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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Tumor Volume Is Better Than Diameter for Predicting the Prognosis of Patients with Early-Stage Non-small Cell Lung Cancer

Hao-jun Xie, MS[1,2,3], Xu Zhang, MD, PhD[1,2,3], Yun-xian Mo, MD[2,4], Hao Long, MD, PhD[1,2,3], Tie-hua Rong, MD[1,2,3], and Xiao-dong Su, MD, PhD[1,2,3]

[1]Department of Thoracic Surgery, Sun Yat Sen University Cancer Center, Guangzhou, People's Republic of China; [2]State Key Laboratory of Oncology in Southern China and Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; [3]Lung Cancer Institute, Sun Yat Sen University, Guangzhou, China; [4]Department of Radiology, Sun Yat Sen University Cancer Center, Guangzhou, China

ABSTRACT

Background. This study aimed to investigate whether tumor volume (TV) is better than diameter for predicting the prognosis of patients with early-stage non-small cell lung cancer (NSCLC) after complete resection.

Methods. This study retrospectively reviewed the clinicopathologic characteristics of 274 patients with early-stage NSCLC who had received pretreatment computed tomography (CT) scans and complete resection. TV was semi-automatically measured from CT scans using an imaging software program. The optimal cutoff of TV was determined by X-tile software. Disease-free survival (DFS) and overall survival (OS) were assessed by the Kaplan–Meier method. The prognostic significance of TV and other variables was assessed by Cox proportional hazards regression analysis.

Results. Using 3.046 cm^3 and 8.078 cm^3 as optimal cutoff values of TV, the patients were separated into three groups. A larger TV was significantly associated with poor DFS and OS in the multivariable analysis. Kaplan–Meier curves of DFS and OS showed significant differences on the basis of TV among patients with stage 1a disease, greatest tumor diameter (GTD) of 2 cm or smaller, and GTD of 2–3 cm, respectively. Using two TV cutoff points, three categories of TV were created. In 54 cases (19.7%), patients migrated from the GTD categories of 2 cm or smaller, 2–3 cm, and larger than 3 cm into the TV categories of 3.046 cm^3 or smaller, 3.046–8.078 cm^3, and larger than 8.078 cm^3.

Conclusion. TV is an independent prognostic factor of DFS and OS for early-stage NSCLC. The findings show that TV is better than GTD for predicting the prognosis of patients with early-stage NSCLC.

Tumor-node-metastasis (TNM) staging of lung cancer is one of the most important prognostic factors guiding the appropriate treatment options to offer patients. The T categories have been mainly evaluated by the prognostic impact of tumor size, which is surrogated by the greatest tumor diameter (GTD) in lung cancers.[1]

The easily measured GTD has proved to be an important prognostic factor for lung cancer.[1] However, GTD cannot always accurately describe the true size of an irregular tumor.[2–4] Questions still remain about how well GTD reflects the true tumor burden, particularly when the masses or nodules are spiculate or irregular. For example, in stage 1 non-small cell lung cancer (NSCLC), tumor size is the dominant outcome determinant affecting the TNM staging. The 5-year survival rates for stage I NSCLC after radical resection range from 68 to 92%.[5] Therefore, identification of additional prognostic biomarkers is needed to stratify high-risk patients for further adjuvant therapy.

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Dr Hao-jun Xie and Dr Xu Zhang have contributed equally.

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X. Su, MD, PhD
e-mail: suxd@sysucc.org.cn

Recent advances in imaging technology have enabled clinicians to measure tumor volume (TV) directly and reproducibly from computer tomography (CT) scans.[6,7] Previous studies demonstrated that the correlations with clinical outcomes have been higher for volumetric-based measures than for diameter.[8] As a biomarker, TV of lung cancer has been investigated in the management of advanced NSCLC.[7,9–12] However, the association between TV and the prognosis of surgically resectable NSCLC has not been well established.

We previously reported that TV is an independent prognostic factor of disease-free survival (DFS) and overall survival (OS) for early-stage NSCLC[13] In the current study, we hypothesized that TV might provide additional prognostic information over GTD and thus investigated whether TV is better than GTD in predicting the prognosis for patients with early-stage NSCLC after complete resection. The primary end point was DFS, and the secondary end point was OS.

