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Clinical Research

Recommendation for Clinical T Staging in Patients with Non-Small Cell Lung Cancer: Volumetric Measurement: A Retrospective Study from Turkey

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Background: Currently, clinical T staging in non-small cell lung cancer (NSCLC) is based on the largest radiological diameter observed on computed tomography (CT). Under this system, tumors with varying shapes—such as spherical, amorphous, or spiculated tumors—can be assigned the same T stage even with different volumes. We aimed to propose a 3-dimensional (3D) volumetric staging system for NSCLC as an alternative to diameter-based T staging and to conduct comparative survival analyses between these methods.
Methods: We retrospectively analyzed data from patients who underwent surgery for pT1-4N0M0 primary NSCLC between January 2018 and May 2022. Digital Imaging and Communications in Medicine data from patient CT scans were uploaded to 3D Slicer software for volumetric tumor measurement. Using the paired samples t-test or the Wilcoxon test, we compared the expected tumor volumes, calculated by tumor diameter, with the actual volumes measured by 3D Slicer. Receiver operating characteristic analysis was employed to determine the cut-off value for tumor volume. Kaplan-Meier analysis was utilized to assess overall survival, while the log-rank method was applied to compare survival differences between groups. The significance of changes in T stage was evaluated using the marginal homogeneity test.
Results: The study included 136 patients. Significant differences were observed between expected and actual tumor volumes (p=0.01), and associated changes in T stage were also significant (p=0.04). The survival analysis performed using tumor volume (p=0.009) yielded superior results compared to that based on diameter (p=0.04) in paients with early tumor stage.
Conclusion: T-factor staging based on tumor volume could represent an alternative staging method for NSCLC.

Keywords: Non-small-cell lung carcinoma, 8th edition TNM, Tumor volume, 3D-Slicer

Introduction

The most important factor for predicting survival in patients with non-small cell lung cancer (NSCLC) is the stage of the tumor. One indicator of T factor in the clinical staging of NSCLC is tumor diameter. In lung cancer cases, clinical staging is crucial for determining the appropriate treatment approach, including whether to perform surgery. For T staging in NSCLC, the International Association for the Study of Lung Cancer (IASLC) indicates that the largest diameter of the tumor should be measured using thoracic computed tomography (CT). However, since tumors are not always spherical, those with identical diameters but different volumes may be assigned the same T stage [1]. Although volumetric measurements have recently been recommended for the monitoring of lung nodules, few studies have examined the role of tumor volume in survival and staging among patients with NSCLC [2]. We evaluated the predictive value of 3-dimensional (3D) volumetric T-staging for survival in patients with NSCLC and explored the

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potential of using 3D tumor volume as an alternative to tumor diameter for staging.

Methods

This study was approved by the Institutional Review Board of the Gazi University Ethics Committee (IRB approval no., 2023-1169). As a retrospective archive study, written informed consent for publication was not required.

Patient selection

Following approval from the local ethics committee, the data of patients who underwent surgery for primary NSCLC at our clinic between January 2018 and May 2022 were retrospectively reviewed. Patients with solid tumors were included if their thoracic CT scans were available. The exclusion criteria were factors that could adversely impact volume measurement or introduce heterogeneity to the survival analysis. Patients who lacked accessible follow-up records had a history of thoracic surgery, demonstrated thoracic wall and mediastinal invasion, had clinical or pathological lymph node metastasis, were ineligible for adjuvant treatment despite its indication based on pathological staging, underwent incomplete resection, displayed ground-glass opacity nodules, had atelectasis accompanying the mass, or had metastatic lung disease or synchronous tumors in the ipsilateral or contralateral lung were excluded from the study. CT scans were performed using a 64-detector Siemens-SOMATOM go.Up device (Siemens Healthineers, Erlangen, Germany) with a slice thickness of 1.1 mm. Digital Imaging and Communications in Medicine (DICOM) files from the CT scans were uploaded to the 3D Slicer program (Slicer Community; https://www.slicer.org/). Two clinicians, working independently and blinded to each other's measurements, used this software to semi-automatically measure actual tumor volume [3] (Fig. 1). The expected volume range was calculated for each

