Clinics in Surgery

Research Article
Published: 27 Nov, 2021

Prognostic Value of Calculated Tumor Volume in Patients with Gastric Cancer

Ji-Hyun Kim[1], Kyong-Hwa Jun[2] and Hyung-Min Chin[2]*

[1]Department of Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Republic of Korea

[2]Department of Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Republic of Korea

Abstract

Background: To evaluate the prognostic value of tumor volume in gastric cancer, we assessed calculated Tumor Volume (cTV) based on pathologic reviews after gastrectomy and investigated its correlation with long-term outcomes of patients.

Methods: In total, 574 gastric cancer patients who underwent curative gastrectomy were enrolled and divided into subgroups according to cTV: 0-160.0 for the cTV1 group, 160.1-468.0 for the cTV2 group, and ≥ 468.1 for the cTV3 group.

Results: Among enrolled patients, 403 (70.2%) were in the cTV1 group, 116 (20.2%) were in the cTV2 group, and 55 (9.6%) were in the cTV3 group. The 5-year overall survival rate of cTV groups were significantly different: 94.4% in cTV1, 86.2% in cTV2, and 69.3% in cTV3. In the multivariate analysis, the cTV group was an independent prognostic factor for OS (HR 2.50, *P*=0.049) and DFS (HR 2.25, *P*=0.044). In the subgroup analysis, there was a significant difference according to the cTV group in both OS and DFS in T4 and N3 gastric cancers.

Conclusion: The cTV showed a significant correlation with the prognosis of gastric cancer patients after surgery even in the same stage. Therefore, it might be used to stratify patients with poorer prognosis in advanced gastric cancer and to provide additional information on the patient's treatment strategies.

Keywords: Gastric cancer; Tumor volume; Overall survival; Prognosis

Abbreviation

TV: Tumor Volume; cTV: Calculated Tumor Volume; TNM: Tumor-Node-Metastasis; DOI: Depth of Invasion; AJCC: American Joint Committee on Cancer; OS: Overall Survival; DFS: Disease Free Survival; HR: Hazard Ratio

Introduction

Gastric cancer remains a common cause of cancer-related death worldwide [1], and the Tumor-Node-Metastasis (TNM) classification is the most reliable system for estimating the prognosis in gastric cancer patients [2]. However, even in the same TNM stage, the outcome of gastric cancer patients may be varied by influence of other prognostic factors, including age, differentiation, tumor markers, immunohistochemistry, and tumor size [3,4]. Prognostic factors play an essential role in predicting survival and determining optimal therapeutic strategies in patients with gastric cancer. Tumor volume has been reported having prognostic value in many solid cancers such as breast cancer, prostate cancer, head and neck cancer, lung cancer and esophageal cancer [5-7]. Hsin et al. [8] demonstrated that tumor volume is a poor prognosticator on recurrence and overall survival for patients with laryngeal cancer receiving definitive radiotherapy. Miyamoto et al. [9] reported that tumor volume is an independent prognostic factor in patients with esophageal carcinoma and can be included in the staging system of esophageal cancer. Some researchers have investigated tumor volume as a prognostic factor in gastric cancer [10]. However, to the best of our knowledge, an association between tumor volume and prognosis in patients with gastric cancer has not been established. In the present study, we retrospectively calculated tumor volumes using the pathologic review of 574 gastric cancer patients and investigated the prognostic value of calculated tumor volume in gastric cancer patients regardless of the TNM stage.

OPEN ACCESS

Correspondence:
Kyong-Hwa Jun, Department of Surgery, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, 93, Jungbudaero, Paldal-gu, Suwon, Gyeonggi-do, 16247, Republic of Korea, Tel: +82-31-881-8636;
E-mail: dkkwkh@catholic.ac.kr

Received Date: *26 Oct 2021*
Accepted Date: *12 Nov 2021*
Published Date: *27 Nov 2021*

Citation:
Kim J-H, Jun K-H, Chin H-M. Prognostic Value of Calculated Tumor Volume in Patients with Gastric Cancer. Clin Surg. 2021; 6: 3373.

