Prognostic value of calculated tumor volume (cTV) in T4 or N3 advanced gastric cancer

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Research

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Abstract

Background: To evaluate the prognostic value of tumor volume in gastric cancer, we assess calculated tumor volume (cTV) based on pathologic reviews and investigate its correlation with long-term outcome of patients who underwent curative gastrectomy.

Methods: In total, 574 gastric cancer patients who underwent curative gastrectomy in a single institution between January 2012 and December 2015 were enrolled and divided into subgroups (cTV group) according to cTV using pathologic tumor size and depth. The cutoff values of calculated cTV for subgroups were designated as 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 V groups were significantly different: 94.4% in cTV1, 86.2% in cTV2, and 69.3% in cTV3. In the univariate analysis, the cTV groups were associated with poor overall survival (OS) and disease-free survival (DFS) with age, tumor location, histologic type, Lauren classification, T stage, and N stage. 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.

Conclusions: Tumor volume plays an additive role in predicting survival in patients with gastric cancer. Moreover, the calculated tumor volume is significant parameter associated with poor prognosis in T4 and N3 advanced gastric cancer regardless of TNM stage.

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. demonstrated that tumor volume is a poor prognosticator on recurrence and overall survival for patients with laryngeal cancer receiving definitive radiotherapy [8]. Miyamoto et al. 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 [9]. Some researchers have investigated tumor volume as a prognostic factor in gastric cancer [10]. However, to the best of our knowledge, an association between [illegible]cer 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.

Materials And Methods

Patients

Patients aged 20 years or older who underwent curative resection for gastric cancer in St. Vincent's Hospital, The Catholic University of Korea from January 2012 to December 2015 were eligible 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, neoadjuvant chemotherapy were excluded. Overall, 574 patients were included in this study. This study was approved by the Institutional Review Board of St. Vincent's Hospital, The Catholic University of Korea (VC18RESI0050). The IRB waived the requirement for obtaining informed consent.

All patients received curative subtotal gastrectomy or total gastrectomy with adequate lymph node dissection (D1 + or D2) according to the recommendation of Korean Gastric Cancer Treatment Guidelines [11]. Postoperative chemotherapy was implemented according to pathologic stage, physical condition, and willingness of the patient. The regimens of chemotherapy mainly consisted of fluoropyrimidine-based or platinum combination therapy. The patients were followed up every 6 months until 3 years after surgery and then annually up to 5 years or until death. The follow-up evaluation involves taking of a medical history, physical examination, chest radiography, laboratory parameters and tumor markers, and abdominal computed tomography (CT). Endoscopy and bone scan were performed annually during follow-up period.

Calculation of tumor volume

All resected specimens were fixed and processed using the whole mount technique with 3- 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: $cTV = a \times b^2 \times 1/2 \times DOI$.

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 ($0 \leq$ Tumor volume ≤ 160.0), 116 patients with cTV2 ($160.1 \leq$ Tumor volume ≤ 468.0), 55 patients with cTV3 (Tumor volume ≥ 468.1) ($P < 0.001$).

Table 1
Five-year overall survival rate by tumor volume (TV) subgroup

TV subgroup	Cases	Events	5 year OS (%)	χ^2 value	*P* value
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**

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and categorical variables as number and percentage. Kaplan–Meier curves were used for OS and disease free survival (DFS) to compare patients with each stage 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 performed 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 classification 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 Figs. 1 and 2 ($P < 0.001$). There were significant differences in both OS and DFS according to cTV groups as well as TNM stage.

Table 2
Baseline characteristics of patients.

Characteristics	Number (%)
Age (years)	62.6 ± 12.0
Gender	381 (66.4)
Male	193 (33.6)
Female	
Tumor location	47 (8.2)
Upper	222 (38.7)
Middle	301 (52.4)
Lower	4 (0.7)
Whole	
Histologic type	318 (55.4)
Differentiated	236 (44.6)
Undifferentiated	
Lauren classification	281 (50.4)
Intestinal	206 (36.9)
Diffuse	71 (12.7)
Mixed	
Tumor size (long axis, cm)	4.1 ± 3.0
Tumor size (short axis, cm)	3.1 ± 2.3
T stage	343 (59.8)
T1	60 (10.5)
T2	62 (10.8)
T3	109 (19.0)
T4	

Characteristics	Number (%)
N stage	390 (67.9)
N0	63 (11.0)
N1	55 (9.6)
N2	66 (11.5)
N3	
TNM stage	373 (65.0)
I	77 (13.4)
II	124 (21.6)
III	
Tumor volume subgroups	403 (70.2)
cTV1	116 (20.2)
cTV2	55 (9.6)
cTV3	

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 poor 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.

