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Is there diagnostic and prognostic importance of serum anti-p53 antibody level in lung cancer?

Akciğer Kanserinde serum anti-p53 antikor düzeyinin tanısal ve prognostik önemi var mı?

Zekiye Hasbek[1], Birsen Yücel[2], Ömer Tamer Doğan[3], Serdar Berk[3], İsmail Sarı[4], Yavuz Silig[5], Mehmet Metin Şeker[6], Seyit Ahmet Ertürk[1]

[1]Department of Nuclear Medicine, Cumhuriyet University School of Medicine, Sivas-Turkey
[2]Department of Radiation Oncology, Cumhuriyet University School of Medicine, Sivas-Turkey
[3]Department of Chest Diseases, Cumhuriyet University School of Medicine, Sivas-Turkey
[4]Department of Biochemistry, Omer Halisdemir University School of Medicine, Niğde-Turkey
[5]Department of Biochemistry, Cumhuriyet University School of Medicine, Sivas-Turkey
[6]Department of Medical Oncology, Turgut Ozal University Faculty of Medicine, Ankara, Turkey
Corresponding author: Zekiye Hasbek, Department of Nuclear Medicine, Cumhuriyet University, Sivas
E-mail: hasbekz@yahoo.com
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SUMMARY

Objective: Lung cancer is the leading cause of cancer-related deaths worldwide. Despite advancement in diagnostic tools and treatment options with technological developments, overall mortality rates in lung cancer patients remains high. Survival rates in lung cancer patients is low especially in advanced diseased inoperable patients in spite of new treatment options like immunotherapy. p53 is mutated in 60-70% of cancer patients and for this reason has been extensively studied recent researches suggest that serum anti-p53Ab can be considered as biomarkers to detect many types of cancers; as ovarian cancer, esophageal cancer, breast cancer and lung cancer. In this study we aimed that are there any diagnostic and prognostic importance of serum anti-p53Ab levels in lung cancer patients.

Method: Patients were included who were referred to our department with the purpose of ^{18}F-FDG-PET/CT imaging for staging due to lung cancer diagnosis (LC) and patients who were performed ^{18}F-FDG-PET/CT for diagnosis in the cause of the suspected pulmonary nodule in thorax CT but not detected pathologic FDG accumulation (NAPN=pulmonary nodule with non-avid-FDG) and healthy volunteers. Serum anti-p53Ab levels were measured with ELISA method in the all patients. Mean follow up time of patients were 13 months.

Results: A total of 65 LC patients (58M/7F), 47 patients with NAPN (20M/27F), and a total of 34 healthy volunteers (26M/8F) were included in this study. Median serum anti-p53Ab levels are 3.4ng/mL in LC patients, 3.77ng/mL in NAPN patients, 3.07ng/mL in healthy volunteers. There is no statistically significant difference for serum anti-p53Ab level between LC patients and NAPN patients (p=0.678). Moreover there is no statistically significant difference for serum anti-p53Ab level between patients and healthy volunteers (p=0.377). Two-year median survival of patients was 14 month. It has been found that there is no effect of serum anti-p53Ab level whether >3.4 or ≤3.4 on the patient survival rate (p=0.652).

Conclusions: Even though anti-p53Ab is very important in carcinogenesis, we think that serum anti-p53Ab level by itself is not important in lung cancer diagnosis and survival rates. There are multiple factors in carcinogenesis and this may be the reason of this situation. There is no known cut off value of serum anti-p53 Ab levels for diagnosis of lung cancer patients. Therefore we think that this antibody is not tumor spesific and serum anti-p53 Ab level measurement is not appropriate for lung cancer screening.

Keywords: Anti-p53Antibody, lung cancer, F18-FDG, PET, p53

ÖZET

Amaç: Akciğer kanseri dünya genelinde kansere bağlı ölümlerin önde gelen nedenidir. Tanısal cihazlar ve teknolojik gelişmelere bağlı tedavi seçeneklerinde ilerlemeye rağmen, akciğer kanseri hastalarında genel mortalite oranı hala yüksektir. Akciğer kanseri hastalarında sağkalım oranları, özellikle ilerlemiş inoperabl hastalıkta, immunoterapi gibi yeni tedavi seçeneklerine rağmen düşüktür. p53, kanser hastalarının %60-70'inde mutasyona uğramaktadır ve bu nedenle son zamanlarda yapılan çalışmalar göstermektedir ki, serum anti-p53 antikorunun, over, özefagus, meme ve akciğer kanseri

gibi bazı kanser türlerinin dedekte edilmesinde biyobelirteç olarak dikkate alınabilir. Bu çalışmada, akciğer kanseri hastalarında, serum anti-p53antikor düzeylerinin tanısal ve prognostik önemini araştırmayı amaçladık.

