

Initial Anthropometric Values and Nutritional Status is Related to Survival in Advanced Non-Small Cell Lung Cancer

İlerlemiş Küçük Hücreli Dışı Akciğer Kanseri Olgularında Başlangıç Antropometrik Değerler ve Beslenme Durumu Sağkalım ile İlişkilidir

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Geliş Tarihi/Received: 17.04.2009

Kabul Tarihi/Accepted: 07.10.2009

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ABSTRACT Objective: Lung cancer is usually preceded by anorexia, frequently leading to weight loss and cachexia. Anthropometric measurements are used to evaluate nutritional states. In this study, it was aimed to reveal the prognostic values of anthropometric measurements and biochemical parameters in advanced non-small cell lung carcinomas (NSCLC). **Material and Methods:** Patients histopathologically diagnosed as advanced stage NSCLC between December 2004 and June 2006 were included in the study. Patients who had undergone surgical resection were excluded. Four anthropometric, three biochemical measurements and the nutritional index of patients were recorded before any treatment. **Results:** A total of 69 male patients, with a mean age of 58.8 years, were followed for 12.98 months on average. Forty-nine (71%) patients were at stage IIIB, whereas 20 (29%) patients were at stage IV. The mean survival period was 12.0 months. Low levels of serum albumin ($p < 0.001$) and prealbumin ($p = 0.002$), body mass index ($p = 0.000$), skin thickness of triceps ($p < 0.001$), and upper arm circumference ($p < 0.001$), as well as high levels of nutritional index ($p < 0.001$) were determined as poor prognostic factors. There was no relation between serum transferrin and survival ($p = 0.229$). **Conclusion:** Lower serum albumin, prealbumin, body mass index, triceps skin thickness, upper arm circumference and higher nutritional index may reflect shorter survival in advanced NSCLC despite good performance status.

Key Words: Lung neoplasms; anthropometry; nutrition assessment; albumins; prealbumin; survival; body mass index

ÖZET Amaç: Anoreksi genellikle akciğer kanseri tanısı öncesinde görülmekte ve sıklıkla kilo kaybına ve kaşeksiye neden olmaktadır. Antropometrik ölçümler beslenme durumunu değerlendirmek için kullanılmaktadır. Bu çalışmada, antropometrik ölçümlerin ve biyokimyasal parametrelerin ilerlemiş küçük hücreli dışı akciğer kanserli (KHDAK) hastalardaki prognostik değerini ortaya koymak amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmaya aralık 2004 ve haziran 2006 yılları arasında histopatolojik olarak ileri evre KHDAK tanısı konan hastalar dahil edilmiştir. Cerrahi rezeksiyon yapılan hastalar çalışmaya dahil edilmemiştir. Herhangi bir tedavi uygulamadan önce, dört antropometrik, üç biyokimyasal ölçüm ile beslenme endeksleri kayıt edilmiştir. **Bulgular:** Ortalama yaşları 58.8 yıl olan toplam 69 erkek hasta, ortalama olarak 12.98 ay takip edildi. Kırkdokuz (%71) hasta evre IIIB, 20 hasta (%29) ise evre IV idi. Ortalama sağ kalım 12 aydı. Serum albumin ($p < 0.001$) ve prealbumin ($p = 0.002$) düzeyinin düşük olması, vücut kitle indeksi ($p = 0.000$), triceps cilt kalınlığı ($p < 0.001$) ve üst kol çevresi ($p < 0.001$) ile yüksek beslenme endeksi kötü prognostik faktörler olarak belirlendi. Serum transferrin ile sağ kalım arasında ilişki yok idi ($p = 0.229$). **Sonuç:** Serum albumin ve prealbuminin düşük olması, vücut kitle indeksi, triceps cilt kalınlığı, üst kol çevresi ve yüksek beslenme endeksi ilerlemiş KHDAK'li hastalarda performans durumu iyi görüle bile daha kısa sağ kalıma işaret edebilir.