MATERIALS AND METHODS

Patients

The methods used in this study are described elsewhere.[13] Briefly, we retrospectively reviewed the clinicopathologic characteristics of 347 consecutive patients with postoperative pathologically proven early-stage NSCLC (T1 or T 2 and N0) who had received pretreatment chest CT scans and had undergone complete surgical resection at the Sun Yat-sen University Cancer Center between 1 January 2007 and 31 December 2010. The TNM staging was determined according to the 8th edition of the TNM Classification.[5] Patients were excluded if they had a history of other cancer or had a residual tumor after surgery (23 patients), had received neoadjuvant chemotherapy (11 patients), or had an invisible nidus shown on CT caused by atelectasis or obstructive pneumonia or other problems (39 patients). Finally, 274 patients were included in this study. The flow chart of selected patients is shown in Fig. S1.

The preoperative workup included physical examination, biochemistry blood test, chest radiography, contrast-enhanced CT scan of the chest and abdomen, brain magnetic resonance imaging (MRI), bone scintigraphy scan, bronchoscopy, pulmonary function test, arterial blood gas measure, and electrocardiography. All the patients had received a lobectomy or bilobectomy with mediastinal lymph node dissection through the surgical approach of open thoracotomy or video-assisted thoracoscopic surgery. Mediastinal lymph node dissection was routinely performed using node station 2R,4R,7,8,9 on the right side and station 4L,5,6,7,8,9 on the left side.

Patient characteristics were obtained from a retrospective medical record review using a standardized data collection form. The histologic types of the tumors were determined based on the criteria of the World Health Organization classification.[14] No patients received postoperative adjuvant therapy. This study was officially approved by the ethics committee of the Sun Yat-sen University Cancer Center (approval no. YB2016073).

TV and GTD Measurement

All the preoperative chest CT scans were performed with a section thickness of 1 mm. The CT images (acquired using PHILIP Ict) were reviewed independently by a thoracic radiologist on standard lung windows (level, –500 HU; width, 1500 HU) without the knowledge of patient outcomes. The radiologist delineated the margin of the tumor in every section on the lung window. The tumor was reconstructed, and the TV was measured automatically by the software program. The TV and GTD were semi-automatically measured by PHILIPS IntelliSpace Portal v5.0.2.40009 software (Philips Healthcare Nederland B.V., Veenpluis 4-6, 5684 PC Best, The Netherlands) (Fig. 1). The radiologist recorded each patient's TV and GTD from the preoperative CT images.

Follow-up Evaluation

A follow-up examination generally was performed every 3–4 months for the first 2 years, then twice a year thereafter in our hospital outpatient clinic. Regular follow-up evaluation included a physical examination, blood chemistry analysis, tumor markers, chest radiograph, abdomen ultrasound, or CT scan. However, follow-up examinations were performed immediately for patients who had specific symptoms.

Recurrent NSCLC was diagnosed on the basis of the diagnostic imaging findings. Pathologic biopsies were performed if clinically feasible. The follow-up time was calculated from the date of surgery to the event or date of the last contact. Follow-up evaluation continued until 21 January 2016. The 5-year follow-up rate was 92.5%. The median follow-up time for all the patients was 77.6 months (range, 0.6–105.7 months).

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 for Windows software system (SPSS Inc., Chicago, IL, USA). Linear and nonlinear regression was used to describe the relationship between GTD and TV. The Pearson