Materials and Methods

Patients

From January 2012 to December 2015, patients aged 20 years or older who underwent curative resection for gastric cancer in St. Vincent's Hospital, The Catholic University of Korea were reviewed for this study. Patients with a history of other malignancy, distant metastasis (e.g., liver, lung, brain, or bone marrow metastasis) and peritoneal dissemination, or palliative resection, and neoadjuvant chemotherapy were excluded. Finally, the clinical outcomes and the pathologic reviews of 574 patients were analyzed in this study. This study received ethical approval from the Institutional Review Board of our institution (VC18RESI0050). Demographic, surgical, and pathologic data of enrolled patients were obtained from electronic medical records retrospectively and anonymized prior to statistical analysis. All patients received radical subtotal gastrectomy or total gastrectomy with adequate lymph node dissection (D1+ or D2) according to the recommendation of Korean Gastric Cancer Treatment Guidelines [11]. In patients with stage II and III gastric cancer, adjuvant chemotherapy consisting mainly of fluoropyrimidine-based or platinum combination regimen was implemented after surgery. The patients were followed up every 6 months until 3 years after surgery and then annually up to 5 years or until death. The mean follow-up period was 44 (range, 2-71) months. Routine follow-up assessments included medical history, physical examination, laboratory parameters and tumor markers, and abdominal Computed Tomography (CT). Endoscopy and bone scan were performed annually during the follow-up period or if the patient had related symptoms.

Calculation of tumor volume

All resected specimens were fixed and processed using the whole mount technique with 3 mm to 5 mm transverse sections. Tumor size was measured as part of the routine pathological assessment by visual estimation. Based on previous studies, TV was calculated using the equation, $a \times b^2 \times 0.5$, in which a and b the largest and smallest diameters (cm) of tumor area, respectively [12]. To reflect the effect of tumor invasion, the Depth of Invasion (DOI) score was set as mucosa or submucosa (T1) =1, muscularis propria (T2) =2, subserosa (T3) =3, serosa (T4a) =4, and invades adjacent structures (T4b) =5. Finally, calculated Tumor Volume (cTV) was defined with the following formula: $cTV = a \times b^2 \times 0.5 \times DOI$.

Optimal cut-point in survival analysis and stratification of patients by cTV

A cut-point analysis was performed to determine the optimal number and location of cutoff points of the cTV values according to survival, which as defined as the greatest actuarial survival difference among the resulting subgroups [13]. In this analysis, we identified 3 optimal cut-points of cTV: 71.0, 160.0, and 468.0 (Table 1). The patients were the stratified by these cut-points which showed distinctive survival rates in their Kaplan-Meier curves. The patients were thus divided into three subgroups: 403 patients with cTV1 (0 ≤ Tumor volume ≤ 160.0), 116 patients with cTV2 (160.1 ≤ Tumor volume ≤ 468.0), 55 patients with cTV3 (Tumor volume ≥ 468.1) (P<0.001).

Statistical analysis

Descriptive statistics were expressed as mean and standard deviation for continuous variables, and categorical variables as number and percentage. Kaplan–Meier curves were used for OS and Disease-Free Survival (DFS) based on the length of time between surgical treatment and the final follow-up or death, and differences in the survival rate between the groups were compared using the log-rank test. A Cox regression model was used to identify variables that influence OS and DFS. Multivariate analysis was performed using variables that had a significant independent relationship with OS and DFS. Significance was defined as a P value less than 0.05. All statistical analyses were conducted using the software package SPSS 21 (Chicago, IL, USA).

Results

Clinicopathologic characteristics

The clinicopathologic characteristics of the patients are shown in Table 2. Of 574 patients, 381 (66.4%) were male, and the mean age was 62.6 ± 12.0 years. The locations of primary tumors were as follows: 47 (8.2%) in the upper third of the stomach; 222 (38.7%) in the middle third of the stomach; 301 (52.4%) in the lower third of the stomach; and 4 (0.7%) in the whole stomach. More than 50% of the tumors were intestinal type among Lauren classification and 318 (55.4%) of the histologic type was differentiated. Pathologically, the average long axis of tumor size was 4.1 ± 3.0 cm and the average short axis of tumor size was 3.1 ± 2.3. The final pathologic stage groups according to the 8th edition AJCC (American Joint Committee on Cancer) staging were 373 (65.0%) patients with stage I disease, 77 (13.4%) with stage II disease, and 124 (21.6%) with stage III disease. Of the 574 patients, cTV classifications were divided into 3 subgroups: 403 (70.2%) patients were cTV1, 116 (20.2%) patients were cTV2, and 55 (9.6%) patients were cTV3. Survival curves of patients according to TNM stage and cTV groups were shown in Figure 1, 2 (P<0.001). There were significant differences in both OS and DFS according to

Table 1: Five-year overall survival rate by Tumor Volume (TV) subgroup.