Anahtar Kelimeler: Akciğer tümörleri; antropometri; beslenme değerlendirmesi; albuminler; prealbumin; sağkalım; beden kitle indeksi

Lung cancer is preceded by anorexia which frequently leads to weight loss and sometimes cachexia. Anthropometric measurements - body weight (BW), per cent ideal weight (PIW), body mass index (BMI), triceps skin thickness (TST), upper arm circumference (UAC) and biochemical parameters are used to evaluate the nutritional state.¹⁻⁵

Body mass index (BMI) [(weight (kg)/square meter height (m²)] below 15 indicates severe nutritional disorder, whereas 15-19 indicate low weight, 20-25 indicates normal weight, 26-30 indicates grade-1 obesity, 31-40 indicates grade-2 obesity and the values over 41 indicates grade-3 obesity.⁵

Triceps skin thickness and subcutaneous adipose tissue thickness are indices for body fat store, and measurements below 10 millimeter (mm) in men and 13 mm in women indicate malnutrition. Upper arm circumference is a measurement for both muscular and adipose tissue and it evaluates muscular tissue and skin thickness together. Levels below 20 cm in men and 18 cm in women are considered pathological.³⁻⁵

Serum albumin is used as an indicator for visceral protein depletion and it decreases in long term malnutrition. Having a half-life of approximately 20 days, albumin is a weak indicator for early protein malnutrition. Levels below 2.1 g/dl reveal severe depletion, whereas 2.1-2.7 g/dl reveals moderate depletion and 2.8-3.5 g/dl reveals mild depletion.³⁻⁵

Serum prealbumin, with a half-life of two days and being rapidly synthesized and degraded, is a more sensitive and reliable parameter indicating malnutrition. The value of 15-10 mg/dl indicates mild, 10-5 mg/dl indicates moderate and below 5 mg/dl indicates severe protein depletion.³⁻⁵

Serum transferrin, a beta globulin, reflects the acute alterations in visceral protein more rapidly than serum albumin, since it has a half-life of 8-10 days. Values below 212 mg/dl indicate protein deficiency. Serum transferrin levels (measured by radial immunodiffusion method) between 150-200 mg/dl indicate mild visceral depletion, 100-150

mg/dl indicates moderate visceral depletion, and below 100 mg/dl indicates severe depletion.³⁻⁵

The stage and the performance status are the main prognostic factors in non-small cell lung cancer (NSCLC), while gender, weight loss, lactate dehydrogenase, albumin, hemoglobin, thrombocytes and leucocyte were also reported as prognostic factors. Besides laboratory parameters, some simple measurements of anthropometric structure are thought to reflect the prognosis in advanced NSCLC. The aim of this study is to display whether the initial values of serum albumin, prealbumin, transferrin, anthropometric measurements and a rarely studied parameter, nutritional index, could be used together to estimate survival in NSCLC.

MATERIAL AND METHODS

PATIENTS

Patients who were histopathologically diagnosed as NSCLC either in the inpatient or the outpatient clinic of Izmir Training and Research Hospital for Thoracic Medicine and Surgery, Izmir, Turkey, between December 2004 and June 2006, with clinical stage III-B or stage IV,⁶ good performance status (Eastern Cooperative Oncology Group [ECOG] 0-2) and without any treatment (neither chemotherapy nor radiotherapy) were included in the present prospective study.

Patients were referred to their chemotherapy and/or radiotherapy (RT) treatments after the measurements required for the study were performed. The response was evaluated via computerized tomography (CT) of the thorax in patients who had been treated with two courses of chemotherapy. The chemotherapy doses of stable or in-regression patients were completed after 4 or 6 courses. Patients who had undergone surgical resection after chemotherapy and/or RT were excluded.