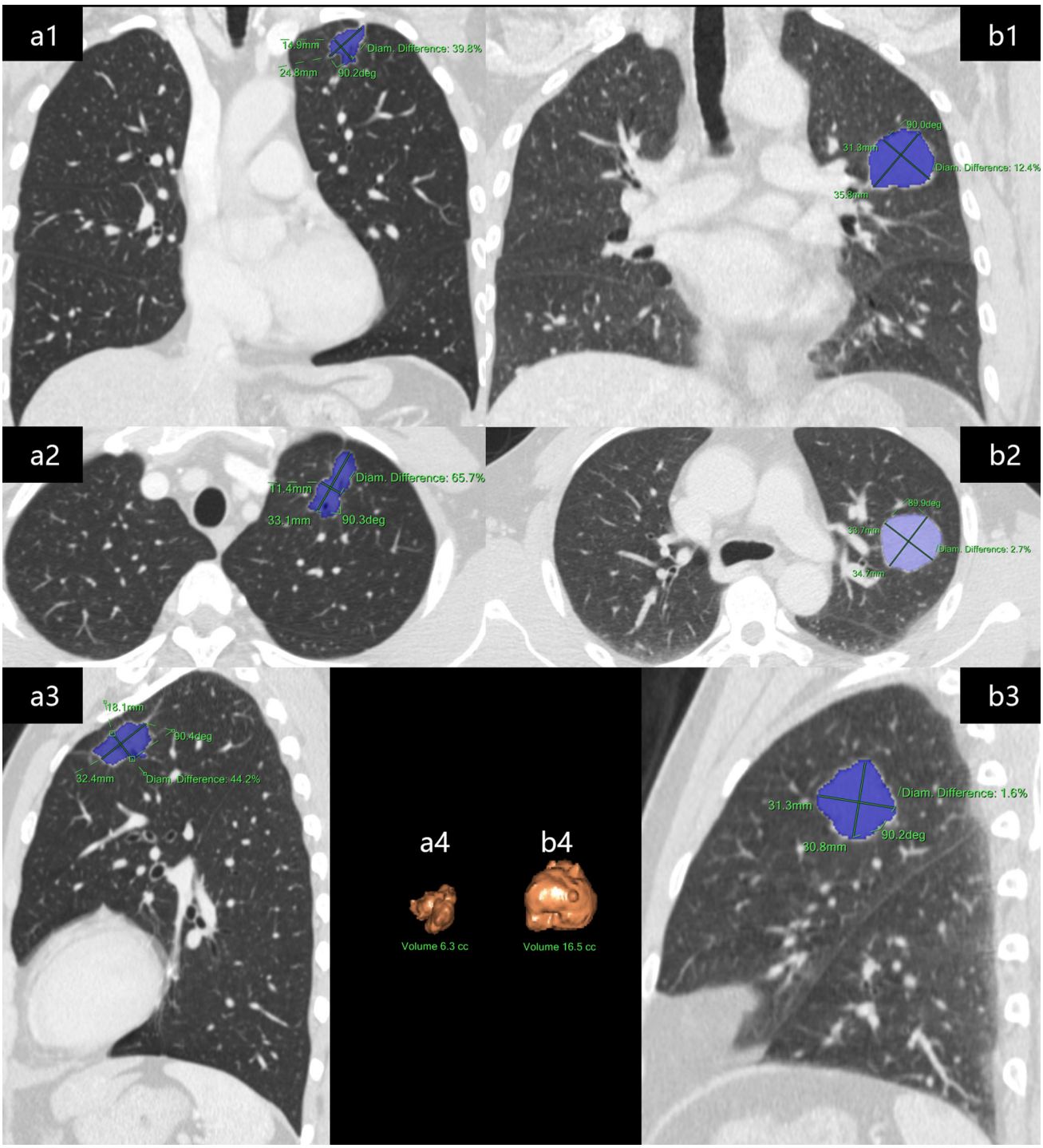

FIG. 1 The measurement of greatest tumor diameter (GTD) on CT images. The reconstruction of tumor and its volume was automatically measured by software. The GTD of tumor **a**, **b** was 3.31 cm and 3.58 cm, respectively; however, the tumor volume of **a**, **b** was 6.3 cm^3 and 16.5 cm^3, respectively

correlation coefficient was used to analyze the correlation between GTD and TV. The linear and non-linear models provided by regression analysis were tested by the F test, and the coefficients and constants of these models were tested by the *t* test. The optimal cutoff values of TV were determined by X-tile version 3.6.1 (Yale University School of Medicine, New Haven, CT, USA).[15]

Survival was calculated by the Kaplan–Meier method and analyzed by the log-rank test. Multivariable analysis was performed using Cox's proportional hazards regression

model with the backward stepwise procedure (entry and removal probabilities were 0.05 and 0.10, respectively). A significant difference was declared if the P value from a two-tailed test was lower than 0.05. Calculation of DFS was from the date of surgery to the date of tumor recurrence or metastasis or death from any cause. Calculation of OS was from the date of surgery to the date of death from any cause.

RESULTS

TV Optimal Cutoff Value and Patient Characteristics

Depending on DFS, the software X-tile divided TV into three parts (Fig. S2). The optimal cutoff values for TV were 3.046 cm^3 and 8.078 cm^3. The characteristics of the 274 study patients are summarized in Table 1.

