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Original Article / *Özgün Makale*

Does tumor volume affect survival in patients with operated early-stage non-small-cell lung cancer?

Erken evre ameliyat edilen küçük hücreli dışı akciğer kanserli hastalarda tümör hacmi sağkalıma etkili midir?

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ABSTRACT

Background: This study aims to investigate whether tumor volume affects survival in patients with operated early-stage non-small-cell lung cancer.

Methods: A retrospective analysis of 156 patients (146 males, 10 females; mean age 62.3±8.0 years; range 38 to 79 years) with non-small-cell lung cancer who underwent anatomical resection and mediastinal lymph node dissection between September 2009 and June 2013 was performed. The tumor volumes were calculated using histopathological data. The effect of tumor volume on prognosis and survival was investigated.

Results: Of the patients, 116 had Stage I disease and 40 patients had Stage II disease. The mean tumor volume was 38.2±54.6 (range, 356.15 to 0.01) cm^3, and the mean largest diameter was 4.2±2.0 (range, 10 to 0.3) cm. In the Cox regression analysis, the tumor volume below the cut-off value (29.69 cm^3) increased survival with an odds ratio (OR) of 2, and this value was statistically significant (p=0.022). The cut-off value per *T* factor was 4.5 cm and the OR was 1.7; however, no significant correlation with the survival was observed (p=0.058).

Conclusion: The present study found a closer correlation between the tumor volume and survival in contrast to the known correlation between the tumor's largest diameter and survival. Based on our study results, it is recommended to calculate and consider the tumor volume along with the tumor diameter in the staging of lung cancer.

Keywords: Lung cancer; prognosis; staging; tumor volume.

ÖZ

Amaç: Bu çalışmada erken evre ameliyat edilen küçük hücreli dışı akciğer kanserli hastalarda tümör hacminin sağkalımı etkileyip etkilemediği araştırıldı.

Çalışma planı: Eylül 2009 - Haziran 2013 tarihleri arasında anatomik rezeksiyon ve mediastinal lenf bezi diseksiyonu yapılan küçük hücreli dışı akciğer kanserli 156 hasta (146 erkek, 10 kadın; ort. yaş 62.3±8.0 yıl; dağılım 38-79 yıl) retrospektif olarak incelendi. Tümör hacimleri histopatolojik veriler kullanılarak hesaplandı. Tümör hacminin prognoz ve sağkalım üzerindeki etkisi araştırıldı.

Bulgular: Hastaların 116'sında Evre I ve 40'ında Evre II hastalık var idi. Ortalama tümör hacmi 38.2±54.6 (dağılım; 356.15-0.01) cm^3 iken, ortalama en büyük çap 4.2±2.0 (dağılım; 10-0.3) cm idi. Cox-regresyon analizinde eşik değerin altında tümör hacmi (29.69 cm^3) 2 olasılık oranı (OR) ile sağkalımı artırmakla birlikte, bu değer istatistiksel olarak anlamlı idi (p=0.022). *T* faktörüne göre eşik değer 4.5 cm olup, OR=1.7 idi; ancak, sağkalım ile arasında anlamlı bir ilişki gözlenmedi (p=0.058).

Sonuç: Bu çalışmada en büyük tümör çapı ve sağkalım arasındaki bilinen ilişkinin aksine, tümör hacmi ile sağkalım arasında daha yakın bir ilişki saptandı. Çalışma bulgularımıza göre, akciğer kanseri evrelemesinde tümör çapı ile beraber tümör hacminin hesaplanması ve göz önünde bulundurulması önerilmektedir.

Anahtar sözcükler: Akciğer kanseri; prognoz; evreleme; tümör hacmi.

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In the developed countries, lung cancer is the second most common cause of cardiac disease-related mortality.[1] The main prognostic factor in lung cancer is the tumor stage, and it is the most important parameter both in terms of the course of treatment and predicting survival, followed by the histopathological cell type.[2-4]

Current lung cancer staging evaluates the largest diameter and localization of the tumor, status of the lymph nodes, and presence of metastasis.[5] However, the *T* factor alone, which describes the largest diameter of the tumor, is not a parameter reflecting the complete tumor mass and volume. It is expected that the three-dimensional volume of the tumor would provide better information on the tumor size, relative to the two-dimensional size. In the light of this perspective, in the present study, we aimed to investigated whether the tumor volume affected the survival in patients with early-stage non-small-cell lung cancer (NSCLC).

