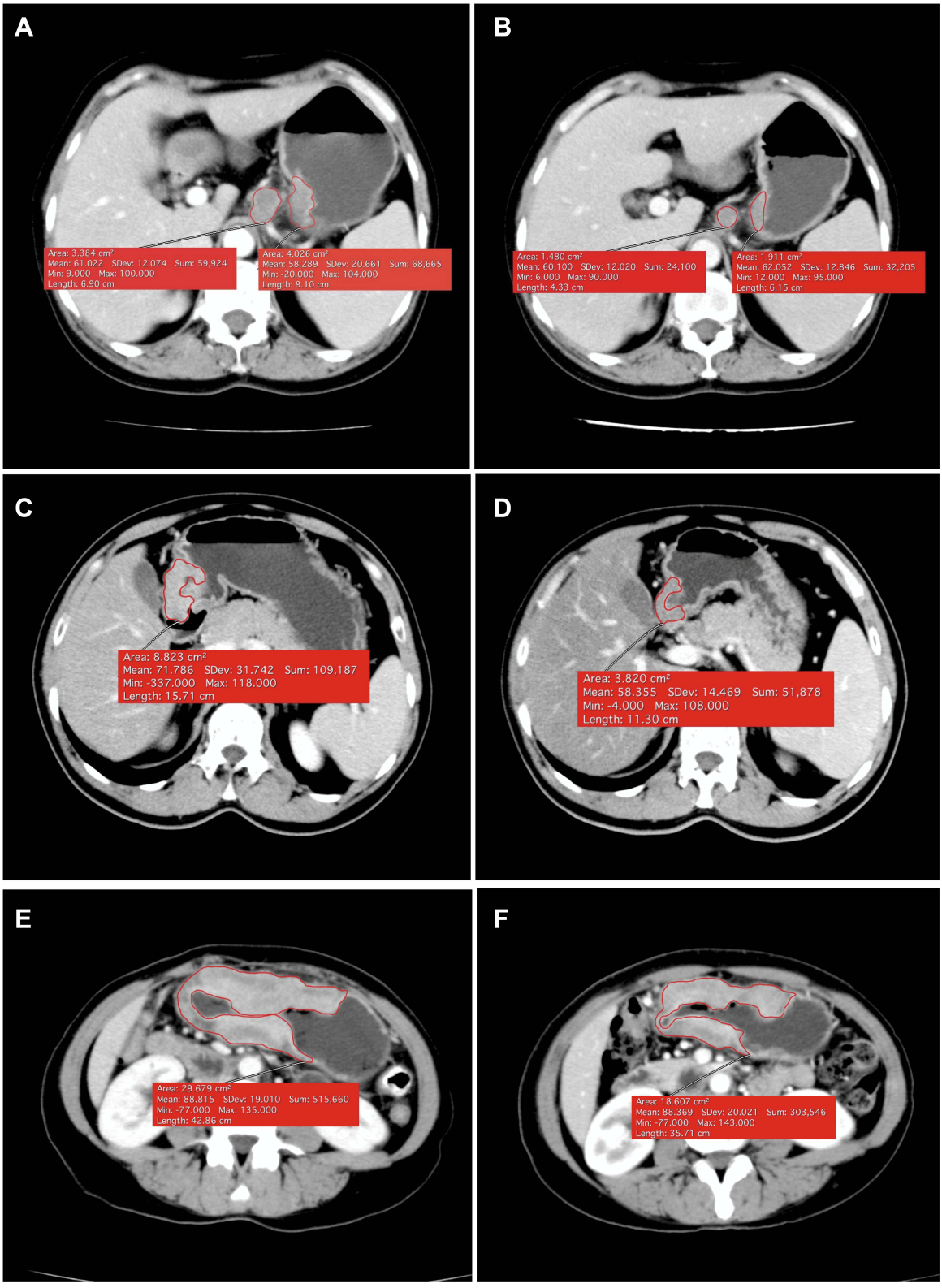

Figure 2 The CT volume measurement of the primary lesions and lymph node before and after neoadjuvant chemotherapy (NAC). Case 1: the total volume was 25.3 cm^3 (primary lesion 21.1 cm^3, the index lymph node 4.2 cm^3) before chemotherapy (**A**), and decreased to 15.0 cm^3 (**B**) after NAC (primary lesion 13.1 cm^3, the index lymph node 1.9 cm^3), the percentage volume reduction rate (VRR) was 40.7%. Case 2: the total volume was 68.6 cm^3 before chemotherapy (**C**), and decreased to 20.8 cm^3 (**D**) after NAC, the VRR was 69.7%. Case 3: the total volume was 171.9 cm^3 before chemotherapy (**E**), and decreased to 101.6 cm^3 (**F**) after NAC, the VRR was 40.9%.

