The Effect of Skeletal Muscle Radiodensity and Psoas Muscle Index on Prognosis of Small-Cell Lung Cancer

İskelet Kası Radyodansitesi ve Psoas Kası İndeksinin Küçük Hücreli Akciğer Kanserinin Prognozu Üzerine Etkisi

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ABSTRACT

Introduction: Small cell lung cancer (SCLC) has a poor prognosis and accounts for about 15% of all lung cancer cases. This study was planned to investigate the prognostic value of skeletal muscle radiodensity (SMD) and psoas muscle index (PMI) in patients with SCLC.

Methods: The archive records of 253 patients with SCLC were retrospectively analyzed and 106 of them were included in the study. The overall survival (OS) and body mass index of the patients were calculated. The images of computed tomography (CT) at the time of diagnosis were retrieved for analysis. The cross-sectional area and the mean radiodensity of the psoas muscle at the third lumbar vertebral level on CT scan were measured for assessing SMD and PMI.

Results: While fifty-seven of 106 patients had an extensive disease, 49 patients were considered as the limited stage. SMD was significantly lower in patients with extensive disease. While OS was significantly different for low and high SMD groups, no difference was observed between them according to PMI categories. The median OS was 8 and 12 months in low and high SMD groups, respectively. In multivariate analysis, SMD remained a significant prognostic factor in terms of stage and age at diagnosis.

Conclusion: In the present study, it was found that SMD was an independent risk factor for OS, but PMI was not. The combined use of demographic and essential clinical information and SMD can enable to help physicians and patients to predict survival and thereby enhance medical decision making for newly diagnosed SCLC patients.

Key words: Small-Cell Lung Cancer, Skeletal Muscle Radiodensity, Psoas Muscle Index, Sarcopenia, Prognosis

ÖZET

Giriş: Küçük hücreli akciğer kanseri (KHAK) kötü bir prognoza sahiptir ve tüm akciğer kanseri vakalarının yaklaşık %15'ini oluşturur. Bu çalışma, KHAK'li hastalarda iskelet kası radyodensitesi (İKD) ve psoas kas indeksinin (PKİ) prognostik değerini araştırmak için planlandı.

Yöntemler: KHAK'li 253 hastanın arşiv kayıtları retrospektif olarak incelendi ve 106 tanesi çalışmaya dahil edildi. Hastaların genel sağkalımı ve vücut kitle indeksi hesaplandı. Tanı anında bilgisayarlı tomografi (BT) görüntüleri değerlendirmeye alındı. İKD ve PKİ'yi değerlendirmek için BT taramasında üçüncü lomber vertebral seviyedeki psoas kasının enine kesit alanı ve ortalama radyodensitesi ölçüldü.

Bulgular: Toplam 106 hastanın 57'sinde yaygın hastalık varken, 49 hasta sınırlı evre olarak kabul edildi. İKD, sağkalım, yaygın hastalığı olan hastalarda önemli ölçüde daha düşüktü. Genel sağkalım, düşük ve yüksek İKD grupları için anlamlı farklılık gösterirken, PKİ kategorilerine göre aralarında fark gözlenmedi. Medyan sağkalım, düşük ve yüksek İKD gruplarında sırasıyla 8 ve 12 aydı. Multivariate analizde; İKD, tanı anındaki evre ve yaş açısından önemli bir prognostik faktör olarak saptandı.

Sonuç: Bu çalışmada, İKD'nin sağkalım için bağımsız bir risk faktörü olduğu, ancak PKİ için olmadığı bulunmuştur. Demografik ve temel klinik bilginin ve İKD'nin birlikte kullanılması, hekimlerin sağkalımı tahmin etmelerine yardımcı olabilir ve böylece yeni teşhis edilmiş KHAK hastaları için tıbbi karar almaya yardımcı olabilir.

Anahtar Kelimeler: Küçük Hücreli Akciğer Kanseri, İskelet Kası Radyodansitesi, Psoas Kas İndeksi, Sarkopeni, Prognoz

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INTRODUCTION

Small cell lung cancer (SCLC) has a poor prognosis and accounts for about 15% of all lung cancer cases (1). Tumor stage, gender, age, carcinoembryonic antigen, neuron-specific enolase, smoking status, and performance status are the significant predictors of overall survival (OS) in patients with SCLC (1,2). Although several prognostic factors have been identified and performance status remains the cornerstone to guide treatment decisions for daily clinical practices in patients with SCLC, there is a need for more precise prognostic factors.