Yöntem: Çalışmaya akciğer kanseri (AK) tanısı nedeniyle evreleme için ^{18}F-FDG-PET / BT görüntüleme amacı ile bölümümüze sevk edilen hastalar, toraks BT'sinde şüpheli pulmoner nodül olup, patolojik FDG birikimi göstermeyen hastalar (NAPN= Non-avid FDG gösteren pulmoner nodül) ve sağlıklı gönüllüler dahil edildi. Serum anti-p53antikor düzeyleri tüm hastalarda ELISA yöntemi ile ölçüldü. Hastaların ortalama takip süresi 13 ay idi.

Bulgular: Çalışmaya toplam 65 AK hastası (58E/7K), 47 NAPN hastası (20E/27K) ve 34 sağlıklı gönüllü (26E /8K) dahil edildi. Ortalama serum anti-p53antikor seviyeleri AK hastalarında 3.4ng/mL, NAPN hastalarında 3.77ng /mL, sağlıklı gönüllülerde 3.07 ng/ mL idi. AK hastaları ile NAPN hastaları arasında serum anti-p53antikor düzeyi için istatistiksel olarak anlamlı fark yoktu ($p = 0.678$). Hatta, hastalar ve sağlıklı gönüllüler arasında serum anti-p53Ab düzeyi için istatistiksel olarak anlamlı fark yoktu ($p = 0.377$). Hastaların iki yıllık medyan sağkalımı 14 aydı. Hastaların sağkalım hızında, serum anti-p53Ab düzeyinin > 3.4 ng/ mL veya ≤3.4 ng/ mL olmasının herhangi bir etkisinin olmadığı bulundu ($p = 0.652$).

Sonuç: Anti-p53antikoru, karsinogeneziste çok önemli olmasına rağmen, serum anti-p53antikor düzeyinin akciğer kanseri tanısında ve sağkalım oranlarında tek başına önemli olmadığını düşünüyoruz. Karsinogeneziste birden fazla faktör vardır ve bu durumun nedeni olabilir. Akciğer kanseri hastalarının teşhisi için serum anti-p53antikor düzeylerinin bilinen bir katof değeri yoktur. Bu nedenle, bu antikorun tümör spesifikliği olmadığını ve serum anti-p53antikor düzeyinin akciğer kanseri taraması için uygun olmadığını düşünüyoruz.

Anahtar sözcükler: Anti-p53antikor, akciğer kanseri, F18-FDG, PET, p53

INTRODUCTION

Lung cancer is one of the most common cancer worldwide. Long–term survival rates in lung cancer have been still low in spite of developing surgical tecniques, chemotherapy regimens and radiotheraphy methods[1]. Whereas surgical resection is the main treatment in early stage non small cell lung cancer, chemoradiotheraphy combination is the main treatment option in advanced stage lung cancers and small cell lung cancers. But treatment is given for only paliation and overall mortality of advanced stage lung cancer patients is high [2]. Therefore staging of lung cancer is very important for optimal treatment choice. High-resolution CT is the main diagnostic method for evaluating local tumor status. National Lung Screening Trial in the USA showed that early detection of lung cancer using low dose spiral computed tomography screening led to a 20 % reduction in lung cancer mortality [3]. But using of thorax CT as a screening tool for lung cancer is limited because of radioactivity exposure and low specifity. Suspicious lesions which detected in thorax CT must be evaluated with integrated positron emission tomography/computed tomography (PET/CT) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG). This method give chance of anatomical and metabolic evaluation of lesion [4]. Diagnostic accuracy, staging, treatment optimisation, evaluation of treatment response, radiotheraphy planning, restaging and prognostication are very important in lung cancer patients. Metabolic and volumetric parameters of PET such as SUVmax and total lesion glycolysis (TLG) have roles in prognosis of SCLC and NSCLC patients [5,6].

