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CT Volumetry and Basic Texture Analysis as Surrogate Markers in Advanced Non—small-cell Lung Cancer

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Abstract

We performed a retrospective study comparing volumetric and unidimensional tumor size measurements in patients with advanced non—small-cell lung cancer. Cox regression analysis of the 77 patients analyzed demonstrated that only change in tumor volume and the initial tumor size predicted survival, indicating that volume is a better marker of survival compared with the diameter measurements that underlie Response Evaluation Criteria In Solid Tumors (RECIST).

Introduction: We evaluated volumetric tumor measurements and computed tomography texture analysis as prognostic indicators in patients with advanced non—small-cell lung cancer when compared with the unidimensional tumor size measurements used in Response Evaluation Criteria in Solid Tumors (RECIST). **Patients and Methods:** In a retrospective review, computed tomography examinations in 77 patients with advanced non—small-cell lung cancer were evaluated before and after 2 cycles of chemotherapy. Baseline and changes in tumor diameter, volume, and texture were analyzed. Survival was analyzed with Cox regression analysis and Kaplan-Meier survival statistics.

Results: Cox regression analysis demonstrated that only change in tumor volume ($\exp(B) = 1.006$; $P = .02$) and the initial sum of the largest target lesion diameters predicted survival ($\exp(B) = 1.013$; $P = .02$). Kaplan-Meier statistics demonstrated that patients with an initial sum of the largest target lesion diameters less than 88 mm had median survival time of 587 days (95% confidence interval [CI], 269-905 days), compared with the survival of those with larger tumor burden of 407 days (95% CI, 235-579 days). Patients in whom tumor volume decreased by more than 29% had a median survival time of 622 days (95% CI, 448-796 days), compared with 305 days for those with less decrease (95% CI, 34-240 days). **Conclusion:** This study demonstrates that change in lung tumor volume is a better marker of patient survival than change of unidimensional diameter measurements in our cohort. If confirmed in larger studies, this suggests that volumetry might improve clinical decision-making for individual patients and allow for faster assessment of new treatments.

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Keywords: Chemotherapy, Diameter, High resolution, Response Evaluation Criteria in Solid Tumors, Survival

Introduction

Although substantial progress has been made in advancing the use of tumor volumetry in the past decade, not the least with the Quantitative Imaging Biomarkers Alliance (QIBA), a major research

initiative of the Radiological Society of North America, numerous practical and evidentiary hindrances still prevent its routine clinical use.

At present, the established Response Evaluation Criteria for Solid Tumors (RECIST) apply 1-dimensional tumor measurements and remain the factual clinical standard for assessing treatment response in lung cancer.¹

Theoretical advantages of using tumor volume measurements over 1-dimensional measurements have been supplemented by clinical evidence that volumetric tumor response may predict patient survival as the ultimate endpoint standard.² In advanced lung cancer, it has been shown that tumor volume estimates derived from unidimensional measurements differ significantly from actually

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CT Volumetry of Advanced NSCLC

measured tumor volume.³ Volumetric determination of tumor size in lung cancer predicts the prognosis in resectable disease better than maximal diameter.⁴ For patients with epidermal growth factor receptor-mutant advanced non-small-cell lung cancer (NSCLC) treated with tyrosine kinase inhibitor chemotherapy, volume change at 8 weeks was associated with overall survival (OS), whereas change in tumor diameter was not.⁵

Previous research has indicated that size response evaluation in advanced lung cancer after 8 weeks can predict outcome,^{6,7} and RECIST guidelines suggest that the response is evaluated after at least 8 weeks.

Volumetric analysis has demonstrated importance in other types of malignancies. For example, in Ewing sarcoma, it has been shown that 3-dimensional tumor measurements with magnetic resonance imaging predict survival better than diameter measurements.⁸ For recurrent malignant brain gliomas, it has also been found that volumetric measurements predict survival, whereas uni- and bidirectional size measurements did not.⁹ Volumetric tumor response has also been found to predict survival in metastatic colorectal cancer.¹⁰

Conversely, the present clinical evidence that volumetric treatment response measurements are superior to diameter measurements is sparse, and one recent investigation failed to show an association in advanced lung cancer.¹¹

Our hypothesis is that computed tomography (CT) volumetry and primary lesion texture predict survival in patients with advanced NSCLC. The purpose of this study was to evaluate volumetric tumor measurements and CT texture analysis as prognostic indicators of OS in patients with advanced NSCLC when compared with RECIST-defined uni-dimensional tumor size measurements.