TV subgroup	Cases	Events	5-year OS (%)	χ^2-value	P value[a]
0.0-0.50	57	1	100		
0.51-1.70	68	1	98.0	0.014	0.905
1.71-3.20	48	1	96.0	0.006	0.941
3.21-5.80	57	3	93.1	0.958	0.328
5.81-11.0	58	3	89.4	1.162	0.281
11.1-27.0	57	5	88.9	2.826	0.093
27.1-71.0	58	2	94.6	0.352	0.553
71.1-160.0	57	7	86.3	5.152	0.023
160.1-468.0	59	7	86.3	5.339	0.021
468.1-	55	13	69.3	15.749	<0.001

Table 2: Baseline characteristics of patients.

Characteristics	Number (%)
Age (years)	62.6 ± 12.0
Gender	
Male	381 (66.4)
Female	193 (33.6)
Tumor location	
Upper	47 (8.2)
Middle	222 (38.7)
Lower	301 (52.4)
Whole	4 (0.7)
Histologic type	
Differentiated	318 (55.4)
Undifferentiated	236 (44.6)
Lauren classification	
Intestinal	281 (50.4)
Diffuse	206 (36.9)
Mixed	71 (12.7)
Tumor size (long axis, cm)	4.1 ± 3.0
Tumor size (short axis, cm)	3.1 ± 2.3
T stage	
T1	343 (59.8)
T2	60 (10.5)
T3	62 (10.8)
T4	109 (19.0)
N stage	
N0	390 (67.9)
N1	63 (11.0)
N2	55 (9.6)
N3	66 (11.5)
TNM stage	
I	373 (65.0)
II	77 (13.4)
III	124 (21.6)
Tumor volume subgroups	
cTV1	403 (70.2)
cTV2	116 (20.2)
cTV3	55 (9.6)

cTV groups as well as TNM stage.

Univariate and multivariate analyses for overall survival and disease-free survival

In univariate analysis, OS and DFS were significantly different according to age, sex, tumor location, Lauren classification, lymphovascular invasion, neural invasion, T stage, N stage, and cTV group (Table 3). Multivariate analysis using the Cox proportional hazard model was performed to evaluate the factors which were identified in univariate analysis (Table 4). Advanced cTV group (cTV1, HR reference; cTV2, HR1.10 [0.34-2.98] and HR2.10 [1.04-4.24] in DFS and OS; cTV3, HR 2.82 [0.98-8.11] and 4.18 [2.02-8.67] in DFS and OS, respectively) with advanced T stage and N stage, was found to be an independent prognostic factors in both OS and DFS. Additionally, age, lymphatic invasion, and neural invasion were independent prognostic factors significantly associated with DFS in patients with gastric cancer.

Overall survival and disease-free survival of cTV groups by each stage

The 5-year survival rates of patients with each T stage, N stage, and TNM stage were investigated according to cTV group. As shown in Table 5, for patients in T4 and N3, significant differences in survival were observed among patients in each cTV group. For patients in each cTV groups, OS and DFS was homologous between those in T4 and N3 (Figure 3). These results suggested that cTV classification has additive information to the TNM classifications for prognostic assessment in advanced stage.

Discussion

To predict the prognosis of cancer patients and to plan patient-specific treatment, it is essential to classify patients considering various prognostic factors. For these purposes, the AJCC TNM stage is widely accepted for most solid cancers, including gastric cancer [14]. Also, T stage and N stage were demonstrated to be the most powerful prognostic factors of gastric cancer patients. In gastric cancer, the T stage reflects the depth of the tumor invasion, whereas tumor diameter is also involved in assessment of the T stage in many other cancers, such as breast cancer, lung cancer, and tongue cancer [15,16]. In previous studies that investigated tumor diameter in gastric cancer, it was closely related with histologic type, lymph node metastasis, tumor invasion, vessel invasion, neural invasion and peritoneal metastasis [17]. Saito et al. [18] found that tumor diameter could also be used to predict the recurrence site of gastric cancer. Moreover, Deng et al. [19] demonstrated that tumor diameter represented a better prognostic stratification ability compared with T stage. However, tumor diameter alone could not accurately reflect the actual tumor burden of gastric cancer due to this cancer's complicated morphology and inconsistent pattern of invasion. Most of these studies have failed to demonstrate the validity of tumor diameter as an independent prognostic factor even if tumor diameter is considered as a significant prognostic parameter. Thus, a new