Tumor markers such as prostate-specific antigen (PSA), carcinoembriyonic antigen (CEA), cancer antigen CA15-3, cancer antigen CA19-9 and cancer antigen CA125 are used for both diagnosis and follow up in some types of cancers. But unfortunately there is no spesific tumor marker in lung cancer patients despite lung cancer has highest prevalance, incidence, mortality and morbitiy rates in worldwide.

Autoantibodies that react with autologous cellular antigens have been described in pre-diagnostic and diagnostic samples from patients with small cell, non-small cell and other forms of lung cancer , and can sometimes be correlated with clinico-pathological parameters [7].

p53 gene is mutated in 60-70% of cancer patients[8]. In the serum of healthy subjects, the presence of p53 protein and anti-p53 antibodies are extremely rare[9]. Antibodies against p53 can be detected in serum samples. Recent researches suggest that serum p53-Abs can be considered as biomarkers to detect many types of cancer, as ovarian cancer, esophageal cancer, breast cancer and lung cancer [9-12].

In this study we aimed that are there any diagnostic and prognostic importance of serum anti-p53 Ab level in lung cancer patients.

MATERIAL AND METHODS

Patients

Patients were included who were referred to our

department with the purpose of ^{18}F-FDG-PET/CT imaging for staging due to lung cancer (LC) diagnosis and patients who were performed ^{18}F-FDG-PET/CT for diagnosis in the cause of the suspected pulmonary nodule in thorax CT but not detected pathologic FDG accumulation (NAPN=pulmonary nodule with non-avid-FDG) and healthy volunteers (control group). Only serum anti-p53 Ab levels were evaluated in conrol group. PET/CT imaging were not performed those patients in control group. Patients had operated for LC, received prior chemotherapy or radiotherapy for lung cancer, and a blood glucose level greater than 150 mg/dL were excluded from the study. This study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the local ethical committee. Oral and written consent was obtained from all patients.

Detection of serum anti-p53 antibodies

Blood samples were collected from peripheral blood vessels. Blood samples were taken before the FDG administration was performed with ^{18}F-FDG PET/CT. All serum were obtained after complete clotting by centrifugation, immediately frozen and stored at -80C° until the time of analysis. Serum anti-p53 Abs levels were measured using Enzyme-linked immuno sorbent assay (ELISA) kit (CUSABIO) according to the manufacturer's instructions. The kit was designed to measure circulating p53 antibodies in human serum samples. Intra-assay precision CV was % <8 and inter-assay precision CV was % <10. Limitation of the kit was only for research use and not for diagnostic procedure.

Imaging Acquisitions/Analysis

Positron Emission Tomography imaging was performed before the beginning of any treatment and images were acquired using a combined PET/CT scanner (Discovery 600 PET/CT GE Medical Systems, USA). Each patient fasted for at least 6 hour before imaging. After ensuring that blood glucose was <150 mg/dl, approximately 370 MBq ^{18}F- FDG were administered i.v. 1 hour before image acquisition and patients were rested. Attenuation correction of PET images with CT data was performed. Firstly, CT scan was performed. Right after CT acquisition, a standard PET imaging protocol was taken from the cranium to the mid-thigh with an acquisition time of 3 min/bed in 3-dimensional mode. All PET studies were acquired in 3-D mode. CT images were acquired with 70 mA, 120 kV, axial slice thickness of 3.75 mm. CT and PET images were matched and fused into transaxial, coronal and saggital images. The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to a processing Workstation (AW Volume Share5 GE Medical Systems S.C.S, France). And then visual and semi-quantitative analysis was performed. Tumor size (three maximum diameters) was measured. SUV is a commonly applied semi-quantitative parameter to express tumor FDG uptake. SUVmax, SUVmean and metabolic tumor volume (MTV) were calculated from attenuation-corrected ^{18}F-FDG PET images for tumor mass. The SUVmax was calculated by using the following formula: maximum pixel value with the ROI activity (MBq/kg)/(injected dose [MBq]/body weight [kg]). SUVmean was determined from the average voxel counts within the tumor region. Automatic volumes of interest (VOI) using an isocontour threshold method was placed over the primary tumor. TLG was then calculated as: "TLG=SUVmean X MTV".