Patients and Methods

Patient Selection

Approval was obtained from the institutional review board, which waived the requirement for informed consent for this retrospective analysis. In compliance with the Health Insurance and Accountability Act (HIPAA), 130 potential patients with biopsy-proven stage III or IV NSCLC were identified. Patients with CT examinations of the thorax dating from 2005 to 2017 with 1- to 1.5-mm axial slice thickness images, in both the pre-therapy and response studies were selected. All patients underwent systemic treatment. Clinically relevant information was obtained from the electronic medical record, including date of birth, gender, cancer stage at the time of the first scan, histologic subtype, and the date of last contact or date of death. Current and prior treatment regimens were recorded, with all patients receiving chemotherapy and a total of 3 receiving immunotherapy.

Inclusion criteria consisted of patients aged ≥ 18 years with NSCLC who received ≥ 2 consecutive CT examinations. Additional imaging studies were frequently available; however, these were excluded because not all patients received more than 2 exams, and the period between the second exam and the subsequent study was highly variable.

CT Protocol and Measurement Acquisition

The pretreatment CT scan technique included intravenous contrast administration in 74 patients and non-contrast examinations in 3 patients. Siemens scanner types included the Somatom

Sensation 64 and the Somatom Definition AS. The reconstruction kernel selected for these scanners was B30 in 33 patients, B31 in 9 patients, B40 in 3 patients, and I41 in 3 patients. General Electric scanners utilized included the Lightspeed 16 and the Lightspeed VCT, with standard body filter used in 29 patients. The slice thickness was 1 mm in 36 patients, 1.25 mm in 28 patients, and 1.5 mm in 13 patients.

The response CT scan technique included intravenous contrast administration in 73 patients and non-contrast examinations in 4 patients. The second CT examination slice thickness was 1 mm in 45 patients, 1.25 mm in 12 patients, and 1.5 mm in 20 patients. B30 reconstruction kernel was used in 46 patients, B31 in 11 patients, B40 in 5 patients, I41 in 2 patients, and standard body filter in 13 patients. The slice thickness was 1 mm in 45 patients, 1.25 mm in 12 patients, and 1.5 in 20 patients.

Contrast-enhanced studies utilized 100 to 125 mL of iohexol 350 injected at a rate of 2.5 mL/s with a delay of 50 seconds as per institution protocol. All scans utilized 120 kVp.

All studies were initially interpreted by board-certified radiologists with target lesions identified in the dictation. Volumetric and basic texture analysis was performed by a resident radiologist (BO) under direct attending supervision (FK). The examinations were analyzed on TeraRecon's Aquarius iNtuition Edition software (version 4.4), with lesions' largest diameter, volume, shape compactness, mean attenuation, attenuation standard deviation, maximum attenuation, and minimum attenuation recorded. Although the time of target lesion analysis was not recorded, each lesion took between 1 and 10 minutes to segment depending on complexity. Figure 1 shows a flow diagram of the process. Figures 2 and 3 illustrate segmentation of a lesion in the right lower lobe.

Statistical Analysis

The baseline and change of the summed largest diameters of thoracic target lesions was obtained, followed by the baseline and change of the summed thoracic target lesion volumes.

The CT texture characteristics studied included baseline and change in mean attenuation of lung target lesion 1, baseline and change in the attenuation standard deviation of lung target lesion 1, and baseline and change in shape compactness of lung target lesion 1.

The Shapiro-Wilk test was performed for statistically significant prognostic indicators to determine normality. Neither the sum of largest diameters of scan 1 nor the percent change in volume demonstrated a normal distribution ($P = .02$ and $P = .00$), so the median value was used to stratify patients for Kaplan-Meier statistics.