Follow-Up

All patients returned for follow-up every 3–6 months for the first 2 years, every 6–12 months during years 3–5, and annually thereafter. Standard follow-up included complete blood count, chemistry profile, and tumor marker measurements and endoscopic and radiological imaging examinations (including CT, magnetic resonance imaging, and positron emission tomography-CT if necessary).

Statistical Analysis

Quantitative values, which were analyzed by the Mann–Whitney *U*-test, were expressed as means ± the standard deviation. Categorical variables were expressed as absolute and relative frequencies (count and percentage) by the $\chi 2$ test. Thirty patients were randomized to investigate the interobserver variability of the tumor volume. Volumetric measurements for these patients were independently performed by two experienced doctors. The data were compared using the Wilcoxon test and Spearman correlation analysis.

The diagnostic accuracy of VRR in predicting the prognosis of patients receiving NAC was evaluated by receiver operating characteristic (ROC) analysis. The optimal cut-off VRR for differentiating favorable from unfavorable prognosis was defined as the point on the ROC curve closest to the 0% false-positive and 100% true-positive mark. Patients who survived more than 3 years were considered to have had a favorable prognosis, and a survival of less than 3 years was considered an unfavorable prognosis. The area under the ROC curve and the corresponding 95% confidence interval (CI) were determined accordingly.

OS was defined as the time from the beginning of chemotherapy to death from any cause. Patients, who were alive or lost to follow-up on June 2, 2017 were censored for the analysis of OS. The Kaplan–Meier method was used for calculation of survival time, and the resulting survival curves were compared by the Log-rank test. Cox's proportional hazards model was used for multivariate analysis.

All statistical tests were two-sided, with P values ≤ 0.05 considered to indicate statistical significance. Statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

Results

Clinical and Pathological Characteristics

A total of 117 eligible patients, consisting of 83 males and 34 females, with a median age of 60 years (range 37–80 years) were included in this study. The chemotherapy regimen was FOLFOX in 49 (41.9%) patients, SOX in 45 (38.5%) patients, and XELOX in 23 (19.6%) patients. The median number of NAC cycles was 3 (range 2–6). The primary lesion was located in the upper, middle, and lower third of the stomach in 27 (23.1%), 34 (29.0%) and 54 (46.2%) patients, respectively. Multiple regions were involved in 2 (1.7%) patients. Fifty-three (45.3%) patients received distal gastrectomy, 57 (48.7%) received total gastrectomy, and 7 (6.0%) received combined resection. Following surgery, 100 (85.5%) patients received postoperative chemotherapy. According to the AJCC TNM staging system (7th edition), 9 (7.7%), 22 (18.8%), and 76 (64.9%) patients were categorized as stage I, II, and III, respectively. Five (4.3%) patients exhibited complete pathological tumor regression after NAC. Of the remaining 5 (4.3%) patients, who could not be classified, 3 were staged as ypT0N1M0 and 2 as ypT0N2M0.

Interobserver Variability

The tumor volumes before and after chemotherapy were independently assessed by two physicians. There were no significant differences between the two physicians in terms of the tumor volume before NAC (44.25 cm^3 vs 45.50 cm^3, $p = 0.43$), tumor volume after NAC (28.59 cm^3 vs 31.40 cm^3, $p = 0.14$) or the VRR (37.2% vs 33.6%, $p = 0.31$). Spearman correlation coefficients for tumor volume before NAC, tumor volume after NAC, and VRR were 0.94 ($p < 0.001$), 0.88 ($p < 0.001$), and 0.88 ($p < 0.001$) respectively, indicating significant reproducibility between the two observers.

CT Volumetry Analysis

Volumetric analysis revealed a mean tumor volume of 53.8 ± 32.6 cm^3 before NAC, which decreased to 35.9 ± 28.4 cm^3 after NAC ($p < 0.001$), with an area under the ROC curve of 0.76 (95% CI, 0.68–0.85). According to ROC analysis, the optimal cut-off VRR was 31.95%, with a sensitivity of 70.4% and a specificity of 71.7% (Figure 3). According to this cut-off level, patients were divided into the VRR-High (VRR $\geq$ 31.95%, n = 63) and VRR-Low group (VRR < 31.95%, n = 54).