MEASUREMENTS

Four anthropometric measurements were performed on the patients: body weight (kg), height (cm), TST (cm) and UAC (cm). TST was measured via a caliper at the midpoint of the distance between olecranon and acromion of the non-dominant arm for the determination of the subcutaneous adipose tissue. UAC

was measured at midpoint of the distance between olecranon and acromion by a tapeline.⁵ The values defined by National Health and Nutrition Examination Survey were used as the reference.⁷

BMI [weight/height²] and PIW (for men) [50 kg + every inch above 5 feet × 1.9] were calculated.⁸

Age, gender, performance status, histology,⁹ stage of tumor,⁶ serum albumin, prealbumin, transferrin, lymphocyte levels, drugs used for chemotherapy, number of chemotherapy courses, radiotherapy applications, survival and lifetime data were recorded.

The blood samples of the patients were kept in tubes containing K3 EDTA for complete blood count, and in tubes containing no additives for biochemical parameters. The complete blood count was analyzed by automatized Coulter Gen-S (Beckman Coulter, USA) equipment. In order to perform albumin, prealbumin and transferring measurements, serum samples of patients were separated by centrifuging blood samples at 5000 rpm for three minutes. Transferrin and prealbumin were measured quantitatively via automatized Array 360 nephelometry (Beckman Coulter, USA) equipment by using original kits of the same company. Albumin was measured by colorimetric method via Olympus AU2700 equipment, by using original kits of the same company. The mean values were accepted as 18-45 mg/dl for prealbumin, 212-360 mg/dl for transferrin, and 3.5-5 g/dl for albumin.

The “group with malnutrition” included those with a nutritional index (NI) above or equal to 0.5, and the “group without malnutrition” included those with a NI below 0.5:¹⁰

$$NI = 20.68 - (0.24 \times ALB) - (19.21 \times PALB) - (1.86 \times TLC) - (0.04 \times PIW)$$

ALB: Serum albumin concentration (g/dl)

PALB: Serum prealbumin concentration (g/dl)

TLC: Total lymphocyte count (10⁹ /L)

PIW: [(present weight/ ideal weight) × 100]

STATISTICAL ANALYSIS

SPSS-13 computer software was used for statistical analyses. Data were analyzed by using Cox-regres-

sion analysis and Kaplan-Meier survival function analysis. Kaplan-Meier survival function analysis, Log Rank Test was used for the comparison of the groups. Differences were assumed to be significant when $p < 0.05$.

The study was approved by the ethics committee. Informed consents were obtained from all patients.

RESULTS

A total of 77 inoperable patients with the stage of either IIIB or IV NSCLC and ECOG 0-2 were included in the study. A total of eight patients who had undergone surgical resection after induction (chemotherapy and/or RT) were excluded. The mean age of the remaining 69 patients was 58.8 ± 9.1 (34-77) years. All the participants were males. Forty-nine (71%) patients were at stage IIIB, whereas 20 (29%) patients were at stage IV. The histologic types are displayed in Table 1.

Chemotherapy was performed in 61 (88.4%) patients, radical RT was performed in 30 (43.5%), and palliative RT was performed in 15 (21.7%) the patients. The drugs used in chemotherapy are presented in Tables 2 and 3. Serum parameters and anthropometric measurements of the patients are shown in Table 4.

TABLE 1: Histology in lung cancer patients.

Histology	n	(%)
NSCLC	43	62.3
Squamous cell carcinoma	15	21.7
Adenocarcinoma	11	15.9
Total	69	

NSCLC: non-small cell lung cancer.

TABLE 2: Drugs used in chemotherapy combined with platin.

Chemotherapy	n	(%)
Gemcitabine	26	42.6
Docetaxel	14	23
MIC	5	8.2
Paclitaxel	12	19.7
Vinorelbine	4	6.5

MIC: mitomycin, ifosfamide, cisplatin.

TABLE 3: Platins used in chemotherapy.

Platin	n	(%)
Cisplatin	54	88,5
Carboplatin	7	11.5
Total	61	

The mean follow-up duration of the patients was 12.98 months, with a mean survival period of 12.0 ± 1.55 (1-36.5) months (Figure 1).