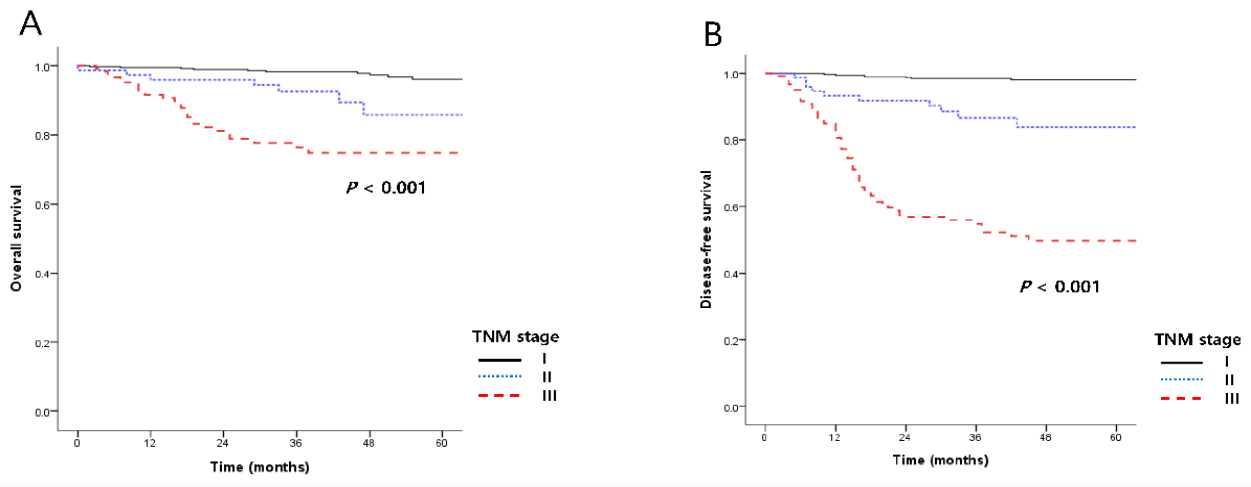

Figure 1: (A) Overall survival according to 8th AJCC TNM classification and (B) Disease free survival according to 8th AJCC TNM classification.

Table 3: Univariate analysis of risk factors for Overall survival and disease-free survival.

Characteristics	Univariate analysis			
	OS survival		DFS survival	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	1.04 (1.00-1.07)	0.022	1.03 (1.00-1.05)	0.007
Gender				
Male	1	0.323	1	0.753
Female	0.66 (0.30-1.48)		0.92 (0.56-1.51)	
Tumor location				
Upper	1	0.014	1	0.001
Middle	0.48 (0.17-1.37)	0.173	0.53 (0.24-1.14)	0.108
Lower	0.39 (0.13-1.09)	0.075	0.59 (0.28-1.24)	0.169
Whole	9.11 (1.71-48.35)	0.009	10.99 (3.33-36.24)	<0.001
Histologic type				
Differentiated	1	0.057	1	0.007
Undifferentiated	1.98 (0.98-4.02)		1.90 (1.19-3.03)	
Lauren classification				
Intestinal	1	0.116	1	0.004
Diffuse	2.12 (1.01-4.45)	0.046	2.36 (1.405-3.979)	0.001
Mixed	1.11 (0.31-3.96)	0.865	1.85 (0.882-3.898)	0.103
Lymphatic invasion	17.78 (5.41-58.41)	<0.001	17.67 (8.103-38.537)	<0.001
Vascular invasion	9.31 (4.63-18.71)	<0.001	10.83 (6.830-17.192)	<0.001
Neural invasion	6.75 (3.35-13.62)	<0.001	7.18 (4.509-11.436)	<0.001
T stage				
T1	1	<0.001	1	<0.001
T2	10.262 (2.452-42.949)	0.001	8.20 (2.847-23.649)	<0.001
T3	8.714 (1.950-38.949)	0.005	12.07 (4.466-32.667)	<0.001
T4	29.887 (8.886-100.799)	<0.001	37.53 (16.039-87.846)	<0.001
N stage				
N0	1	<0.001	1	<0.001
N1	1.405 (0.164-12.035)	0.756	5.64 (2.338-13.624)	<0.001
N2	14.184 (4.636-43.399)	<0.001	15.34 (7.299-32.260)	<0.001
N3	30.826 (11.396-83.381)	<0.001	27.33 (13.805-54.138)	<0.001
Tumor volume				
cTV1	1	<0.001	1	<0.001
cTV2	5.673 (2.281-14.108)	<0.001	8.047 (4.385-4.769)	<0.001
cTV3	18.109 (7.465-43.928)	<0.001	19.055 (10.234-35.476)	<0.001