PATIENTS AND METHODS

In this retrospective study, a total of 439 patients with NSCLC who underwent anatomical pulmonary resection and mediastinal lymph node dissection between September 2009 and June 2013 were included. Among these, 156 patients with Stage I and Stage II disease, in whom only the tumor size affected the disease stage, were included. The patients having factors other than the tumor size affecting the tumor stage were excluded from the study. All patients underwent preoperative thoracic computed tomography (CT), positron emission tomography-CT (PET-CT), cranial magnetic resonance imaging (MRI), and metastasis screening, and estimated pulmonary reserve capacities were calculated using the respiratory function tests (RFTs). Tumor volumes were calculated based on the largest length of postoperative pathological pieces in three dimensions and after the radiological confirmation of this data. The tumor sizes, measured in three axes, were used to calculate the volumes using the ellipsoid volume formula: $4 \div 3 \prod abc$.

A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The data were analyzed using the IBM SPSS for Windows version 22.0 (IBM Corp., Armonk, New York, USA) and MedCalc 9 (Acacialaan 22, B-8400 Ostend, Belgium) programs. The compatibility of the data with normal distribution was evaluated considering the Shapiro-Wilk test and variation coefficients, while parametric methods were used to analyze the normally distributed data and non-parametric methods were used to analyze the non-normally distributed variables. The two independent groups were compared using the independent-samples t-test and Mann-Whitney U (exact) test. The correlations of the variables with each other were analyzed using the Spearman's rho test, whereas the categorical data were compared using the Pearson chi-square (exact) test. The effects of the factors on mortality were examined using the Kaplan-Meier (product-limit method) - log-rank (Mantel-Cox) analysis. The Cox regression analysis was used to measure the effects of prognostic variables on lifetime based on the main factor. The relationship between the actual classification and the classification of the patient groups using the cut-off value calculated according to the variables was examined and expressed through sensitivity and specificity using the Receiver Operating Characteristics (Honley & Mc Nell) analysis. The quantitative data were expressed in mean ± standard deviation (SD), median ± interquartile range (IQR), and median (min-max) values. Categorical data were expressed in number (n) and percentage (%). A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Of the study patients, 146 were (93.5%) males and 10 were (6.5%) females, and the mean age was 62.3±8.0 (range, 38 to 79) years. Based on the 7th Tumor-Node-Metastasis (TNM) staging of NSCLC, 116 patients (74.4%) had Stage I disease (Stage IA: 62, Stage IB: 54) and 40 patients (25.6%) had Stage II disease (Stage IIA: 24, Stage IIB: 16). When the data of survivors were evaluated, compared to non-survivors, the mean age was 61.3±8.2 years among survivors and 64.3±7.5 years among non-survivors, indicating a statistically significant difference (p=0.024).

When histopathological diagnoses of the patients were examined, 72 patients (46.1%) had a squamous-cell carcinoma, 68 patients (43.6%) had an adenocarcinoma, 12 patients (7.7%) had a large-cell carcinoma, and four patients (2.6%) had a non-small-cell carcinoma with no identified type. The patients who survived in the study group were classified into two groups based on the mortality status, 45 patients had an adenocarcinoma, 46 patients had a squamous-cell carcinoma, nine patients had a large-cell carcinoma, and two patients had other NSCLC. In the non-survivor group, 23 patients had an adenocarcinoma, 26 patients had a squamous-cell carcinoma, three patients had a large-cell carcinoma, and two patients had other

Table 1. Distribution of volume and T factor by stages in survivors and non-survivors

	Survived			Exitus		
	Stage I	Stage II		Stage I	Stage II	
	Mean±SD	Mean±SD	p	Mean±SD	Mean±SD	p
Volume (cm^3)	8.6±19.5	73.8±54.1	<0001	11.8±3	82.6±96.8	<0001
T (cm)	3.0±2	6.5±1	<0001	3.3±1.5	7.0±2	<0001

SD: Standard deviation.

NSCLC; and there was a homogeneous distribution between the two groups (p=0.897).