Overall survival of the patients whose serum albumin and prealbumin levels below the threshold were found significantly shorter (Kaplan-Meier survival function analysis Log Rank test, $p < 0.001$ and $p = 0.002$) (Figures 2 and 3). However, there was no correlation between transferrin level and survival ($p = 0.229$) (Figure 4). The survivals of patients with lower TST and UAC were statistically shorter ($p < 0.001$ and $p < 0.001$) (Figures 5 and 6). Patients with a NI above or equal to 0.5, as well as the patients with a BMI below 20, were found to have a significantly shorter survival ($p < 0.001$ and $p < 0.001$) (Table 5) (Figures 7 and 8).

In Cox-regression analysis, there were positive correlations between survival duration and serum albumin levels ($p = 0.001$), prealbumin levels ($p = 0.001$) and BMI ($p = 0.005$). However, a negative correlation was determined between survival duration and NI ($p < 0.001$). Nonetheless, no correlation was found between survival duration and serum transferrin levels ($p = 0.262$), TST ($p = 0.424$) and UAC ($p = 0.957$).

DISCUSSION

Lower serum albumin, prealbumin, BMI, TST and UAC, and high NI in patients with advanced NSCLC are related with short survival.

The performance status, weight loss and stage of disease in NSCLC patients were reported as the most important prognostic factors, whereas serum lactate dehydrogenase and albumin levels, as well as sex, age, histological properties and biological factors, were reported as potential prognostic factors.¹¹ Malnutrition and weight loss are frequently encountered at the time of diagnosis in cancer patients and is associated with advanced disease. Patient's weight is also insufficient to indicate the nutritional state and to reflect the alterations in calory intake due to treatment or the disease.¹² Patients with malnutrition have a longer hospitalization period,¹³ a lower quality of life,¹⁴ and lower survival period¹⁵ compared to well nourished patients. The incidence of malnutrition during advanced stages of lung cancer is 90%.¹⁶⁻¹⁸

In a study including 5000 patients with inoperable NSCLC, non-anatomical factors such as performance status of the patients, stage of the disease and weight loss were determined as the most relevant prognostic factors,¹⁹ while in another study including 651 patients, presence of symptoms, performance status, weight loss and age were stressed as the most important prognostic factors.²⁰

Lai and Perg evaluated anthropometric measurements (weight-height ratio, TST and UAC)

TABLE 4: Serum parameters and anthropometric measurements.

Parameter	Min	Max	Mean	Standard deviation
Age (years)	34	77	58.83	9.128
Albumin (gr/dl)	2.7	4.8	3.723	.4719
Prealbumin (mg/dl)	0	42	21.46	8.427
Transferrin (mg/dl)	103	370	216.33	51.786
Triceps skin thickness (cm)	0.6	3.2	1.439	.4790
Upper arm circumference (cm)	17	31	24.57	3.787
Body mass index	15.0	29.5	21.993	3.5464
Nutritional index	(-) 1.1356	8.6649	3.5862	2.5108

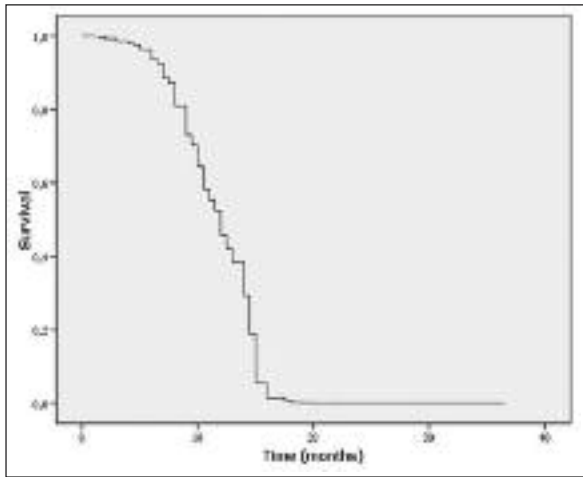


FIGURE 1: General survival in patients with lung cancer.