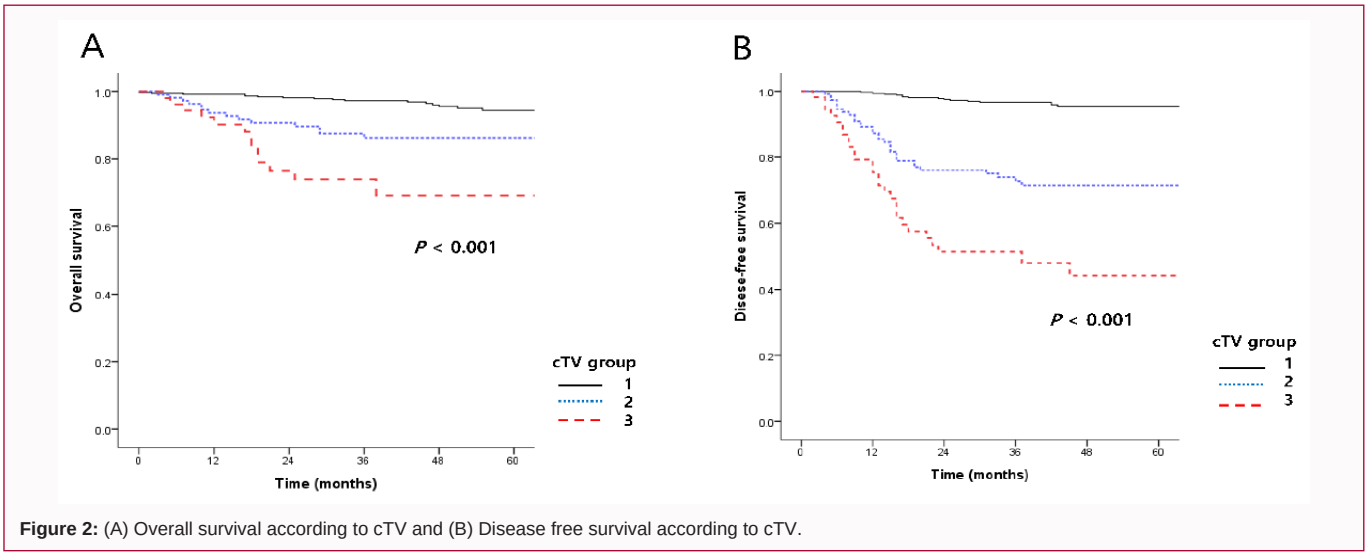

Figure 2: (A) Overall survival according to cTV and (B) Disease free survival according to cTV.

index, such as tumor volume, which could better reflect the actual burden of these tumors, is needed for investigation. In numerous previous studies, investigators tried to estimate tumor volume with imaging tools, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) -Computed Tomography (CT), and their results sought that it was contributing to poor prognosis of patients [20-23]. However, in these studies, errors with the actual tumor range, including the inability to measure in image studies according to tumor shape and pattern, cannot be overlooked. Assessment of tumor volume based on histological measurements is varied in several previous studies, and there is no standardized formula worldwide [9,10,13]. In this study, we propose a new formula using histological measurements to assess tumor volume of gastric cancer. The formula used in this study included both the long and short axis, and the calculation of these parameters was applied based on previous cancer research