The summed largest diameters and the volumetric data were compared using a log-rank survival analysis as percentage differences compared with the median as the data did not fit a normal distribution. Absolute differences were also obtained. Prognostic factors demonstrated to be statistically significant with Cox regression analysis were analyzed using Kaplan-Meier survival statistics. Statistical calculations were performed using IBM SPSS Statistics 25.

Results

Demographics

Of the 130 patients evaluated, 77 were included (Table 1). The power of this size cohort was found to be 0.98 using a 1-arm

Figure 1 Flow Chart of Measurement Acquisition

Abbreviations: CT = computed tomography; NSCLC = non-small-cell lung cancer.

nonparametric survival model.¹² The median time from the initial CT scan to loss of patient contact, patient death, or their most recent follow-up visit was 487 days, with a standard error of 82 days (10th percentile, 281 days; 90th percentile, 692 days). The median period between the first CT scan and the first follow-up scan was 69 days (10th percentile, 45 days; 90th percentile, 131 days). During the total observation period, 69 patients died.

Survival Analysis

Cox regression analysis demonstrated that the sum of the largest diameters on the baseline scan was clinically significant ($\exp(B) = 1.012$; $P = .01$) (Table 2). Additionally, the change in target lesion volume from baseline to follow-up scan was significant ($\exp(B) = 1.006$; $P = .015$). The change in summed diameters from the baseline CT to the follow-up CT was not significant ($\exp(B) = 1.010$; $P = .11$), nor was the initial summed volume of target lesions ($\exp(B) = 1.001$; $P = .782$).

In terms of CT texture, the attenuation standard deviation of target lesion 1 on the baseline scan was significant ($\exp(B) = 0.989$; $P = .05$). No other CT texture parameter was clinically significant, which includes the mean attenuation of target lesion 1 on the baseline scan, change in attenuation standard deviation, baseline target lesion shape compactness, and change in target lesion shape compactness.

Figure 2 Axial and Coronal Segmentations of Right Lower Lobe Lesion on Pre-therapy Computed Tomography **Figure 3** Axial and Coronal Segmentation of the Right Lower Lobe Lesion on Response Scan, Demonstrating a 5% Decrease in Diameter and 55% Decrease in Volume. The Time From the Pre-therapy Scan Until the Last Date of Contact in the Electronic Medical Record was 2784 Days, When the Patient Entered Hospice

CT Volumetry of Advanced NSCLC

Table 1 Patient Characteristics

Characteristics	N (%)	Median Survival, d ^a
Total patients	77	487
Gender		
Male	38	568
Female	39	317
Age (range), y	65 (37-88)	
Stage		
III	6 (8)	611
IV	71 (92)	487
Histology		
Adenocarcinoma	41 (53)	427
Squamous cell carcinoma	8 (10)	587
Not specified NSCLC	28 (36)	622
Brain metastasis at time of first CT	18 (23)	
Treatment regimen		
Carboplatin and paclitaxel	44 (57)	
Carboplatin and pemetrexed	8 (18)	
Erlotinib	9 (12)	
Carboplatin, paclitaxel, bevacizumab	5 (6)	
Reason excluded		
No measurable disease	22 (41)	
No thin axial images	18 (34)	
No sequential CTs	13 (24)	

Abbreviations: CT = computed tomography; NSCLC = non-small-cell lung cancer

^aNo statistical significance in survival was found.

Kaplan-Meier statistics demonstrated that patients with a sum of the largest diameters of target lesions of scan 1 greater than the median value of 88 mm had a median survival time of 407 days (10th percentile, 235 days; 90th percentile, 579 days) compared with patients with summed largest diameters less than 88 mm (587 days; 10th percentile, 269 days; 90th percentile, 905 days) (Figure 4A).

Patients with a percent decrease in target lesion tumor volume greater than the median decrease in size of 28.7% demonstrated a median survival time of 622 days (10th percentile, 448 days; 90th

percentile, 796 days) compared with 305 days in patients with a percent change less than the median (10th percentile, 34 days; 90th percentile, 240 days) (Figure 4B).