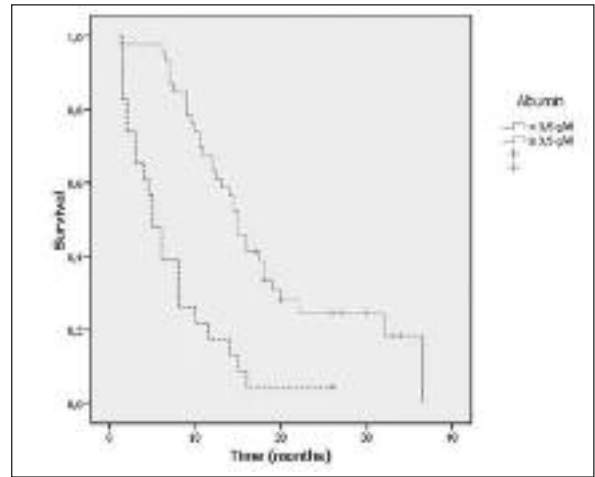


FIGURE 2: Survival according to serum albumin level.

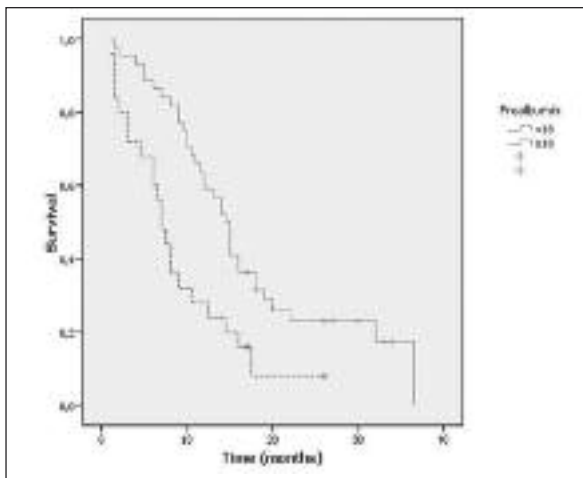


FIGURE 3: Survival according to serum prealbumin level.

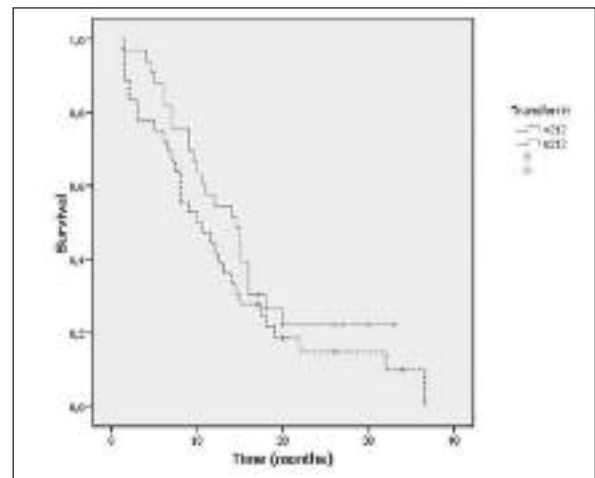


FIGURE 4: Survival according to serum transferrin level.

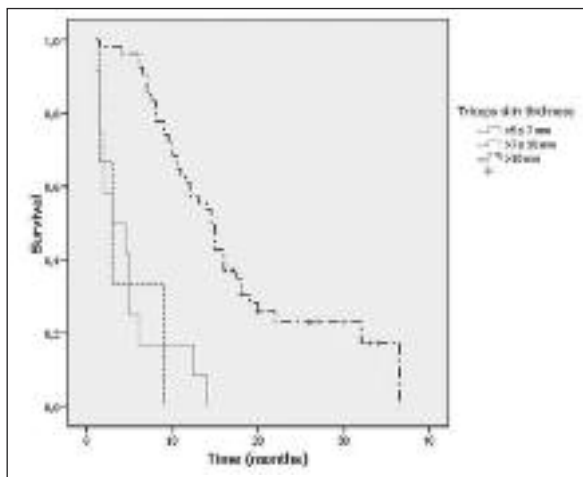


FIGURE 5: Survival according to triceps skin thickness.