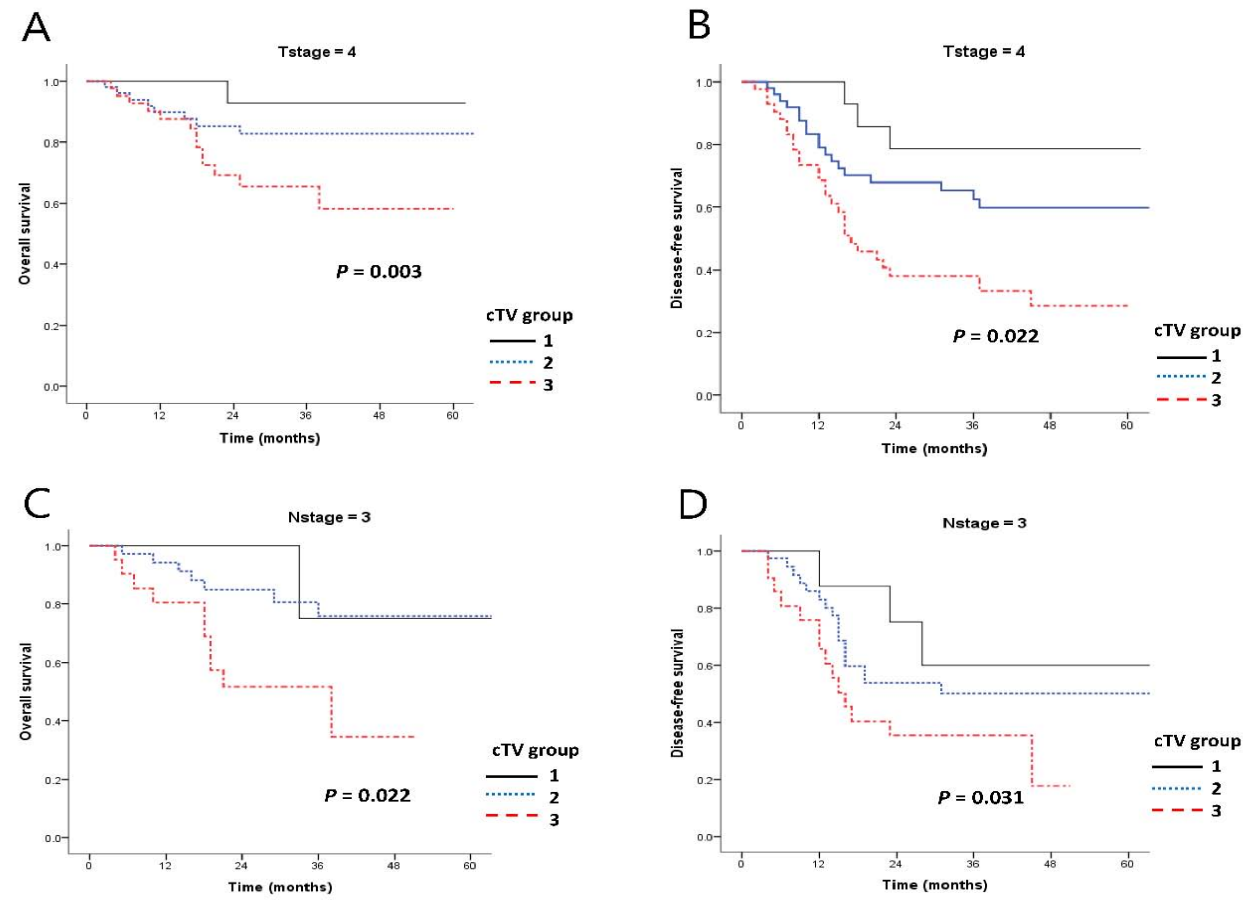

Figure 3: Overall survival and disease-free survival according to cTV in T4 stage (A, B) and N3 stage (C, D).

Table 4: Multivariate analysis of risk factors for overall survival and disease-free survival.

	Multivariate Analysis			
	OS survival		DFS survival	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	1.03 (0.99-1.07)	0.078	1.02 (1.00-1.05)	0.016
Lymphatic invasion	4.71 (0.98-22.67)	0.053	3.16 (0.65-5.53)	0.032
Neural invasion			2.27 (1.34-3.84)	0.002
T stage				
T1	1	0.056	1	0.002
T2	5.23 (1.10-24.83)	0.037	4.21 (1.26-14.01)	0.019
T3	2.37 (0.41-13.47)	0.330	4.08 (1.23-13.51)	0.021
T4	5.51 (1.15-26.27)	0.032	7.78 (2.52-24.01)	< 0.001
N stage				
N0	1	0.001	1	0.018
N1	0.47 (0.04-4.70)	0.527	1.90 (0.65-5.53)	0.239
N2	3.76 (0.88-16.05)	0.073	3.32 (1.23-8.99)	0.018
N3	7.16 (1.72-29.67)	0.007	3.88 (1.43-10.53)	0.008
Tumor volume				
cTV1	1	**0.039**	1	**< 0.001**
cTV2	1.10 (0.34-2.98)	0.973	2.10 (1.04-4.24)	**0.037**
cTV3	2.82 (0.98-8.11)	**0.045**	4.18 (2.02-8.67)	**< 0.001**