A decrease in target lesion tumor diameter of greater than the median decrease of 8.04% demonstrated a median survival time of 588 days (10th percentile, 616 days; 90th percentile, 1117 days) compared with 342 days in those with a change less than the median (10th percentile, 359 days; 90th percentile, 693 days) (Figure 4C).

Finally, survival time for patients with an attenuation standard deviation of target lesion 1 greater than the median of 132 Hounsfield units was 488 days (10th percentile, 535 days; 90th percentile, 1037 days), compared with those less than the median of 487 days (10th percentile, 431 days; 90th percentile, 830 days) (Figure 4D).

Discussion

Uses of Volumetry

This analysis demonstrates that volumetric analysis of tumor response was a better predictor of survival in patients with advanced NSCLC than length measurements in a single-center analysis.

This insight is important for patient care because the purpose of assessing treatment response is to direct treatment of individual patients, and changes in tumor size are used as a surrogate marker of patient outcome. Consequently, use of tumor volumetry can be expected to improve patient survival, as a more accurate assessment of treatment success allows for an earlier adjustment of therapy.

Although theoretical and some practical advantages of tumor volumetry have been shown previously, the clinical evidence to support its use is still lacking. It has been shown previously that uni- and bi-dimensional measurements of tumor size differ from volumetric measurements.¹³

An earlier study demonstrated an advantage of tumor volumetry to predict patient survival in 56 patients with epidermal growth factor receptor-mutant advanced NSCLC treated with tyrosine kinase inhibitors; however, another study on the same subject found that RECIST-type unidimensional measurements were associated with patient survival.^{5,14} That study found the greatest treatment effect occurred later than the former.

Another study that included a less selective patient group did not show an association of tumor volume response and patient

Table 2 Cox Regression Analysis

Variable	B	SE	Sig	Exp(B)
Sum of the largest target lesion diameters at scan 1	0.012	0.004	0.01	1.012
Percent change in diameters ^a	0.006	0.006	0.317	1.006
Sum of the target lesion volumes in scan 1	0.002	0.003	0.472	1.002
Percent change in volume ^a	0.006	0.002	0.017	1.006
Lung target lesion mean attenuation at scan 1	-0.008	0.005	0.103	0.992
Change in lung target lesion mean attenuation	-0.007	0.007	0.318	0.993
Lung target lesion attenuation standard deviation	-0.012	0.006	0.048	0.988
Change in lung target lesion attenuation standard deviation	0.005	0.005	0.298	1.005
Lung target lesion shape compactness	-0.028	0.026	0.282	0.972
Change in lung target lesion shape compactness	-0.003	0.018	0.853	0.997

^aChange is from scan 1 to scan 2.

Figure 4 A, Kaplan-Meier Curve of Summed Target Lesion Diameters. The Curve Demonstrates Improved Survival in Patients With a Summed Target Lesion Diameter of less than the Median Decrease in Size of 88 mm. B, Kaplan-Meier Curve of Percent Change in Target Lesion Tumor Volume. The Curve Demonstrates Improved Survival in Patients With a Change in Volume Greater than the Median Decrease of 28.7%. C, Kaplan-Meier Curve of Percent Change in Target Lesion Diameter. The Curve Demonstrates Improved Survival in Patients With a Decrease in Tumor Diameter of Greater than 8.04%. D, Kaplan-Meier Curve of Lung Target Lesion 1 Attenuation Standard Deviation at Scan 1. Illustration of Survival in Patients With Target Lesion One Demonstrating a Higher Attenuation Standard Deviation Compared With the Median of 132.0 Hounsfield Units

Abbreviations: CT = computed tomography; TL1 = target lesion 1.

survival.¹¹ One possible explanation is that this study used volume estimates derived from CT data with a lesser spatial resolution, defined by CT slice thickness.¹⁵

Our results are plausible as the initial tumor burden was also related to patient outcome; the basis of the TNM classification.¹⁶ This was not the case on the prior attempt to demonstrate volumetry as a surrogate marker of survival.¹¹