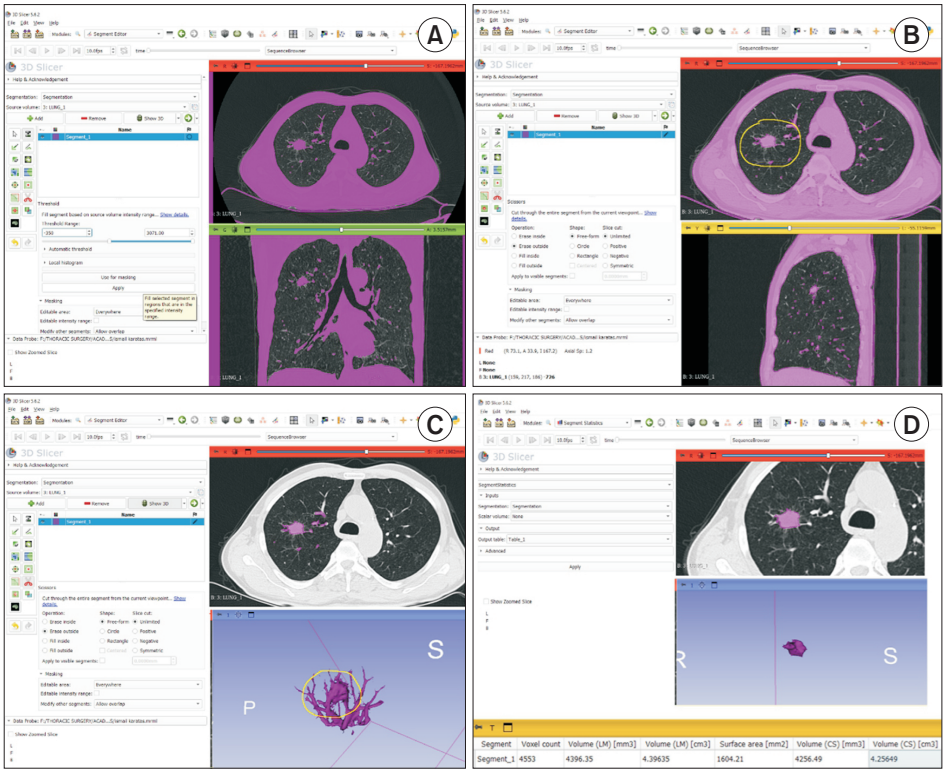


Fig. 1. Sample measurement of 3-dimensional (3D) tumor volume using 3D Slicer software. (A) After uploading the DICOM (Digital Imaging and Communications in Medicine) extension section to 3D Slicer, the "Threshold" tool is selected. The threshold Hounsfield unit (HU) value is set to include the density values of the nodule, with a preferred range of −350 to +3,000 HU. The software then assigns the tissues within the selection to the relevant segment and excludes tissues outside the range. (B) The "Erase outside" mode is selected for the "Scissors" tool. Using this tool, the periphery of the nodule is outlined on the axial plane, encompassing its borders, and the surrounding tissues are excised from the segment. (C) "Show 3D mode" is activated. Surrounding tissues of similar density to the nodule are excised using the "Scissors" tool to achieve the final version of the 3D model. (D) The "Segment Statistics" module provides the measured volume of the nodule. In the given example, the nodule volume is calculated as 4.25 cm^3.

T stage based on the tumor diameter in cubic centimeters (cm^3), assuming a spherical shape and using the formula for the volume of a sphere ($4/3\pi r^3$).

Statistical analyses

Statistical analysis was conducted using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA). We examined the difference between the expected volume based on diameter and the actual volume derived from the T factor using paired samples t-tests for normally distributed variables and Wilcoxon tests for variables with skewed distributions. Diameter-based T staging was performed in line with the guidelines of the eighth edition of the tumor-node-metastasis (TNM) classification. The actual tumor stage was determined using tumor diameter, while the expected tumor stage was assigned based on volume measurements. The marginal homogeneity test was applied to identify any differences in staging between these methods. Pearson correlation analysis was used to assess the significance of the correlation between tumor diameter and tumor volume. The consistency of tumor volume measurements obtained by the 2 clinicians was evaluated using the paired samples t-test. Overall survival (OS) analysis was conducted with the Kaplan-Meier method, and differences in survival between groups were analyzed using the log-rank test. The cut-off value for tumor volume affecting OS was established through receiver operating characteristic (ROC) analysis. All statistical analyses employed a 95% confidence interval, and a p-value of less than 0.05 was considered to indicate statistical significance.