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

	Univariate analysis			
Characteristics	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	1	0.323	1	0.753
Male	0.66 (0.30–1.48)		0.92 (0.56–1.51)	
Female				
Tumor location	1	0.014	1	0.001
Upper	0.48 (0.17–1.37)	0.173	0.53 (0.24–1.14)	0.108
Middle	0.39 (0.13–1.09)	0.075	0.59 (0.28–1.24)	0.169
Lower	9.11 (1.71–48.35)	0.009	10.99 (3.33–36.24)	< 0.001
Whole				
Histologic type	1	0.057	1	0.007
Differentiated	1.98 (0.98–4.02)		1.90 (1.19–3.03)	
Undifferentiated				
Lauren classification	1	0.116	1	0.004
Intestinal	2.12 (1.01–4.45)	0.046	2.36 (1.405–3.979)	0.001
Diffuse	1.11 (0.31–3.96)	0.865	1.85 (0.882–3.898)	0.103
Mixed				
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	1	< 0.001	1	< 0.001
T1	10.262 (2.452–42.949)	0.001	8.20 (2.847–23.649)	< 0.001
T2	8.714 (1.950-38.949)	0.005	12.07 (4.466–32.667)	< 0.001
T3	29.887 (8.886-100.799)	< 0.001	37.53 (16.039–87.846)	< 0.001
T4				

	Univariate analysis			
N stage	1	< 0.001	1	< 0.001
N0	1.405 (0.164–12.035)	0.756	5.64 (2.338–13.624)	< 0.001
N1	14.184 (4.636–43.399)	< 0.001	15.34 (7.299–32.260)	< 0.001
N2	30.826 (11.396–83.381)	< 0.001	27.33 (13.805–54.138)	< 0.001
N3				
Tumor volume	1	< 0.001	1	< 0.001
cTV1	5.673 (2.281–14.108)	< 0.001	8.047 (4.385–4.769)	< 0.001
cTV2	18.109 (7.465–43.928)	< 0.001	19.055 (10.234–35.476)	< 0.001
cTV3				

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	1	0.056	1	0.002
T1	5.23 (1.10-24.83)	0.037	4.21 (1.26–14.01)	0.019
T2	2.37 (0.41–13.47)	0.330	4.08 (1.23–13.51)	0.021
T3	5.51 (1.15–26.27)	0.032	7.78 (2.52–24.01)	< 0.001
T4				
N stage	1	0.001	1	0.018
N0	0.47 (0.04–4.70)	0.527	1.90 (0.65–5.53)	0.239
N1	3.76 (0.88–16.05)	0.073	3.32 (1.23–8.99)	0.018
N2	7.16 (1.72–29.67)	0.007	3.88 (1.43–10.53)	0.008
N3				
Tumor volume	1	0.039	1	< 0.001
cTV1	1.10 (0.34–2.98)	0.973	2.10 (1.04–4.24)	0.037
cTV2	2.82 (0.98–8.11)	0.045	4.18 (2.02–8.67)	< 0.001
cTV3				

Overall survival and disease free survival of cTV groups by each stages

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 (Fig. 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 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 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 values showed significant differences between groups in OS and DSF.

In the 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 calculated tumor volume correlates with postoperative patient prognosis regardless of TNM stage. Moreover, it also allows for additional information on the patient's treatment strategies by stratifying patients who would have poorer prognosis in T4 or N3 advanced gastric cancer. Therefore, this cTV could be a useful index when predicting survival and recurrence and planning management strategies in gastric cancer patients.

Abbreviations

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

Declarations

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None.

Authors’ contributions

KJ and HC contributed to study design, data analysis, manuscript editing, and article revision. JH interpreted the clinicopathologic data and wrote this manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of St. Vincent's Hospital, The Catholic University of Korea (VC18RESI0050).