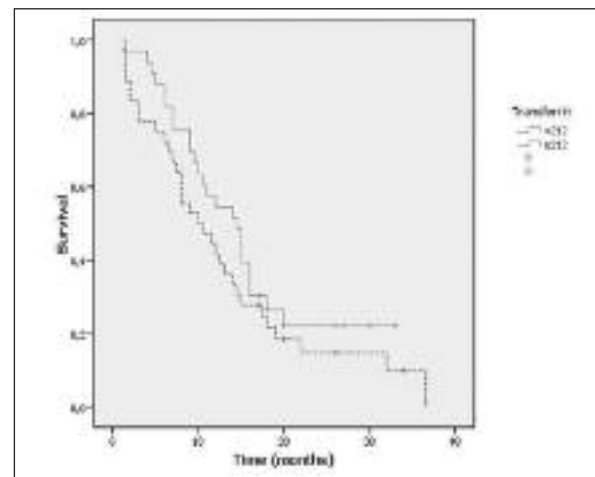
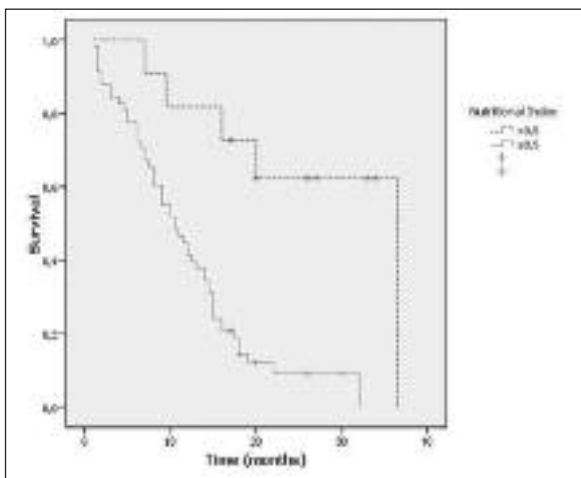
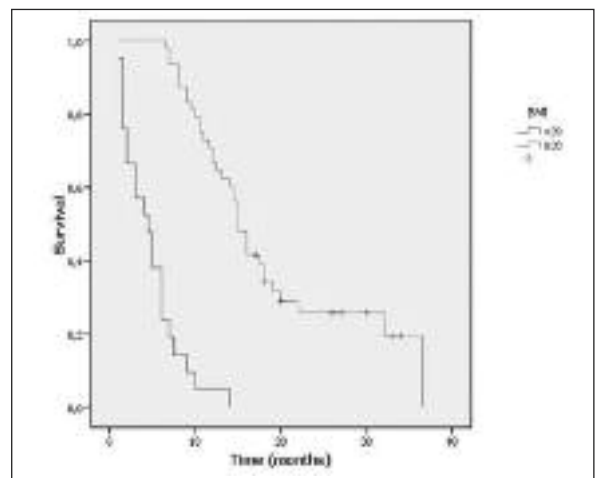


FIGURE 6: Survival according to upper arm circumference.

TABLE 5: The relation of serum parameters and anthropometric measurements with survival (multivariate analysis).

Parameter	n (%)	Survival Period (months)	p (OR)	One Year Survival (%)
Albumin (gr/dl)				
<3.5	23 (33.3)	5.0	0.000	17
≥3.5	46 (66.7)	15.0	(3 x 1017)	63
Prealbumin (mg/dl)				
<18	25 (36.2)	7.0	0.002	24
≥18	44 (63.8)	14.5	(2.6 x 103)	59
Transferrin (mg/dl)				
<212	36 (52.2)	10.0	0.229	41
≥212	33 (47.8)	14.5	(0.996)	54
Triceps skin thickness (mm)				
≤ 5 mm	0	-	-	-
>5 ≤ 7 mm	3 (4.3)	3.0	0.000	0
>7 ≤ 10 mm	12 (17.4)	3.0	(1.656)	83
>10 mm	54 (78.3)	14.5		57
Upper arm circumference (cm)				
≤23 cm	25	5.0		12
>23 ≤ 26 cm	24	12.0	0.000	50
>26 ≤ 28 cm	10	17.5	(0.985)	70
>28 cm	10	36.5		87.5
Nutritional index				
<0.5	11 (15.9)	36.5	0.000	81.8
≥0.5	58 (84.1)	11.9	(4.6 x 106)	41
Body Mass Index				
<20	21 (30.4)	4.5	0.000	0
≥20	48 (69.6)	15.0	(1.4 x 103)	66