The clinical characteristics, including sex, age, chemotherapy regimen, surgical procedure, and primary tumor site, were not significantly different between the VRR-High and VRR-Low groups (Table 1). The proportion of patients with pathological $T_{0\text{-}1}$ stage was 20.6% in the VRR-High group and 5.6% in the VRR-Low group. The proportion of patients with pathological N_0 stage was 36.5% in the VRR-High group and 11.1% in the VRR-Low group. In addition,

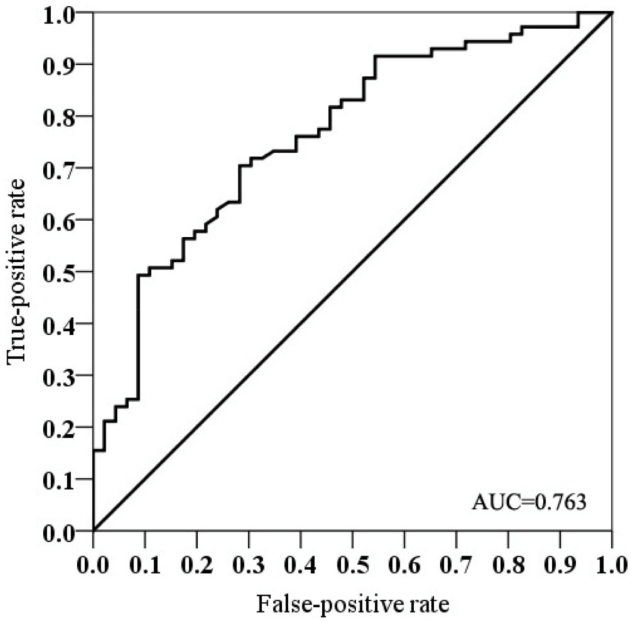

Figure 3 Receiver operating characteristic (ROC) analysis of the volume reduction rate (VRR). The area under the curve was 0.763. When the optimal cut-off level of VRR was determined to be 31.95%, a sensitivity of 70.4% and a specificity of 71.7% were achieved.

four patients in the VRR-High group exhibited complete pathological tumor regression after NAC, compared with only one patient in the VRR-Low group (Table 1).

Survival Analysis

The median follow-up interval was 53.0 months (range 7–120 months). Among all patients, the 3- and 5-year survival rates were 61.5% (95% CI, 52.68–70.32) and 48.7% (95% CI, 39.68–57.72), respectively. The VRR-Low group exhibited a worse prognosis compared with the VRR-High group (HR, 2.85; 95% CI, 1.69–4.82, p <0.001), with 3-year survival rates of 40.7% (95% CI, 27.57–53.83) and 79.4% (95% CI, 69.4–89.40) and 5-year survival rates of 31.5% (95% CI, 19.15–43.85) and 63.5% (95% CI, 51.54–75.46), respectively (Figure 4). The VRR and ypN stage were identified as independent prognostic factors in Cox's proportional hazards models (Table 2).

Table 1 The Clinical and Pathological Characteristics of the VRR-High and VRR-Low Group

	VRR-High (N=63)	VRR-Low (N=54)	P value†
Gender			0.13
Male	41	42	
Female	22	12	
Age			0.75
≤ 60 years	32	29	
>60 years	31	25	
Chemotherapy Regimen			0.76
FOLFOX	28	21	
SOX	24	21	
XELOX	11	12	
Surgery			0.32
Total gastrectomy	30	27	
Distal gastrectomy	31	22	
Combined resection	2	5	
Primary tumor site			0.49
Upper	15	12	
Middle	19	15	
Lower	29	25	
Multiple regions involved	0	2	
ypT stage			0.003
ypT0-1	13	3	
ypT2-3	10	2	
ypT4	40	49	
ypN stage			0.005
ypN0	23	6	
ypN1	14	14	
ypN2	17	15	
ypN3	9	19	
ypTNM stage*			0.003
pCR	4	1	
I	8	1	
II	16	6	
III	31	45	

Notes: †χ2 test; VRR-Low: volume reduction rate <31.95%; VRR-High: volume reduction rate ≥31.95%. *Five patients could not be classified: three patients were T0N1M0, and two were T0N2M0.

Abbreviations: yp, yield pathological; pCR, pathological complete regression; FOLFOX, oxaliplatin plus 5-fluorouracil plus leucovorin; SOX, oxaliplatin plus S-1; XELOX, oxaliplatin plus capecitabine.