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Figures

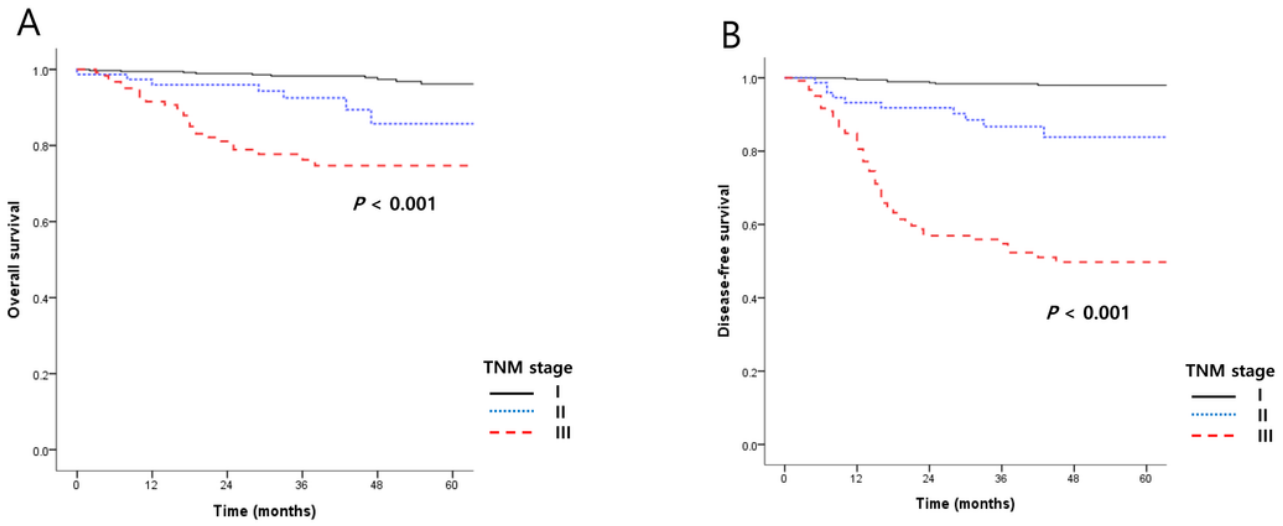

Figure 1

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

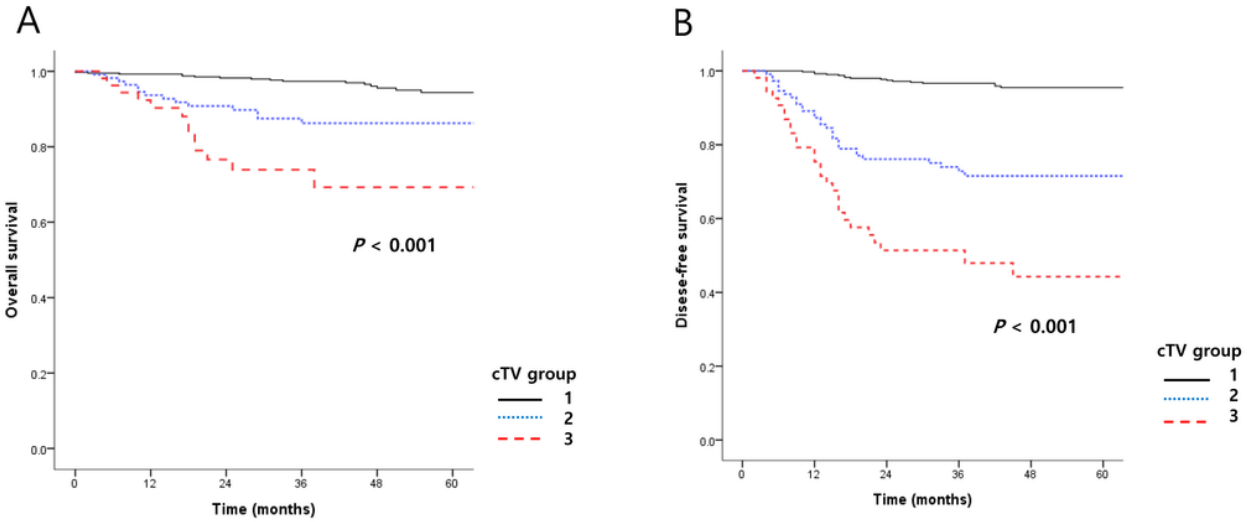

Figure 2

(A) Overall survival according to cTV and (B) Disease free survival according to cTV