Considering the *T* status of the overall group, the mean diameter was 4.2±2.0 cm. The mean *T* factor was 3.5±2.5 cm in the survivor and 4.5±3.5 cm in the non-survivor group; the difference between the two groups was statistically significant (p=0.015). When the *T* status was evaluated based on stages, the mean *T* was 3±1.6 cm and 7±2 cm in the Stage I and Stage II patient groups, respectively, and there was a statistically significant difference between the two groups (p<0.001). When the *T* status was evaluated based on the stages in the survival group, the mean *T* was 3.0±2 cm in Stage I and 6.5±1 cm in Stage II, and the difference was significant (p<0.001). In the non-survivor group, the mean value was 3.3±1.5 cm and 7.0±2 cm in Stage I and Stage II, respectively, and this difference was significant (p<0.001) (Table 1).

The mean tumor volume was 38.2±54.6 cm^3 in the overall group. The mean tumor volume was 13.4±34.1 cm^3 in the survivor group, compared to 31.4±53.6 cm^3 in the non-survivor group, indicating a statistically significant difference (p=0.023). When the tumor volume was evaluated based on the stages, it was 9.0±20 cm^3 in the Stage I patient group, compared to 81.4±86.7 cm^3 in the Stage II patient group, a statistically significant difference between the two groups (p<0.001). When the tumor volume was evaluated based on the stages in the survival group, the mean value was 8.6±19.5 cm^3 in Stage I and 73.8±54.1 cm^3 in Stage II (p<0.001). In the non-survivor group, the mean value was 11.8±3 cm^3 and 82.6±96.8 cm^3 in Stage I and Stage II, respectively (p<0.001) (Table 1). The cut-off value for tumor volume was 29.69 cm^3. The number of patients with a tumor volume ≤29.69 cm^3 was 71 and the number of patients with a tumor volume >29.69 cm^3 was 32 in the survivor group. In the non-survivors group, the number of patients with a tumor volume ≤29.69 cm was 25 and the number of patients with a tumor volume >29.69 cm^3 was 28. Comparison of the two groups revealed that there was a significantly higher number of patients below the cut-off value in the survivor group (p=0.019).

When the effect of volume on survival was examined, the three-year survival rate was 88.9% below the cut-off value and 75.4% above the cut-off value (Figure 1). There was a statistically significant difference in the survival between the two groups and survival was observed to increase with the decreasing tumor size (Table 2).

In this study, the odds ratios (ORs) for the three factors having a statistical impact on survival were 2 for the tumor size 1.7 for *T* (the longest diameter) and 1.6 for the tumor stage. When the variables were associated with mortality in accordance with these ratios, only the volume value had a significant effect on mortality (p=0.022), and the other two factors approached to statistical significance, although the p values were higher than 0.05 (Table 3).

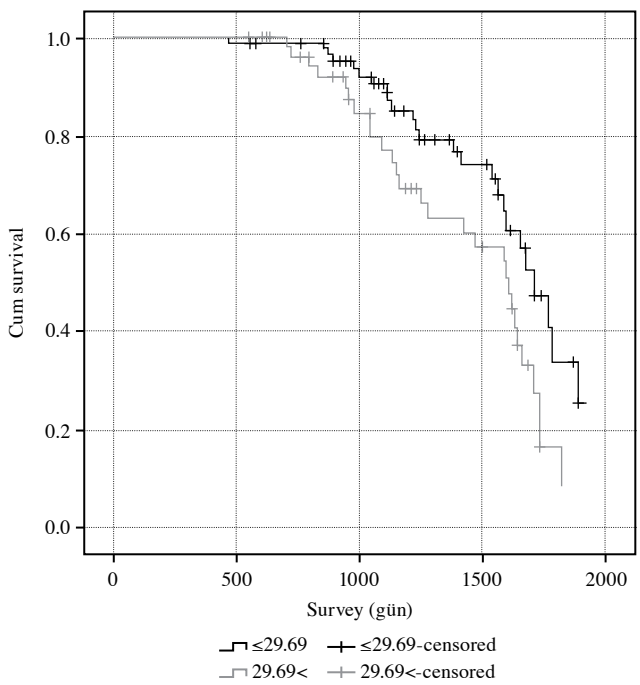

Figure 1. Survival analysis.

Table 2. Comparison of three-year survival by volume cut-off values

	Life expectancy	3-year survival rate		
	Mean±SD	≤29.69	29.69<	p
Volume (≤29.69 / 29.69<)	53.6±1.5 / 48.2±1.8	88.9%	75.4%	0.020

SD: Standard deviation.