Using the cutoff value of 3.046 cm^3 and 8.078 cm^3, we divided the patients into three groups: the small-volume group (SVG) (TV $\leq$ 3.046 cm^3), the medium-volume group (MVG) (TV $>$ 3.046–8.078 cm^3), and the large-volume group (LVG) ($>$ 8.078 cm^3). The 5-year DFS was 88% for SVG, 73.6% for MVG, and 62.1% for LVG ($P < 0.001$), and the 5-year OS was 91.4% for SVG, 84.5% for MVG, and73.3% for LVG ($P < 0.001$). The DFS for SVG was better than for MVG ($P = 0.035$) or LVG ($P < 0.001$), and the DFS for MVG also was better than for LVG ($P = 0.040$). The OS for LVG was significantly lower than for SVG ($P = 0.001$) or MVG ($P = 0.004$), but the difference in OS between SVG and MVG was insignificant ($P = 0.303$) (Fig. S3).

TABLE 1 Characteristics of the study patients

Variables	*n* (%)
Total	274 (100)
Sex	
Male	166 (60.6)
Female	108 (39.4)
Age (years)	
$<$ 60	126 (46.0)
$\geq$ 60	148 (54.0)
Histology	
Adenocarcinoma	194 (70.8)
Squamous cell carcinoma	52 (19.0)
Other NSCLC	28 (10.2)
Histologic differentiation	
Poorly	76 (27.7)
Moderately	150 (54.7)
Well	48 (17.6)
Visceral pleural invasion	
Absent	104 (38.0)
Present	170 (62.0)
TNM stage	
1a	80 (29.2)
1b	148 (54.0)
2a	46 (16.8)
Greatest tumor diameter (cm)	
$\leq$ 1	0
$>$ 1–2	66 (24.1)
$>$ 2–3	103 (37.6)
$>$ 3–4	59 (21.5)
$>$ 4–5	46 (16.8)
Tumor volume (cm^3)	
$\leq$ 3.046	62 (22.6)
$>$ 3.046–8.078	89 (32.5)
$>$ 8.078	123 (44.9)

NSCLC non-small cell lung cancer, *TNM* tumor-node-metastasis

Correlation Between GTD and TV

The regression model between GTD and TV is shown in Fig. S4. The results of correlation analysis are shown in Table S1. The results suggest that a correlation between GTD and TV is in accordance with the exponential growth model. The equation of the growth model is as follows: $y = e^{1.017x-0.907}$ (y = TV, x = GTD). Calculated from this equation, a TV of 3.046 cm^3 corresponds to a GTD of 1.99 cm, whereas a TV of 8.078 cm^3 corresponds to a GTD of 2.95 cm.

Uni- and Multivariable Analyses

The results of the uni- and multivariable analyses are shown in Table 2. The multivariable analysis showed that age and TV were independent factors associated with DFS. Gender, age, histology, visceral pleural invasion (VPI), and TV were independent factors associated with OS.

Subgroup Analysis

By using the cutoff values of 3.046 cm^3 and 8.078 cm^3, we divided the stage 1a patients into three groups: SVG (TV $\leq$ 3.046 cm^3), MVG (TV $>$ 3.046–8.078 cm^3), and LVG (TV $>$ 8.078 cm^3). The 5-year DFS was 96.2% for SVG, 80% for MVG, and 62.7% for LVG ($P < 0.001$), and the 5-year OS rate was 96.2% for SVG, 90% for MVG, and 84.2% for LVG ($P = 0.025$) (Fig. S5).

Using X-tile, the optimal cutoff values of TV were obtained for the patients with a GTD less than 2 cm, 2–3 cm, and larger than 3 cm. On the basis of the TV cutoff points, the patients with a GTD smaller than 2 cm

TABLE 2 Uni- and multivariable analyses of potential prognostic factors in non-small cell lung cancer (NSCLC)