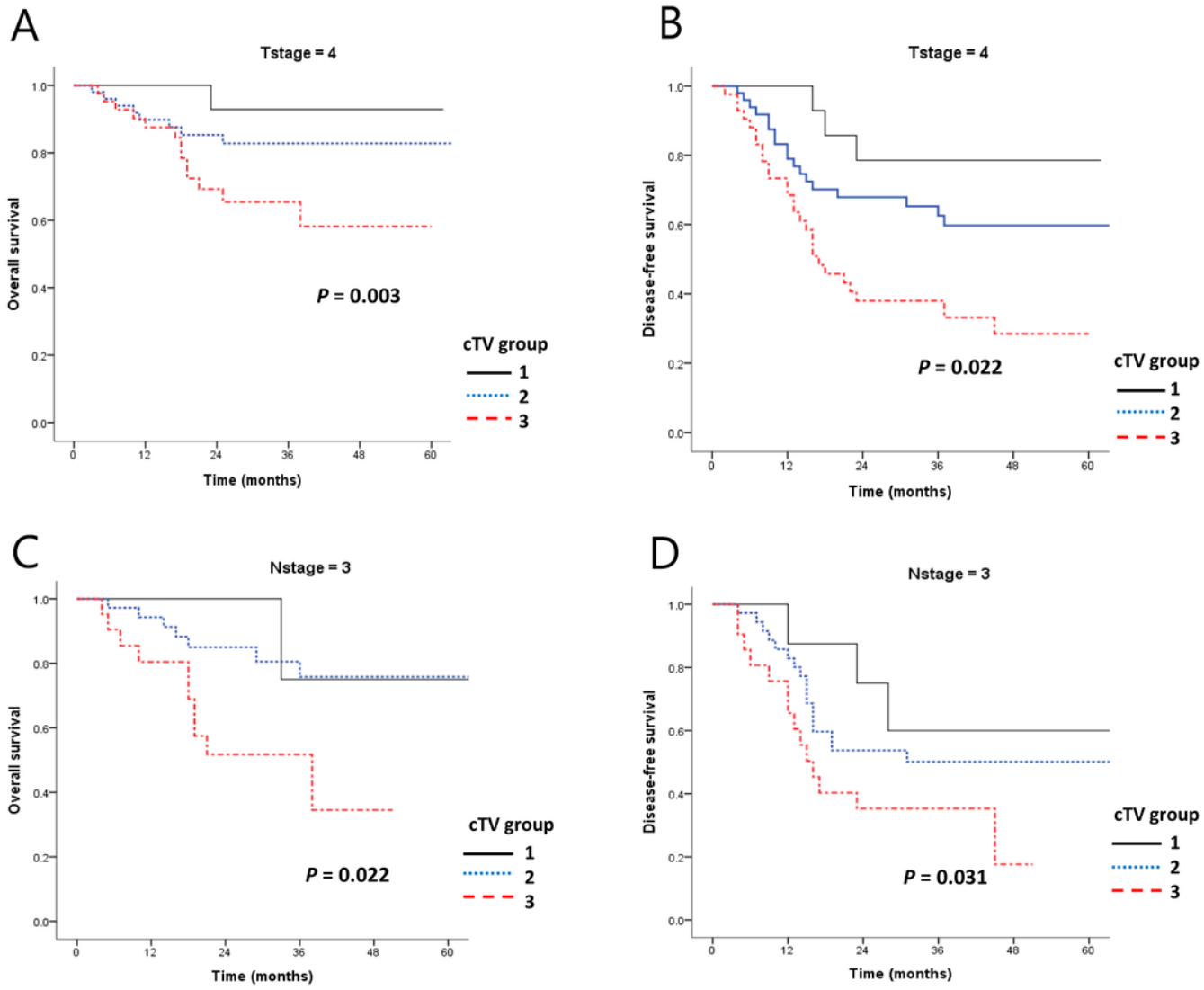

Figure 3

Overall survival and disease free survival according to cTV in T4 stage (A, B) and N3 stage (C,D)