Sarcopenia is associated with functional disability and disturbance and is characterized by low muscle strength and reduced skeletal muscle along with physical performance (3). Sarcopenia is defined as a secondary condition due to immobility, malnutrition, malignancy, chronic diseases, and the aging process (4). Sarcopenia has been reported to occur in patients with lung cancer at a range of 46–79% (5). Sarcopenia is a prevalent condition in cancer patients and is associated with higher mortality rates (6). There is a need for understanding sarcopenia mechanisms better. It is considered as an essential component of cancer cachexia syndrome and has a prognostic significance in the oncologic setting (7–9). Since changes in muscle mass may not be associated with changes in weight and body mass index, their follow-up may not be used to predict prognosis in clinical practice, but psoas muscle index (PMI) and skeletal muscle radiodensity (SMD) measurements can be evaluated (10).

Dual-energy X-ray absorptiometry, computed tomography (CT) imaging, and bioelectrical impedance analysis are several options for body composition assessment (11). Analyses of CT images are convenient for oncology practice in the evaluation of body composition due to its frequent use in routine diagnosis, staging, treatment evaluation, and follow-up. Researchers use CT images at the third lumbar level (L3) to assess body composition because it is correlated with the estimated total lean body skeletal muscle mass (11–14). This method also makes it possible to measure SMD. SMD is expressed as the mean Hounsfield Units (HU) and its low levels refer to increased fat deposits and is associated with advanced age (15–17). Besides, low values measured at the L3 level have been found to be associated with a low survival rate in cancer patients (18,19). In SCLC, muscle loss and cancer cachexia are common and associated with worse prognosis and poor survival, and some studies have revealed that severe muscle mass loss may predict survival in lung cancer (18,19).

The purpose of this study is to examine whether or not the PMI, which reflects the skeletal muscle mass of the whole body, and its radiodensity at the time of diagnosis are independent prognostic factors for overall survival in SCLC patients (20).

METHODS

Participants of the Study

The hospital archive records of 253 patients with SCLC between 2012 and 2020 at the Akdeniz University Oncology Department were retrospectively analyzed. One hundred and six patients with SCLC who had noncontrast enhancement CT or positron emission tomography (PET) images suitable for evaluating the L3 vertebra level at the time of diagnosis were included in the study. The patient characteristics at the time of diagnosis were recorded. The clinical staging was based on CT and/or PET with fluorine-18 fluorodeoxyglucose imaging. Additionally, the overall survival of the patients was calculated. The exclusion criteria were the absence of pretreatment CT imaging records, lack of adequate cancer diagnosis, and lack of follow-up information.

Table 1. Characteristics of patients with SCLC according to SMD and PMI.

Variables		Overall	Skeletal muscle density (SMD)		Psoas muscle index (PMI)		
		Low SMD	High SMD	P-value	Low PMI	High PMI	P-value
Number, n (%)	106	53 (50%)	53 (50%)	-	7 (7%)	99 (93%)	-
Gender, n (%) **Male** **Female**	90 (85%) 16 (15%)	41 (39%) 12 (11%)	49 (46%) 4 (4%)	0.23 <0,001	2 (2%) 5 (5%)	88 (83%) 11(10%)	<0.001 0.03
Age at diagnosis, years median (min-max)	62 (38 - 82)	63 (38 - 82)	60 (41 - 81)	0.005	56 (38 - 79)	62 (41 - 82)	0.95
BMI, (kg/m^2) median (min – max)	24.7	25.2 (17.5 - 40.9)	24.2 (17.3 - 33.3)	0.69	24.0 (19.4 - 31.0)	24.9 (17.3 - 40.9)	0.43
Stage, n (%) **Limited** **Extensive**	49 (46%) 57 (54%)	20 (19%) 33 (31%)	29 (27%) 24 (23%)	0.08	3 (3%) 4 (4%)	46 (43%) 53 (50%)	0.85
SMD, HU median (min-maxi)	28.1	23.5 (6.9-27.9)	33.9 (28.4 - 57.03)	<0.001	21.3 (8.5 - 27.5)	28.9 (6.9 - 57.03)	0.019
PMI, cm^2/m^2 median (min – max)	3.83	3.41 (2.04 - 6.6)	4.47 (2.5 - 8)	<0.001	2.3 (2.0 - 2.4)	4 (2.5 - 8)	0.019

Abb. SCLC; Small-cell lung cancer, SMD; Skeletal muscle radiodensity, PMI; Psoas muscle index, BMI; Body mass index, HU; Hounsfield Units

Ethical Considerations

The ethics committee approval was obtained from the Akdeniz University Faculty of Medicine Ethics Committee and conducted in accordance with the principles of the Helsinki Declaration and all applicable regulations. Since this study was conducted retrospectively, informed consent was not obtained from the patients.