Characteristic	Univariable survival analysis		Multivariable survival analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
DFS				
Gender: male versus female	1.86 (1.17–2.96)	0.009	1.52(0.94–2.45)	0.085
Age: ≥ 60 versus < 60 years	1.57(1.02–2.42)	0.041	1.48(0.96–2.30)	0.079
Histology		0.649		0.362
ADC	0.78(0.40–1.52)	0.464		0.614
SCC	0.94(0.44–2.02)	0.867		0.231
Other NSCLC	1	–		–
Histologic differentiation		0.079		0.450
Poorly	2.27(1.12–5.00)	0.024		0.404
Moderately	1.92(0.94–3.91)	0.072		0.987
Well	1	–		–
VPI: absent versus present	1.58(1.00–2.50)	0.050		0.214
Stage: 1a versus 1b & 2a	1.67(1.01–2.78)	0.048		0.475
GTD (cm)		0.010		0.795
≤2	0.40(0.22–0.75)	0.004		0.672
>2–3	0.65(0.41–1.03)	0.069		0.836
>3	1	–		–
TV		< 0.001		0.005
≤3.046	0.28(0.14–0.57)	< 0.001	0.33(0.16–0.67)	0.002
>3.046–8.078	0.61(0.39–0.98)	0.040	0.64(0.40–1.04)	0.070
. > 8.078 cm^3	1	–	1	–
OS				
Gender: male versus female	2.42(1.33–4.40)	0.004	2.09(1.11–3.95)	0.023
Age: ≥ 60 versus < 60	2.16(1.24–3.74)	0.006	2.25 (1.25–4.05)	0.007
Histology		0.056		0.019
ADC	0.46(0.23–0.94)	0.032	0.37(0.18–0.76)	0.007
SCC	0.76(0.34–1.69)	0.498	0.35(0.15–0.83)	0.016
Other NSCLC	1	–	1	–
Histologic differentiation		0.065		0.598
Poorly	3.12(1.18–8.24)	0.022		0.977
Moderately	2.23(0.87–5.72)	0.094		0.525
Well	1	–		–
VPI: absent versus present	2.04(1.14–3.67)	0.017	1.85 (1.00–3.40)	0.048
Stage: 1a versus 1b & 2a	2.14(1.11–4.13)	0.023		0.910
GTD (cm)		0.011		0.427
≤2	0.31(0.14–0.71)	0.005		0.476
>2–3	0.60(0.35–1.04)	0.068		0.192
> 3	1	–		–
TV		0.001		0.028
≤3.046	0.26(0.11–0.62)	0.002	0.41(0.17–0.99)	0.047
>3.046–8.078	0.42(0.23–0.77)	0.005	0.48(0.25–0.92)	0.027
>8.078 cm^3	1	–	1	–

HR hazard ratio, *CI* confidence interval, *DFS* disease-free survival, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *VPI* visceral pleural invasion, *GTD* greatest tumor diameter, *TV* tumor volume, *OS* overall survival

and those with a GTC of 2–3 cm were separated into two groups with significantly different DFS and OS. On the basis of TV, DFS and OS differed insignificantly for the patients with a GTD larger than 3 cm (Fig. 2).