literatures. In addition, DOI was weighted because, even for tumors with the same volume, we cannot ignore the effect of its depth in gastric cancer. Our results confirmed the validity of this calculation of TV, as the classification of patients using this value showed significant differences between groups in OS and DSF. In this study, we also analyzed the survival rates of cTV groups in each T and N stage to prove the effect of TV as a prognostic factor in the same stage. It was confirmed that the prognosis differed significantly according to tumor volume in T4 and N3 stage. However, as we expected, the effect of this tumor volume did not significantly affect prognosis in early gastric cancer. For early gastric cancer, it is difficult to estimate the tumor burden by volume compared to advanced gastric cancer due to morphological characteristics, such as a flat shape. Meanwhile, for advanced gastric cancer, the interactions between tumors burden

and lymphovascular invasion would likely increase with increasing tumor volume. Therefore, as tumor volume increase, so would the probability of micrometastases migrating from the tumor through the lymphatic vessels, increasing the postoperative recurrence rate and resulting in poorer prognosis [20,24,25]. Moreover, for tumors that invade the serosa, thus penetrating the gastric wall, tumor size is likely associated with a larger area of serosal invasion, increasing the likelihood of intraperitoneal dissemination and poorer prognosis. At the same time, tumor stroma produces cytokines that modulate immune reactions, which are responsible for signal transduction and facilitate tumor invasiveness [26-28]. All of these factors increase the possibility of recurrence, leading to poorer prognosis. The current study has some limitations. First, although we did our best to estimate the tumor volume, the obtained tumor volume is still not the true tumor volume. In fact, tumors have various shapes such as flat, fungating or ulcerative. And in principle, different formulas should be used to calculate each tumor volume [10,13]. Thus, we tried to complement this problem by adding the effect of tumor invasion to the volume calculation currently used in many oncologic studies. Second, due to the limitations of the retrospective study design, the collection of information for adjuvant chemotherapy was insufficient. Depending on compliance with chemotherapy, it may be a variable in the prognosis of the patient. However, according to our institution's policy, patients with gastric cancer at the same stage generally follow the same treatment policy; thus, the results of subgroup analysis are more reliable. Furthermore, to establish a scientific basis, it is necessary to perform external validation using other patient cohorts.