Statistical Analysis

The statistical analysis of the study was performed using SPSS statistical software (version 22, SPSS, Inc, Chicago, IL, USA). The patients were divided into two groups based on SMD and PMI: low and high. Multivariate analysis was performed using logistic regression model to compare the differences between patient characteristics of the groups. While descriptive data were presented as either means or medians for continuous variables, frequencies and percentages were reported for categorical variables. The distribution of the variables was determined via Kolmogorov-Smirnov test. Survival curves were constructed using the Kaplan–Meier method and overall survival rates were compared using the log-rank test. Pearson X^2 test is used to assess the correlations in categorical variables. The independent clinical factors associated with survival were calculated using the Cox proportional hazard model. Multivariate analysis was performed via the Cox regression method. The results were accepted as statistically significant for $p \leq 0.05$.

Body Composition Assessment and CT analysis

The body mass index (BMI) was calculated as follows; BMI = weight (kg)/height (m^2). CT images at the time of diagnosis were retrieved for analysis. The cross-sectional area (cm^2) of the right and left psoas muscle

Table 2. Univariable and multivariable logistic regression analysis for overall survival (OS) in patients with SCLC (n = 106)

	OVERALL SURVIVAL		
	Univariate analysis	**Multivariate analysis**	
	P-value	**HR (95 % CI)**	**p-value**
Age at diagnosis (> 65 years)	0.009	1.59 (1.15 - 2.87)	0.010
Gender (male)	0.92	1.09 (0.55 - 2.19)	0.78
BMI	0.098	0.42 (0.42 - 1.03)	0.067
Stage (Extensive)	<0.001	1.83 (1.46 - 3.66)	<0.001
SMD(High SMD)	0.018	0.69 (0.31 - 0.79)	0.004
PMI(High PMI)	0.48	1.03 (0.40 - 2.61)	0.94

Abb. SCLC; Small-cell lung cancer, SMD; Skeletal muscle radiodensity, PMI; Psoas muscle index, BMI; Body mass index

at the third lumbar vertebral (L3) level on CT scan was measured by manual tracing. The PMI was normalized for stature by dividing the total psoas muscle area at L_3 level by the square of patients' height (cm^2/m^2). As mentioned in previous studies, we determined the PMI cut-off value for sarcopenia as 3.70 cm^2/m^2 and 2.50 cm^2/m^2 in men and women, respectively (9).

SMD was assessed as the mean radiodensity of the measured cross-sectional total psoas muscle area at the L3 level. ROC analysis was performed for both male and female patients independently. No appropriate cut-off value was obtained. The median value of SMD was used in the statistical analysis for cut-off value independently from gender.

RESULTS

One hundred and six patients were included in the study. While ninety of these patients were male, sixteen patients were female. The mean age of the patients was 61.9 years, ranging from 38 to 82 years. The patients were divided into two major groups based on muscle density and PMI. The cut-off value of the muscle density was determined to be 28 HU and the patients were grouped based on low and high muscle density. Both groups had equal numbers of patients (n=53). The other categorization factor was PMI with cut-off values of 4.80 and 3.64 cm^2/m^2 for men and women, respectively. While seven of the patients were in the low muscle index group, most of the patients had high muscle index values. Table 1 summarizes the patients' characteristics according to major groups.

The patients were also grouped according to the stage, BMI, and age. The stratification values for age and BMI were 65 years and 25 kg/m^2, respectively. While the patients with limited disease had a median OS of 14 months, this period is 7 months in patients with the extended stage ($p < 0.001$). SMD was not affected by the stage of the disease. The median values were not different between limited and extensive disease ($p = 0.11$). There was a positive correlation between SMD and PMI ($p < 0.001$, $r = 0.48$). The median OS was not different according to PMI groups. ($p = 0.48$) The median survival was for low and high muscle density groups were 6 and 10 months, respectively. The median survival of the patients was 8 and 12 months in SMD low and high groups, respectively (Figure-1). In univariate analysis, age, stage, and SMD were associated with OS. In multivariate analysis, the

prognostic effect of the age, stage, and SMD remained (Table 2).

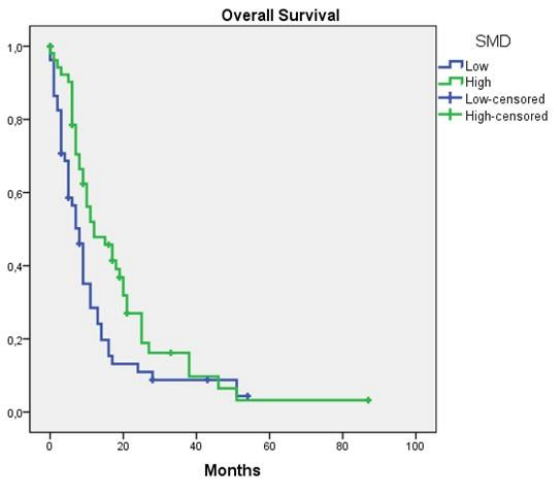

Figure 1. The Kaplan-Meier curves of the patients according to SMD

DISCUSSION

Sarcopenia, defined as low muscle function or strength in the presence of low muscle mass, is prevalent in lung cancer patients and has a prognostic significance in SCLC (21). There were many measurement modalities of analysis and proposed cut-off values for the definition of sarcopenia because of diverse patient groups such as type of disease, stage of the disease, age, and gender. Thus, there is a need to formulate an original definition of sarcopenia that can predict overall survival and prognosis in patients with SCLC. Low skeletal muscle mass defined by Hamaguchi et al., was < 2 SD below the mean PMI of healthy individuals, under 3.92 cm^2/m^2 in women and 6.36 cm^2/m^2 in men (20).