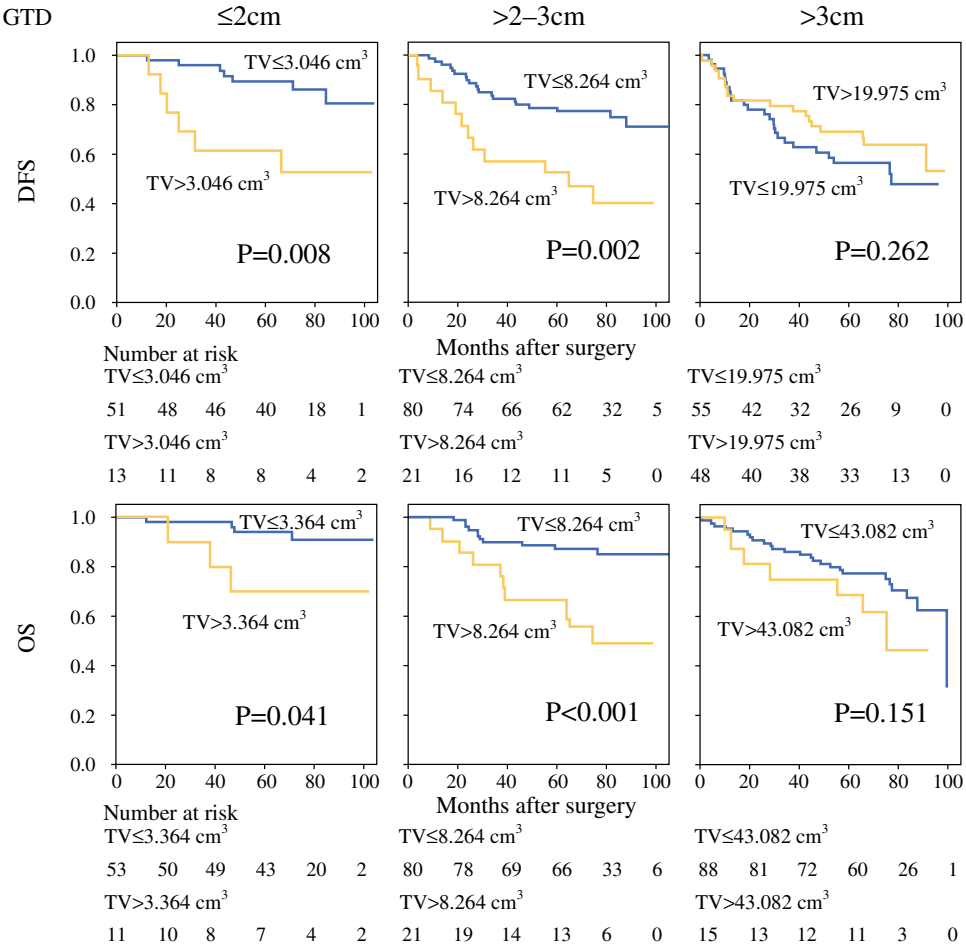

FIG. 2 Tumor volume cutoff values, disease-free survival, and overall survival curves in patients with greatest tumor diameter less than 2 cm (left), 2–3 cm (middle), and larger than 3 cm (right)

Using two TV cutoff points, we created three categories of TV as follows: smaller than 3.046 cm^3, 3.046–8.078 cm^3, and larger than 8.078 cm^3. Table 3 shows the relationship between the GTD categories and the TV categories. In 54 cases (19.7%) patients migrated from the GTD categories of smaller than 2 cm, 2–3 cm, and larger than 3 cm into the TV categories.

TABLE 3 The relationship between TV and GTD

TV	GTD			
	≤ 2 cm	> 2–3 cm	> 3 cm	Total
≤ 3.046 cm^3	52	10	0	62
> 3.046–8.078 cm^3	14	69	6	89
> 8.078 cm^3	0	24	99	123
Total	66	103	105	274

TV tumor volume, *GTD* greatest tumor diameter

DISCUSSION

This study used both GTD and TV to describe the tumor size of lung cancer and to investigate their prognostic impact on patients with early-stage NSCLC. Instead of using a receiver operating characteristic (ROC) curve, we chose X-tile for TV cutpoint selection because it uses both the end results and survival time of patients to determine the cut point.[15] Furthermore, two optimal cut points are obtained simultaneously, which allows division of the study population into three groups.[15]

The univariable analysis showed TV, staging, and GTD to be associated with DFS and OS. Only TV was an independent prognostic factor in the multivariable analysis. According to the current TNM staging system, tumor size, which is surrogated by the GTD, is the major prognostic factor for early-stage NSCLC.[5] Our results suggested that TV was more strongly associated with prognosis than staging and GTD in early-stage NSCLC.

To our knowledge, only a limited number of studies have investigated the prognostic significance of TV for patients with early NSCLC after surgical resection. Hyun

et al.[16] evaluated the prognostic significance of volume-based parameters of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) in early-stage NSCLC and reported that metabolic TV was an independent prognostic factor for survival in addition to pathologic TNM stage and a promising tool for better prediction of outcome for 529 consecutive patients with early-stage NSCLC. Takenaka et al.[17] reported that the whole TV and solid part volume, obtained semi-automatically from CT reconstruction, were associated with DFS in a series of 255 patients with clinical stage 1a NSCLC. In a series of 161 consecutive patients who had stage 3A-N2 NSCLC treated with neoadjuvant concurrent chemoradiotherapy followed by surgery, Hyun et al.[18] reported that a higher total metabolic TV, measured by pretreatment 18F-FDG PET/CT, was associated with worse outcome and independent of yp stage.

Adjuvant chemotherapy currently is the standard of care in the treatment of stages 2 and 3 NSCLC after radical resection.[19] The use of adjuvant chemotherapy for patients with stage 1 NSCLC remains controversial.[20] According to a clinical consensus, adjuvant chemotherapy is not recommended for stage 1A disease. For stage 1B disease, patients with a tumor larger than 4 cm may benefit from adjuvant chemotherapy.[21]

Although surgical resection remains the treatment of choice for early-stage NSCLC, approximately 10–20% of patients with stage 1A and 30% of patients with stage 1B NSCLC relapse and die within 5 years after curative resection.[5] Therefore, it is necessary to find more reliable methods for identifying patients at high risk of recurrence and most likely to benefit from adjuvant treatment.