Discussion

NAC is widely regarded as a successful therapeutic option for AGC. Accurate and timely evaluation of the tumor response to NAC is of critical importance when making surgical decisions and may help to determine the post-operative chemotherapy regimens.[19,20] Therefore, how to evaluate the tumor response to NAC is a critical issue. Until now, the common tumor response evaluation methods in clinical include RECIST, JCGC, and histo-pathologic tumor regression; however, certain limitations must be considered when using these methods. The RECIST are not recommended for evaluating primary gastric cancer lesions due to the irregular tumor shape, while the JCGC criteria do not address metastatic lesions, including lymph nodes. Therefore, the validity of these two methods in evaluating gastric cancer responses to

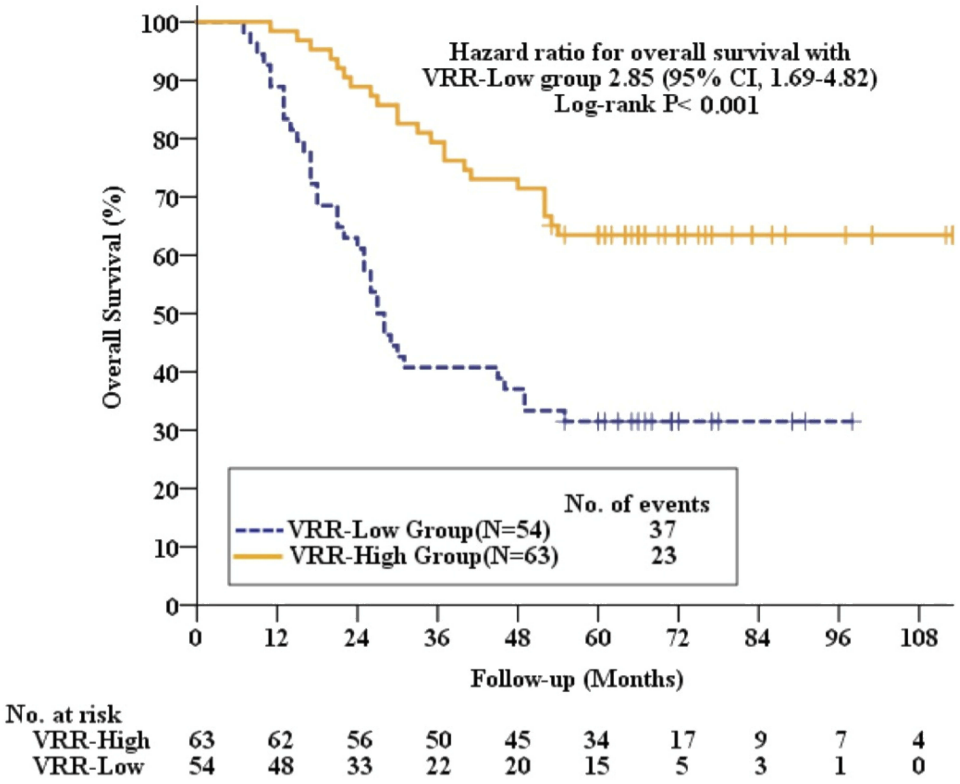

Figure 4 Survival analysis of the VRR-High group and VRR-Low group. VRR-Low group had worse survival rates compared with VRR-High group (HR, 2.85; 95% CI, 1.69–4.82, P<0.001).

chemotherapy remains uncertain and inconsistent. In a recent study, Kurokawa et al found that histological evaluation was a more effective assessment of the treatment response than radiological evaluation, and the OS of responders was significantly longer than that of non-responders evaluated by histological criteria.[21] Despite these findings, histopathological tumor regression was not identified as an independent prognostic factor, even though it was found to be associated with survival in a large retrospective study of esophagogastric cancer.[22]

In recent years, CT volumetry has garnered significant attention as a tool for evaluating tumor responses to neoadjuvant treatment in gastrointestinal cancers. The VRR was found to be superior to the RECIST for predicting the pathological response of rectal cancer treated with neoadjuvant chemoradiation,[23] while CT volumetry predicted the long-term survival of esophageal cancer patients treated with NAC followed by surgical resection.[24] However, only a few studies have used CT volumetry to assess the tumor response to NAC in gastric cancer. One study showed that patients with a VRR greater than 35.6% at 8 weeks after NAC could be categorized as pathologic responders with 100% sensitivity.[15] This cut-off level was much higher than that seen in a different study, in which only patients with a VRR greater than 14.8% were considered responders.[16] Nevertheless, the sample sizes of both studies were small, and the correlation of CT volumetry with long-term survival was not investigated.