Table 1. Clinicopathologic characteristics of study participants (n=136)

Characteristic	Value
Age (yr)	63.7±8.2
Tumor diameter (cm)	2.4 (0.7–9)
Expected tumor volume[a] (cm^3)	7.23 (0.18–448)
Real 3D tumor volume[b] (cm^3)	6.3 (0.1–523.9)
Length of stay (day)	7 (2–29)
Sex	
Female	32 (23.5)
Male	104 (76.5)
Radiologic T factor (eighth TNM)	
T1a	9 (6.6)
T1b	47 (34.6)
T1c	27 (19,8)
T2a	17 (12.5)
T2b	14 (10.3)
T3	14 (10.3)
T4	8 (5.9)
3D volumetric stage[c]	
T1	86 (63.2)
T2	27 (19.9)
T3	16 (11.8)
T4	7 (5.1)
Expected stage[d]	
T1	77 (56.6)
T2	37 (27.2)
T3	13 (9.6)
T4	9 (6.6)
Surgery	
Wedge	5 (3.7)
Lobectomy	117 (86.0)
Segmentectomy	11 (8.1)
Pneumonectomy	3 (2.2)
Histopathology	
Adenocarcinoma	67 (49.3)
Squamous cell carcinoma	58 (42.6)
Other[e]	11 (8.1)

Values are presented as mean±standard deviation, median (minimum–maximum), or number (%).
3D, 3-dimensional; TNM, tumor-node-metastasis.
[a]Expected volume was calculated with the formula $4/3\pi r^3$, assuming a spherical tumor. [b]Real volume was calculated using 3D Slicer software. [c]3D volumetric stage defines the T-stage according to the actual measured volume of the tumor. [d]Expected stage defines the T-stage that the tumor should be in according to its volume calculated according to its diameter. [e]Other histopathological findings included adenosquamous cell carcinoma, pleomorphic carcinoma, and large cell carcinoma.

Results

The study included data from 136 eligible patients. Of these, 32 (23.5%) were female, with a mean age of 63.7±8.2 years. Regarding clinical stage, most participants were in the T1b group, comprising 47 patients (34.6%). The median tumor diameter was 2.4 cm (range, 0.7–9 cm). Adenocarcinoma was the most prevalent tumor histopathology, ob-

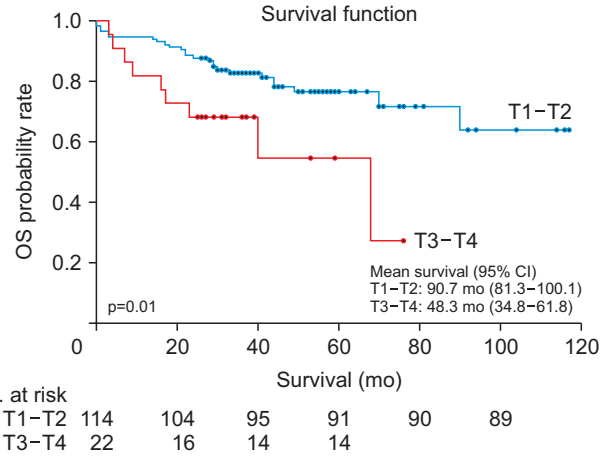


Fig. 2. A survival difference was evident between early and advanced stages, as determined by radiologic tumor diameter. OS, overall survival; CI, confidence interval.

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served in 67 patients (49.3%), and lobectomy was the most common type of resection, performed in 117 patients (86%). The patient characteristics are detailed in Table 1. Tumors were classified as early (T1 or T2) or advanced (T3 or T4) based on radiological diameter. A significant survival difference was noted between the early and advanced tumor groups, as determined by tumor diameter (p=0.01) (Fig. 2). The cut-off value for 3D tumor volume across all T stages was established at 10.55 cm^3 through ROC analysis (p=0.009) (Fig. 3A). Tumor volume measurements were repeated independently by two different clinicians, and the measurement results were compared using a paired sample t-test. As a result, no significant difference was detected (p=0.59, t=0.53; 95% CI, -0.06 to 0.1). Tumors were categorized as low- or high-volume according to this cut-off value. A more pronounced difference in OS was observed between these groups compared to the T-stage groups defined by tumor diameter (p=0.003) (Fig. 3B). The ROC analysis for early-stage (T1–T2) tumors revealed a significant cutoff value of 4.57 cm^3 for tumor volume in relation to OS (Fig. 4). After again establishing high- and low-volume groups based on this value, we found that survival predictions based on tumor volume were more accurate than those based on tumor diameter (p=0.009 versus p=0.04) (Fig. 5). However, the results of the ROC analysis were not significant for advanced-stage (T3–T4) tumors (p=0.3). The median expected tumor volume, calculated using the formula $4/3\pi r^3$, was 7.23 cm^3 (range, 0.18–448 cm^3), while the median actual tumor volume, determined using the 3D Slicer program, was 6.3 cm^3 (range, 0.1–523.9 cm^3). Wilcoxon test analysis indicated that this volume difference was statistically significant (p=0.001). When the proposed volumetric staging was used, changes in the T stage were observed for 24 patients (17.6%), while subgroup transitions within T1 and T2 were detected for 35 patients (31.8%). Table 2 presents the ranges of expected and measured volumes by T stage, and Table 3 displays the rates of upstaging and downstaging across T stages, with downstaging being more prevalent. The difference in T stage between methods was statistically significant according to the marginal homogeneity test (p=0.04) (Fig. 6). Additionally, a weak but significant correlation was found between radiological tumor diameter and tumor volume using Pearson correlation analysis (p=0.03; r=0.19; 95% CI, −0.06 to 0.1) (Fig. 7).