The current findings suggest that patients may be stratified by prognosis on the basis of TV in the whole population of patients with early-stage NSCLC and in stage 1a disease and some categories of GTD. We divided the patients with stage 1a tumors into three groups on the basis of two TV cutoff points with a significant difference in DFS and OS.

In the 8th TNM Classification for lung cancer,[5] the division of the category T1 into T1a, T1b, and T1c on the basis of new diameter cutoff points of 1 and 2 cm has resulted in the assignment of these cases to stages 1a1, 1a2, and 1a3, respectively, thus reflecting the statistically different OS values (5-year OS was 90% for 1a1, 85% for 1a2, and 73% for 1a3).

On the basis of TV, our results were consistent with this proposal, but not on the basis of GTD. The reason may be the limited number of cases in our study. Furthermore, all GTDs were greater than 1 cm in the whole cohort of our study. It was difficult for us to find a small lung nodule due to the absence of low-dose CT scans for lung cancer screening in the medical checkup procedure during the study period in our country. In the T category of GTD (tumor < 2 cm and 2–3 cm), our result also showed that the outcomes for the patients with a smaller TV tended to be better than for those with a larger TV.

All these findings suggest that TV might be more sensitive in predicting the prognosis of early-stage NSCLC. Patients with a larger TV may be candidates for the adjuvant treatment in early-stage NSCLC. Larger samples are needed for further investigation into the prognostic impact of TV.

Although GTD is one of the important prognostic factors of NSCLC,[1] TV may reflect the true tumor burden better than a one-dimensional measurement of GTD, particularly when the masses or nodules are spiculate or irregular. In the current study, using two TV cutoff points, we created three categories of TV as follows: smaller than 3.046 cm^3, 3.046–8.078 cm^3, and larger than 8.078 cm^3. Compared with the category of GTD, we found nearly a 20% variation between individual volume and diameter measurement, with a greater variation for small nodules. Of the patients who had nodules with a GTD smaller than 3 cm, 28% migrated from GTD categories into TV categories, which means that the distribution of TV was discrete even in the same category of GTD. These results suggest that the shape of nodules is frequently irregular and support the conclusion that TV represents the real tumor size and tumor burden better than GTD.

Assessment of the change in tumor burden is one important feature of clinical evaluation of cancer therapies. The Response Evaluate Criteria in Solid Tumors (RECIST) is currently the quantitative standard used to assess the change of tumors in clinical trials.[22] The measurement standard for tumor sizing used as part of RECIST is the longest diameter of a tumor. Concerns have been raised about RECIST-based response assessments, in part because tumors do not always expand or contract uniformly, with changes in line lengths representing only a small fraction of the available information in the images.[3]

In an effort to address the limitation of RECIST and to potentially improve the sensitivity of the measurement to true tumor changes, volumetric sizing has been proposed as an alternative approach for measuring anatomic change in a lesion. In a critical review article on the change in lung TV as a biomarker of treatment response, Mozley et al.[8] found that correlations with clinical outcomes have been higher for volumetric-based measures than for uni- or bidimensional diameters in a few clinical trials. These findings further demonstrate that volumetric measurement can be more informative than measurement of a line length placed on a single CT slice.

Our study had several limitations. First, it was inherently limited by its retrospective observational study design with its potential biases. Second, only early-stage NSCLC was

included in the study population. The relationship between TV and N staging needs to be investigated. Third, using standardized protocols, volumetric measurement of solid nodules surrounded by lung parenchyma was demonstrated to be reproducible,[2] but TV cannot be obtained if the lesion is combined with atelectasis or obstructive pneumonia. Therefore, we had to exclude 39 patients in our study. Finally, the patients received various treatments after recurrence, which might have affected the outcomes of OS analysis. Therefore, DFS was used as the primary end point in this study.

In conclusion, TV is better than GTD for reflecting the true tumor burden and for predicting the prognosis of patients with early-stage NSCLC. More studies are needed to further demonstrate the impact of TV as a biomarker to influence treatment decisions for patients with NSCLC.

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