Change in uni-dimensional measurements was not found to be a significant predictor of survival, concordant with prior studies.^{17,18}

Future research is needed to confirm our results in a larger patient group and in more diverse settings. Such research should include non-thoracic tumor manifestations, and consider other established prognostic factors such as performance status, as well as molecular tumor characteristics, specific treatment regimens, and additional time points. Lastly, the benefit of using tumor volumetry as a surrogate marker of treatment success will need to be demonstrated in prospective clinical trials that adopt volumetry to steer treatment

decisions, and compare outcomes with RECIST-based decision-making.

To translate the more accurate prognostic information contained in volumetric tumor size measurements, it will be necessary to define response categories that steer treatment decisions, similar to the RECIST categories. The definition of response category thresholds is beyond the scope of this study and material for additional argument.

Basic CT Texture Analysis

The use of biomarkers other than size to monitor treatment has been demonstrated to be of benefit in malignancies. Choi criteria in neuroendocrine tumors uses tumor density to monitor response in gastrointestinal stromal tumors.¹⁹ In NSCLC, heterogeneity has been shown to have histopathologic correlation with tumor hypoxia and angiogenesis.²⁰ Tumor heterogeneity can be a predictor of patient outcomes.^{21,22} This basic texture analysis of target lesion

CT Volumetry of Advanced NSCLC

change from pretreatment scan to the response scan did not demonstrate statistical significance, suggesting these are unlikely to be of benefit in assessing response to treatment.

Study Limitations

This exploratory research spanned 10 years at a single center, which led to a limited number of subjects. Utilizing a single center allowed for the advantage of a well-defined CT protocol. The patient population size demonstrated significant power.

As a tertiary referral center, our patient population received heterogeneous treatment regimens, with studies spanning a time frame of 12 years. By utilizing a pragmatic approach and remaining agnostic to the treatment method, these results are applicable to a wide range of different therapies. The increasing use of immune checkpoint inhibitors such as programmed death-ligand 1 inhibitors, which can demonstrate pseudo-progression, may cause RECIST to underestimate response to therapy; however, the National Comprehensive Cancer Network (NCCN) guidelines have not clearly stated an alternative for progression end points.²³⁻²⁶ As more clinical evidence emerges, it is perceivable that different treatment response biomarkers are identified for specific tumor types, genetic aberrations, and treatment agents.

Obtaining volumetric measurements adds time and effort to the radiologist's interpretation and requires additional software. For routine application, the software used needs to be United States Food and Drug Administration-approved and allow an integrated workflow as the additional effort may not be reimbursable by insurance. There is no established method of quality control of volumetric measurements, although this is emerging through the efforts of the Quantitative Imaging Biomarker Alliance. Because change in volume was demonstrated to be a more powerful predictor of survival, however, our work helps foster this effort as it confirms that this information adds significant patient value.

This study only accounted for intrathoracic tumor manifestations. Although it would be ideal to evaluate total body tumor burden, only known tumor manifestations are followed for response as current guidelines do not support systematic total body imaging. Thus, systematic whole body imaging is not retrospectively available.

Finally, our texture analysis was limited to basic characteristics that were available on the Aquarius iNtuition software and does not exclude other texture parameters as useful response biomarkers. Other texture features will need to be assessed in future work as the presently included texture features were only a few and not exhaustive or complete.

Conclusion

This research suggests that volumetric response assessment is superior to standard diameter measurements.

Clinical Practice Points

- RECIST, the clinical standard for assessing treatment response in lung cancer, currently relies on 1-dimensional tumor measurements. Although volumetric analysis has been used to assess response in other malignancies, there is little clinical evidence of its utility for advanced NSCLC.

- This study suggests that change in tumor volume is a better predictor of patient survival than change in diameter. Consequently, use of tumor volumetry can be expected to improve patient survival, as a more accurate assessment of treatment success allows for an earlier adjustment of therapy.

Disclosure

The authors have stated that they have no conflicts of interest.

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