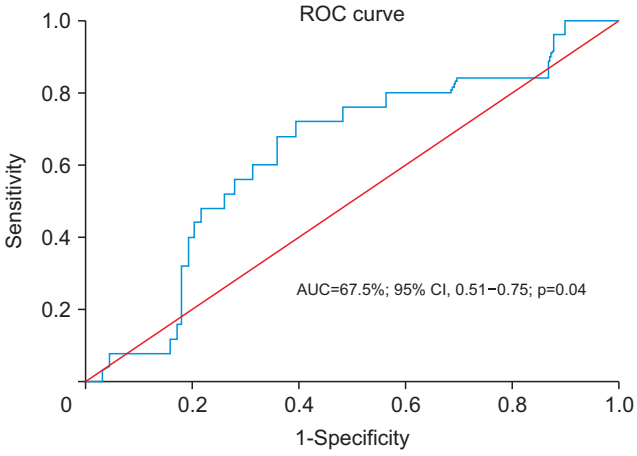


Fig. 4. Receiver operating characteristic (ROC) curve based on tumor volume in early radiological T stages (T1 and T2). Diagonal segments are produced by ties. AUC, area under the curve; CI, confidence interval.

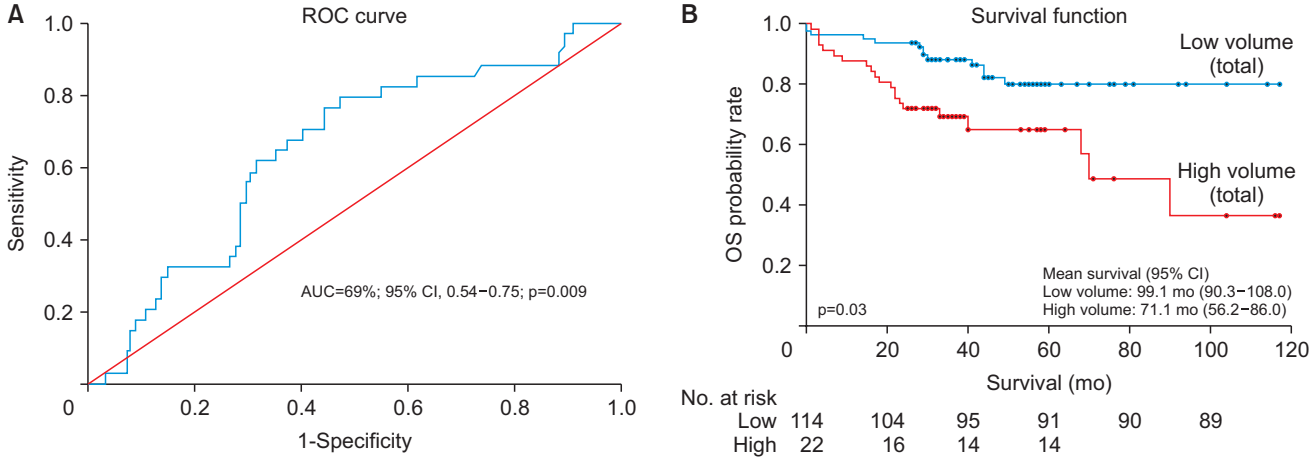


Fig. 3. (A) Receiver operating characteristic (ROC) curve based on tumor volume across all radiological T stages. Diagonal segments are produced by ties. (B) The survival rate differed significantly when tumor volume was categorized using the cut-off value determined via ROC analysis. AUC, area under the curve; CI, confidence interval.