In the present study, the presence of correlation of SMD with PMI and their prognostic value were investigated in SCLC patients. Also it was revealed that SMD was a significant independent prognostic factor for overall survival in SCLC; whereas, muscle mass measured as the cross-sectional total psoas muscle area at L3 level, and expressed as PMI, was not present.

Recently, SMD has reduced in several types of cancer and its negative prognostic effect including solid tumors, adrenocortical carcinoma, malignant melanoma, pancreatic cancer, and metastatic renal cell carcinoma or distal cholangiocarcinoma has emerged (18,22–24).

Increased catabolism caused by systemic inflammation, tumor metabolism, and other tumor-mediated effects is significant in cancer cachexia syndrome. Population-based studies suggest that inflammatory response is involved in age-related loss of muscle mass (sarcopenia) and strength (25,26). Inflammation plays a key role in the immune response. It can become chronic, promote the generations of reactive oxygen and nitrogen species, and stimulate cellular proliferation and angiogenesis. All the mechanisms play key roles in carcinogenesis (27,28). Systemic inflammation is accused in various cancer etiologies and has been shown to have prognostic significance in different cancers, including SCLC (2,29,30).

Previous studies emphasized the importance of nutritional status in cancer and reported that 30-85% of progressive cancer patients had malnutrition (31). This fact is associated with weight and muscle loss, higher risk of infection, reduced immune competence, decreased quality of life, higher psychosocial distress, intolerance to antineoplastic treatments, worse prognosis, poorer survival, longer hospital stays, and as a result, increased hospital costs (4,32–34). As a result, monitoring the body composition by computerized tomography at the time of diagnosis could be very useful to provide medical and nutritional interventions to optimize treatment and reduce the toxicity of chemotherapy (35,36).

Recently, many studies have indicated that the cross-sectional imaging of third lumbar vertebra (L3) is strongly correlated with total body tissue areas (11,37).

In a large and recent study analyzing retrospectively 734 patients with advanced non-small-cell lung cancer, the prognostic relationship between SMD and skeletal muscle index (SMI) was evaluated, and consequently, SMD was an independent prognostic factor for overall survival ($p = 0.001$), whereas SMI was not ($p = 0.329$) (19).

In the present study, it was found with the multivariate analysis that pretreatment low SMD worsened median survival, and reduced SMD was an independent risk factor influencing overall survival, but PMI was not. The results were consistent with the aforementioned study both for SMD and PMI.

In summary, the results of the present study have several clinical implications. Lower SMD has a significant correlation with shorter OS in SCLC patients. The SCLC patients having low SMD need additional treatment options such as radiotherapy or induction therapy, adjuvant chemotherapy, and more intense postoperative follow-up.

In the present study, a weak correlation was found between SMD and PMI, however, the prognostic effect was detected in SMD, but not in PMI. Consequently, these results suggested that measurement of muscle mass may not be sufficient for a proper assessment, and examining the quality of muscle tissue may be more meaningful than the area measurement of the same tissue.

Limitations

The study was retrospectively designed and had a relatively small sample group, including heterogeneous patients from a single center. The fact that the patients were diagnosed in a relatively long period between 2012 - 2020 created heterogeneity in the treatment. Although procedures were included in the multivariate model, a simplified dichotomized treatment variable may not responsible for changes in regimens for near ten years. It may not provide predictive models for the effect of different radiotherapy doses and techniques or chemotherapy combinations on patient survival. Despite all these limitations, pretreatment SMD can be used as a prognostic marker in SCLC since CT is frequently used in routine clinical practice.

CONCLUSION

The present study showed the correlation between PMI and SMD on the prognosis of SCLC. Consequently, based on the results of the present study with a hospital-based cohort, it can be recommended to use SMD as an independent prognostic marker for overall survival in SCLC and to validate it in future clinical trials further. SMD may be a proper, readily available, relatively cost-effective, and reliable biomarker with prognostic potential for SCLC. The combined use of demographic and essential clinical information and SMD can enable help physicians and patients to predict survival and thereby enhance medical decision making for newly diagnosed SCLC patients. Accordingly, these findings need to be validated in further evaluation with a large number of patients to understand the prognostic value of SMD and PMI in patients with SCLC.

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