In the present study, no significant interobserver variability in the measurements of CT tumor volumetry was found between the two observers, which indicated that CT volumetry was reproducible. Our sample size (117 patients) makes this the largest study investigating the use of CT volumetry to evaluate the tumor response to NAC in gastric cancer to date. The median follow-up time was 53.0 months (range 7–120 months). The cut-off VRR was determined to be 31.95% by ROC analysis and was used to identify 63 (53.8%) patients as responders. Meanwhile, the maximum number of measurable lesions in this study was five, which was in accordance with the RECIST. Furthermore, the cut-off VRR of 31.95% was very close to the definitive endpoint for a partial response (≥30% decrease in the sum of the target lesion diameters) used in the RECIST.

Validated prognostic factors for patients with AGC treated with NAC followed by R0 resection have not been established. A meta-analysis of patient outcomes

Table 2 Univariate and Multivariate Analyses of Prognostic Factors

Prognostic Factor	No.	Survival			
		Univariate		Multivariable	
		HR (95% CI)	P value	HR (95% CI)	P value
Age					
≤ 60	61	1 [Reference]		ND	
> 60	56	0.73(0.44–1.21)	0.22	ND	
Gender					
Male	83	1[Reference]		ND	
Female	34	1.61(0.95–2.73)	0.07	ND	
Tumor site					
Upper	27	1 [Reference]		ND	
Middle	34	1.80(0.86–3.80)	0.12	ND	
Lower	54	1.53(0.76–3.07)	0.23	ND	
Multiple involved	2	5.61(1.23–25.63)	0.03	ND	
NAC regimen					
FOLFOX	49	1 [Reference]		ND	
SOX	45	0.62(0.34–1.12)	0.11	ND	
XELOX	23	1.13(0.59–2.17)	0.72	ND	
Gastrectomy					
Distal	53	1 [Reference]		ND	
Total	57	0.97(0.57–1.63)	0.89	ND	
Combined resection	7	1.47(0.51–4.20)	0.47	ND	
yp T stage					
ypT_{0-1}	16	1 [Reference]		1 [Reference]	
ypT_{2-3}	12	4.75(0.96–23.56)	0.06	2.04(0.40–10.55)	0.40
ypT_4	89	6.95(1.69–28.58)	0.007	2.13(0.50–9.13)	0.31
ypN stage					
ypN_0	29	1 [Reference]		1 [Reference]	
ypN_1	28	8.11(1.81–36.24)	0.006	6.10(1.33–27.95)	0.02
ypN_2	32	14.52(3.40–60.09)	< 0.001	10.58(2.42–46.37)	0.002
ypN_3	28	35.28(8.28–150.32)	< 0.001	23.24(5.23–103.28)	< 0.001
VRR					
VRR-High	63	1[Reference]		1[Reference]	
VRR-Low	54	2.85(1.69–4.82)	< 0.001	1.87(1.07–3.29)	0.03

Notes: VRR-Low: VRR<31.95%; VRR-High: VRR≥31.95%.

Abbreviations: No, number; HR, hazard ratio; CI, confidence interval; ND, no data; NAC, neoadjuvant chemotherapy; yp, yield pathological; VRR, volume reduction rate; FOLFOX, oxaliplatin plus 5-fluorouracil plus leucovorin; SOX, oxaliplatin plus S-1; XELOX, oxaliplatin plus capecitabine.

found that ypN stage, resection status, and age were all independent predictors for patients who receive NAC, but ypT stage was not.[25] Although ypN and ypT stages were strongly associated with OS in the univariate analysis in this study, only ypN stage was an independent prognostic factor, consistent with previous studies.[6,25] One possible explanation is that the effects of chemotherapy made it difficult to assess the influence of ypT stage on prognosis.

Although the findings of our study are encouraging, several limitations should be considered when evaluating these findings. First, although the section thickness of the CT scans was 5 mm, the small lesions (<5 mm) could not be assessed well compared with thin-section CT scanning. Second, although the lesions were still detected by CT after NAC, some patients achieved complete pathological regression of the tumor. Finally, despite a significantly larger sample size compared with previous studies, a much larger multi-center

study will be necessary to fully evaluate these findings. Hence, CT tumor volumetry combined with some imaging biomarkers,[26,27] such as the apparent diffusion coefficient from diffusion-weighted magnetic resonance imaging and the textural features from contrast-enhanced multidetector computed tomography, may represent a better choice for evaluating tumor response to NAC.

Conclusions

The data presented here indicate that CT volumetry is a feasible and reliable method for assessing the tumor response to NAC in patients with AGC. Patients with a VRR exceeding 31.95% after NAC would be categorized as clinical responders.

Abbreviations

NAC, neoadjuvant chemotherapy; AGC, advanced gastric cancer; VRR, volume reduction rate; ROC, receiver operating characteristic; ROI, region of interest.

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Disclosure

The authors declare that they have no conflict of interest.

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