**FIGURE 7:** Survival according to nutritional index.**FIGURE 8:** Survival according to body mass index.

and biochemical parameters (albumin, transferrin, total lymphocyte count and creatinin-height index) in 150 newly diagnosed patients with lung

carcinoma.²¹ The abnormality percent of nutritional parameters was between 15-31%, and at least one abnormal parameter was observed in most

(59%) of the patients. As the number of abnormal nutritional parameters increased, the survival period decreased. Both anthropometric and biochemical nutritional parameters were reliable indicators in evaluating the performance status and survival of the patients with lung carcinoma.²¹ We assessed laboratory and anthropometric measurements together to analyze their roles as prognostic factors. Lower serum albumin and prealbumin, lower BMI, TST and UAC, and higher nutritional index were related to poor survival in advanced NSCLC.

When the seven nutritional status variables (TST, UAC, holding power, hemoglobin levels, protein and albumin) were analyzed in 15 lung cancer patients who were treated by cisplatin, TST was determined as the most sensitive indicator for the nutritional status during the chemotherapy. It was reported that periodical evaluation of nutritional status was beneficial during the chemotherapy protocol, and handling nausea, vomiting and anxiety as well as protection from infections and continuing adequate nutrition were equally important.²²

In a study in which eight clinical variables (age, sex, performance status, type of tumor cell, clinical stage, TNM factors), five anthropometric measurements (weight, height, TST, UAC, wrist circumference), and laboratory tests (serum total protein, albumin, transferrin, haptoglobin, calcium, creatinin, phosphorus, iron) of 388 patients with lung carcinoma were evaluated, TST and UAC were found to be significantly correlated with the survival duration, whereas the correlation between wrist circumference and survival duration was not significant. Serum iron, albumin, transferrin and haptoglobin were found to be strong indicators of survival duration, and prognostic factors were listed according to their importance as stage of the disease, performance status, haptoglobin and albumin levels.⁷

In the present study, in recently diagnosed high stage NSCLC patients, it was determined that the overall survival of patients with lower TST, UAC and BMI was shorter compared to patients in

whom low values were not observed. Shorter mean survival period was also determined in patients with a NI above 0.5 when compared to the ones with a NI below 0.5. There was no relation between serum transferrin value and survival.

Serum albumin concentration was found to be related to the prognosis in 13 of 14 studies regarding NSCLC and small cell lung carcinoma.⁷ No correlation was found between survival period and prealbumin, evaluated together with laboratory tests such as ferritin, C-reactive protein, beta-2 microglobulin, in both univariate and multivariate analyses.²³

Many studies have shown that prealbumin concentration is a sensitive and cost effective method in detecting the severity of malnutrition in patients with either serious or chronic diseases, as well as in cancer patients.²⁴⁻²⁶ In the latter, prealbumin measurement is a test that can disclose protein-energy malnutrition. In the present study, serum albumin and prealbumin were found to be correlated with lower survival periods, being factors for poor prognosis. However, correlation was not shown between serum transferrin levels and survival period.

NSCLC are heterogeneous groups, and the importance of their histological subgroups as prognostic factors is still controversial.^{19,27} In the present study, the histological subgroups were not evaluated since the number of the subjects was limited, and the differentiation of subgroups was inadequate in particular cases.

Weight loss, BMI, TST and UAC are the main parameters primarily analyzed in NSCLC to predict the prognosis. This study analyzed another nutritional parameter, nutritional index, and detected a relation between higher nutritional index and survival.

Lower serum albumin and prealbumin, lower body mass index, triceps skin thickness and upper arm circumference, and higher nutritional index may reflect a poor survival in advanced NSCLC patients, even in those with a good performance status.

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