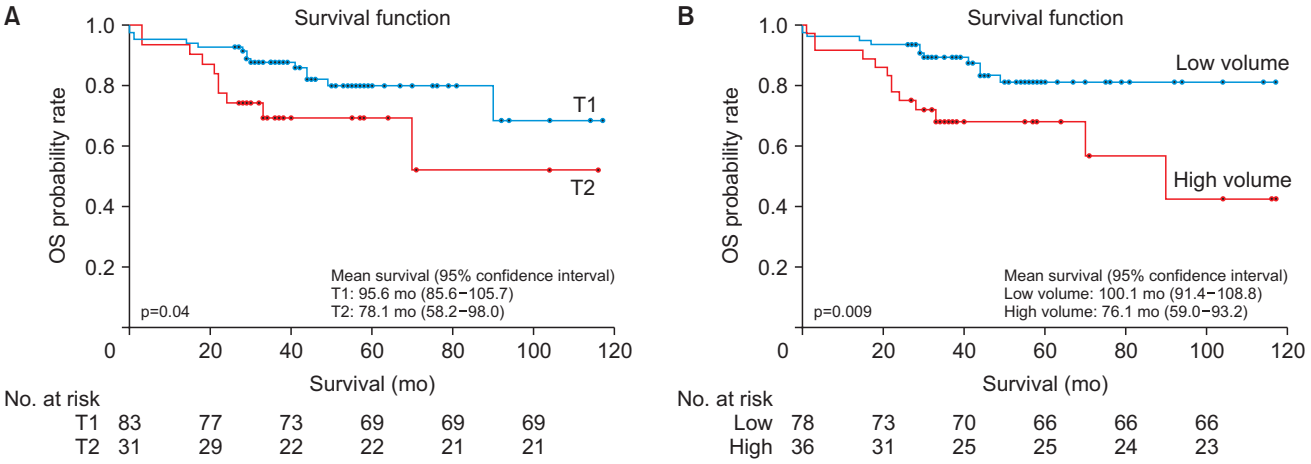


Fig. 5. (A, B) Tumor volume provided a more accurate prediction of overall survival than tumor diameter in patients with non-small cell lung cancer in early radiological T stages. OS, overall survival; CI, confidence interval.

Table 2. Expected and measured volume ranges by tumor stage

	Expected volume ($V=4/3\pi r^3$) (cm^3)	Real (measured) volume (cm^3)	
	Range	Mean	Range
T1	0–14.13	4.02	0.01–39
T2	14.14–65.44	40.97	4.44–211.1
T3	65.45–179.59	78.63	0.62–268.8
T4	>179.59	191.86	58.98–523.99

Table 3. Changes in T stage and its subgroups based on expected and actual tumor volumes

No.	Expected volumetric stage	Actual volumetric stage
3	T1a	T1b ↑
7	T1b	T1c ↑
8	T1b	T1a ↓
8	T1c	T1b ↓
1	T1c	T1a ↓
4	T2a	T2b ↑
4	T2b	T2a ↓
5	T2	T3 ↑
1	T1	T2 ↑
1	T3	T4 ↑
3	T4	T3 ↓
10	T2	T1 ↓
4	T3	T2 ↓

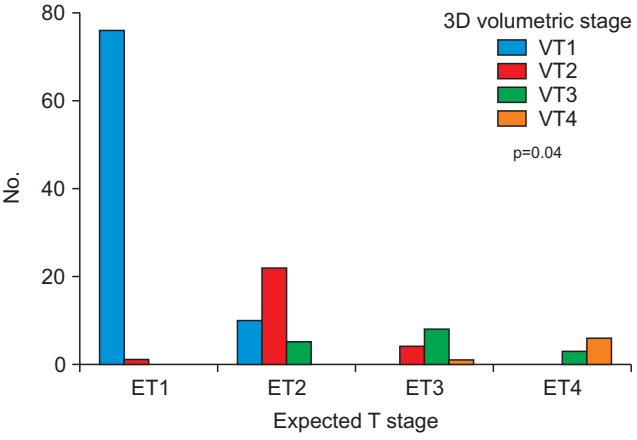


Fig. 6. Significant differences in tumor stage were observed when comparing expected and actual tumor volumes (p=0.04, as determined using the marginal homogeneity test).