Conclusion

The cTV showed a significant correlation with the prognosis of gastric cancer patients after surgery even in the same stage. Therefore, it might be used to stratify patients with poorer prognosis in advanced gastric cancer and to provide additional information on the patient's treatment strategies.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. In H, Solsky I, Palis B, Langdon-Embry M, Ajani J, Sano T. Validation of the 8th edition of the AJCC TNM staging system for gastric cancer using the national cancer database. Ann Surg Oncol. 2017;24(12):3683-91.
3. Taniguchi K, Ota M, Yamada T, Serizawa A, Noguchi T, Amano K, et al. Staging of gastric cancer with the clinical stage prediction score. World J Surg Oncol. 2019;17(1):47.
4. Jiang Y, Li T, Liang X, Hu Y, Huang L, Liao Z, et al. Association of adjuvant chemotherapy with survival in patients with stage II or III gastric cancer. JAMA Surg. 2017;152(7):e171087.
5. Drukker K, Li H, Antropova N, Edwards A, Papaioannou J, Giger ML. Most-enhancing tumor volume by MRI radiomics predicts recurrence-free survival "early on" in neoadjuvant treatment of breast cancer. Cancer Imaging. 2018;18(1):12.
6. Ito Y, Udo K, Vertosick EA, Sjoberg DD, Vickers AJ, Al-Ahmadie HA, et al. Clinical usefulness of prostate and tumor volume related parameters following radical prostatectomy for localized prostate cancer. J Urol. 2019;201(3):535-40.
7. Mukoyama N, Suzuki H, Hanai N, Sone M, Hasegawa Y. Pathological tumor volume predicts survival outcomes in oral squamous cell carcinoma. Oncol Lett. 2018;16(2):2471-7.
8. Hsin LJ, Fang TJ, Tsang NM, Chin SC, Yen TC, Li HY, et al. Tumor volumetry as a prognostic factor in the management of T4a laryngeal cancer. Laryngoscope. 2014;124(5):1134-40.
9. Miyamoto H, Kunisaki C, Sato S, Tanaka Y, Sato K, Kosaka T, et al. Tumor volume index as a prognostic factor in patients after curative esophageal cancer resection. Ann Surg Oncol. 2019;26(6):1909-15.
10. Liu Z, Gao P, Liu S, Zheng G, Yang J, Sun L, et al. Tumor volume increases the predictive accuracy of prognosis for gastric cancer: A retrospective cohort study of 3409 patients. Oncotarget. 2017;8(12):18968-78.
11. Lee JH, Kim JG, Jung HK, Kim JH, Jeong WK, Jeon TJ, et al. Clinical practice guidelines for gastric cancer in Korea: An evidence-based approach. J Gastric Cancer. 2014;14(2):87-104.
12. Jun KH, Gholami S, Song TJ, Au J, Haddad D, Carson J, et al. A novel oncolytic viral therapy and imaging technique for gastric cancer using a genetically engineered vaccinia virus carrying the human sodium iodide symporter. J Exp Clin Cancer Res. 2014;33:2.
13. Jiang N, Deng JY, Ding XW, Liu Y, Liang H. Tumor volume as a prognostic factor was superior to the seventh edition of the pT classification in resectable gastric cancer. Eur J Surg Oncol. 2015;41(3):315-22.
14. Son T, Sun J, Choi S, Cho M, Kwon IG, Kim HI, et al. Multi-institutional validation of the 8th AJCC TNM staging system for gastric cancer: Analysis of survival data from high-volume Eastern centers and the SEER database. J Surg Oncol. 2019;120(4):676-84.
15. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: Breast cancer. Ann Surg Oncol. 2018;25(7):1783-5.
16. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8(th) lung cancer TNM classification and clinical staging system: Review of the changes and clinical implications. Quant Imaging Med Surg. 2018;8(7):709-18.
17. Guo P, Li Y, Zhu Z, Sun Z, Lu C, Wang Z, et al. Prognostic value of tumor size in gastric cancer: An analysis of 2,379 patients. Tumour Biol. 2013;34(2):1027-35.
18. Saito H, Osaki T, Murakami D, Sakamoto T, Kanaji S, Oro S, et al. Macroscopic tumor size as a simple prognostic indicator in patients with gastric cancer. Am J Surg. 2006;192(3):296-300.
19. Deng J, Zhang R, Pan Y, Ding X, Cai M, Liu Y, et al. Tumor size as a recommendable variable for accuracy of the prognostic prediction of gastric cancer: A retrospective analysis of 1,521 patients. Ann Surg Oncol. 2015;22(2):565-72.
20. Chen XL, Pu H, Yin LL, Li JR, Li ZL, Chen GW, et al. CT volumetry for gastric adenocarcinoma: Association with lymphovascular invasion and T-stages. Oncotarget. 2018;9(15):12432-42.
21. Ma JT, Han CB, Zheng JH, Sun HZ, Zhang SM, Xin J, et al. Hybrid PET/MRI-based delineation of gross tumor volume in head and neck cancer and tumor parameter analysis. Nucl Med Commun. 2017;38(7):642-9.
22. Fei Z, Chen C, Huang Y, Qiu X, Li Y, Li L, et al. Metabolic tumor volume and conformal radiotherapy based on prognostic PET/CT for treatment of nasopharyngeal carcinoma. Medicine (Baltimore). 2019;98(28):e16327.
23. Rosa C, Caravatta L, Delli Pizzi A, Di Tommaso M, Cianci R, Gasparini L, et al. Reproducibility of rectal tumor volume delineation using diffusion-weighted MRI: Agreement on volumes between observers. Cancer Radiother. 2019;23(3):216-21.
24. Kikuchi S, Hiki Y, Shimao H, Sakakibara Y, Kakita A. Tumor volume: A novel prognostic factor in patients who undergo curative resection for gastric cancer. Langenbecks Arch Surg. 2000;385(3):225-8.
25. Lu J, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, et al. Consideration of tumor size improves the accuracy of TNM predictions in patients with gastric cancer after curative gastrectomy. Surg Oncol. 2013;22(3):167-71.
26. Waldmann TA. Cytokines in cancer immunotherapy. Cold Spring Harb Perspect Biol. 2018;10(12).

27. Maddaly R, Subramaniyan A, Balasubramanian H. Cancer cytokines and the relevance of 3D cultures for studying those implicated in human cancers. J Cell Biochem. 2017;118(9):2544-58.

28. Raja UM, Gopal G, Shirley S, Ramakrishnan AS, Rajkumar T. Immunohistochemical expression and localization of cytokines/chemokines/growth factors in gastric cancer. Cytokine. 2017;89:82-90.