DISCUSSION

The main prognostic factor in lung cancer is the tumor stage, followed by histopathological cell type.[3,4] The gold standard method of treatment for NSCLC is radical anatomic pulmonary resection.[6,7] In 1973, a new staging system was developed by the American Joint Committee on Cancer (AJCC) under the leadership of Mountain, by means of using the general principles of the TNM staging system.[4,8,9] The Union for International Cancer Control (UICC) and AJCC reached a consensus over the data of the International Association for the Study of Lung Cancer (IASLC), the committee collecting the data of lung cancer patients worldwide, and published the 7th T NM staging in 2009, which is currently in use.[2,10] The updating studies of the routine assessments in terms of TNM are still ongoing. Some multifactorial parameters are expected to be included in the consideration in the studies conducted to establish more accurate conclusions. The present study brings a different perspective particularly to the effect of *T* factor on survival in this regard and examines the effect of three-dimension form of the tumor. In this context, the ellipsoid volumes of T_1 and T_2 tumors were calculated according to the 7th TNM staging and compared.

Review of the literature reveals that there is a similar study conducted by Jefferson et al.,[11] investigating the effect of volume on survival. The aforementioned study also calculated the tumor volume by taking the maximum lengths of all three dimensions of the tumor in the postoperative pathological piece. The study concluded that the mean volume was 91.6±8.6 cm^3 in Stage I, 92.4±13 cm^3 in Stage II, and 178.8±24.2 cm^3 in Stage IIIA. Two-year and five-year survival rates were 73.2%, 53.4%, and 41.8% and 60.8%, 45%, and 34%, respectively. The authors showed that there was an increase in the disease stage along with the increased volume which affected survival. This study included patients from all stages including N2s; however, the present study examined the isolated effect of tumor volume on prognosis and compared that with the tumor diameter currently in use.

Chandrachud et al.[12] calculated the cut-off value of tumor volume as 36 cm^3 in their study. They found that the two-year survival rate was 66.7% in the patient group below the cut-off value, compared to 25% in the patient group above the cut-off value, indicating a significant difference in survival between these two groups (p=0.02). In the present study, the cut-off value of tumor size was 29.69 cm^3 in the patient group. The mean life expectancy was 53.6±1.5 months in the patient group below the cut-off value, compared to 48.2±1.8 months in the group below the cut-off value. Three-year survival rates of these two groups were 88.9% and 75.4%, respectively, and there was a statistically significant difference (p=0.020). This comparative study included all stages; however, the present study considered only Stage I and II patients to obtain more objective, target-specific data. Thus, other data affecting lung cancer staging were excluded, and only the results of the size and volume effect were evaluated.

Previous multivariate analyses also showed the effect of tumor volume on survival.[11,13] Similarly, the present study demonstrated that increased tumor volume had a negative effect on survival. The patients with a tumor volume below the calculated cut-off value had a longer survival.

Currently, positron emission tomography is also one of the most commonly used imaging tools for lung cancer staging. As it is well-known, the false negativity rate is high in small-size lesions.[14,15] Therefore, several studies were conducted to investigate the association between tumor volume and metabolic activity. The study by Sridhar et al.[16] showed a statistically significant increase in the metabolic activity along

Table 3. Rates of survival-affecting factors to create a risk factor

Mortality	OR	95% CI	p
Volume (cm^3) (29.69<)	2	1.1-3.3	0.022
T (cm) (4.5<)	1.7	0.9-2.9	0.058
Stage	1.6	0.9-2.8	0.105

OR: Odds Ratio: CI: Confidence interval.

with the increased tumor volume ($p<0.001$). A PET-CT study from Turkey, which included esophageal cancer patients, showed that a one-unit increase in volume caused a 1.1-fold increase in the risk ratio.[13]

The cut-off value was 2-3 cm in the $T_1N_0M_0$ patient group and 3-7 cm in the $T_2N_0M_0$ patient group in the 7th TNM staging.[17] In the present study, the cut-off value of *T* factor was 4.5 cm in the overall group. Tumor volume is not used in the current staging system and the present study offers a new perspective to staging. The tumor volume at the calculated cut-off values was shown to be more sensitive in estimating survival in the study population than the *T* factor.

In conclusion, this study suggests that tumor volume is of particular importance in prediction of prognosis. In addition, tumor volume can be suggested to guide in case that an adjuvant therapy is required. Further studies including larger patient populations would be helpful to suggest recommendations for the calculation and consideration of the tumor volume with the tumor diameter in lung cancer staging. Following such studies, it would be possible to formulate the hypothesis that additional treatment planning is required in patients with a tumor volume higher than the cut-off value.

Declaration of conflicting interests

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