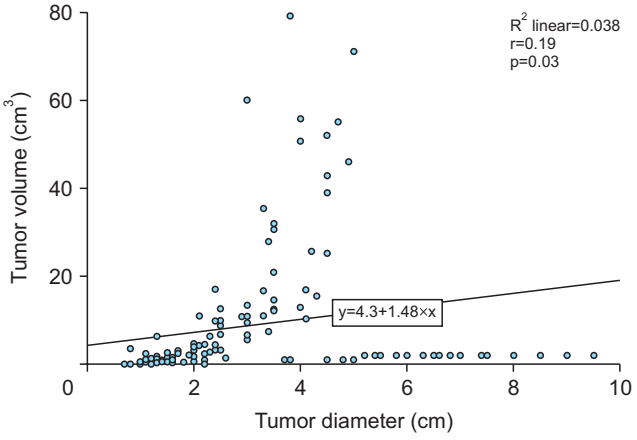


Fig. 7. Pearson correlation analysis revealed a weak but significant correlation between tumor diameter and volume (p=0.03; r=0.19; 95% confidence interval, −0.06 to 0.1).

Discussion

In this study, we proposed an alternative volumetric measurement for T staging in patients with NSCLC. The tumor stage is the most important determinant of prognosis in NSCLC, with clinical staging governing operability

and treatment options [2]. The current TNM staging system of the IASLC uses tumor diameter, invasion status, and the presence of satellite nodules to determine the T factor [4]. Clinical T staging relies on the largest radiologically measured tumor diameter. For spherical tumors, the diameter may accurately reflect volume, as measurements along each axis are equal. However, lobular or spiculated lesions can vary in volume despite having identical diameters. Accordingly, volumetric measurements have recently been reported to be effective, especially for evaluating the growth of pulmonary nodules [5]. Radiologic follow-up of pulmonary nodules has shown that growth along the short axis of a nonspherical lesion can occur without changes in the largest diameter, potentially leading to misinterpretation [6]. The latest guidelines of the Fleischner Society underscore this issue and recommend volumetric follow-up of pulmonary nodules [7]. The present study supports the use of volumetric measurements over radiological diameter assessment in NSCLC staging. We found that lesions classified in the same T stage based on radiological diameter sometimes had different stages when tumor volume was considered; furthermore, volumetric measurements were superior to diameter evaluation in predicting OS. Unlike tumor diameter measurement, which is pixel-based, the calculation of 3D volume is voxel-based. The literature contains various studies on the prognostic impact of tumor volume in patients with cancer. One study on pleural mesothelioma suggested that thoracic CT volumetry correlates with pathological tumor volume and represents a significant prognostic factor [8]. Other research has demonstrated the influence of tumor volume on survival in gastric, thyroid, and endometrial cancers, although studies of NSCLC are limited [9-11]. Xie et al. [12] measured lung cancer tumor volumes semiautomatically and found that volume (classified as low, medium, or high) is a more influential prognostic factor than diameter. Aligning with our results, Su et al. [2] reported that tumor volume is a better predictor of survival than diameter in patients with stage I NSCLC. Duran et al. [13] established a cutoff value for tumor volume in patients undergoing surgery for stage I–III NSCLC and identified a significant survival difference between groups in univariate and multivariate analyses. While our study confirms that tumor volume is a superior prognostic indicator, unlike previous studies, it also reveals changes in T factor when determined using expected versus actual 3D tumor volume.

The first limitation of our study is its retrospective nature; the second is the limited number of patients included. Consequently, while a significant difference was observed between volumetric and diameter-based methods for stages T1–T4, no such change was detected between the T1–T2 subgroups. Another limitation concerns the semiautomatic measurement of tumor volumes, which may lead researchers to perceive volumetric tumor measurement as challenging to implement in a clinical setting. Automatic measurements utilizing artificial intelligence could offer improvements in terms of time efficiency and standardization. Furthermore, the addition of a volume-measuring interface within segmentectomy modeling software could be beneficial. However, implementing a fully automatic volume measurement system would require the input of large amounts of patient data. Despite the small sample size, our study may inspire larger series and multicenter studies. As the effectiveness of volumetric staging is further validated by research and adopted by lung cancer study groups at various institutions, it may supplant the traditional diameter-based staging approach. An additional limitation was our inability to perform a correlation analysis between increases in tumor volume and OS during follow-up. Most patients with nodules that were enlarged during follow-up had prior CT scans that were unsuitable for 3D volumetry. Future research in this area could demonstrate that the rate of volume increase is also a viable prognostic indicator.

In conclusion, volumetric staging may represent an alternative to diameter-based staging for the clinical assessment of lung cancer. Further research involving a larger patient sample and longer follow-up periods are required to substantiate these findings.

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editing: MS, AK, MTA, IA, ICK, AC. Final approval of the manuscript: MS, AK, MTA, IA, ICK, AC.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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