Statistical analysis

The statistical tests were performed using SPSS (version 14.0; SPSS, Inc.). The frequencies test was applied to evaluate the statistical significance of the parameters. Correlations among serum anti-p53 Ab levels, tumor volume, tumor size, SUVmean, SUVmax, TLG and age were examined by the Spearman's rank correlation test. Relations between serum anti-p53 Ab levels and case groups, histopathological subtype of cancer patients and stage of cancer were evaluated by using Kruskal Wallis analysis due to parametric hypothesis could not be tested. Relation between serum anti-p53 levels and tobacco smoking status and sex of cases were evaluated with Mann-Whitney U test. Survival rates were calculated according to the Kaplan-Meier method. A multivariate analysis (Cox regression analysis) was used to evaluate independent risk factors affecting survival. Significance levels were presented as p values. It was assumed that the observed differences were statistically significant at the $p<0.05$ levels.

RESULTS

A total of 65 LC patients (median age: 63 years, range 37-80; 58 male/7 female), 47 patients with NAPN (median age: 57 years, range 22-80; 20 male/27 female), and a total of 34 healthy volunteers (median age: 63 years, range 44–89; 26 male/8 female) were included in this study. In our study 65.8 % of men and 11.4 % of women are cigarette-smoker ($p<0.001$). General features of patients in our study are presented in (Table 1).

Median serum anti-p53 Ab levels are 3.4 ng/mL (range:0.94-111.57 ng/mL) in LC patients, 3.77 ng/mL (range:0.67-92.19 ng/mL) in NAPN patients, 3.07 ng/mL (range:1.4-52 ng/mL) in healthy volunteers. There is no statistically significant difference for serum anti-p53 Ab level in LC and NAPN patients. Moreover there is no statistically significant difference for serum anti-p53 Ab levels in patients and healthy volunteers (p=0.377). In our lung cancer patients, there are 41 patients of squamous cell carcinoma, 13 patients of adenocarcinoma , 10 patients of small cell carcinoma and 1 patients of large cell carcinoma. There are 7 stage I patients (10.8 %), 8 stage II patients (12.3%), 19 stage III patients (29.2 %) and 31 stage IV patients (47.7 %). In according to stage status the highest serum anti-p53 Ab levels were found in stage I patients. But this data was not statistically significant (p=0.156). Median serum anti-p53 Ab level in 55 NSCLC patients was 3,4 ng/mL (range: 0,94-111,57) and median serum anti-p53 Ab level in 10 SCLC patients was 2.01 ng/mL (range:0,97-7,49) (p=0.069). When taking into consideration all patients, median serum anti-p53 Ab levels of men was found higher than women (p=0.003) (Table 2).

Table 1. General characteristics of the patient groups

	Control group 34 (23%)	NAPN 47 (32%)	Lung cancer 65 (45%)	*p* value
Gender				
Male	26 (76)	20 (43)	58 (89)	0.001
Female	8 (24)	27 (57)	7 (11)	
Smoking status				
Smoker	25 (74)	37 (79)	7 (11)	<0.001
Nonsmoker	9 (26)	10 (21)	58 (89)	
Age	63(44-89)	57 (22-80)	63 (37-80)	0.207

Table 2. Patients and volunteers characteristics and comparison of serum anti-p53 Ab levels among these groups.

	N (%)	p53 (ng/mL) (median, range)	*p* value
Gender			
Female	35 (24)	2.77 (0.67-89.20)	0.003*
Male	111 (76)	3.42 (0.8-111.57)	
Case groups			
Lung cancer group	65 (45)	3.4 (0.94- 111.57)	0.377
NAPN	47 (32)	3.77(0.67-92.19)	
Control group	34 (23)	3.07 (1.4-52.0)	
Smoking status			
Smoker	69 (47)	3.2 (0.67-92.19)	0.316
Nonsmoker	77 (53)	3.4 (0.97-111.57)	
Histopathology			
Squamous cell carcinoma	41 (63)	3.16 (1.09-111.57)	0.069
Adenocarcinoma	13 (20)	3.67 (0.94-104.19)	
Small cell carcinoma	10 (15)	2.01 (0.97-7.49)	
Large cell carcinoma	1 (2)	4.5*	
Stage			
Stage I	7 (11)	4.74 (0.94-111.57)	0.156
Stage II	8 (12)	2.96 (1.94-95.51)	
Stage III	19 (29)	3.94 (1.12-81.18)	
Stage IV	31 (48)	2.65 (0.97-104.19)	

*Because it is a case of large cell carcinoma group, these patients were excluded from statistical analysis.

Median primary tumor size was found 55 mm (range:10-149) in lung cancer patients.Median tumor TLG value of primary tumor was found 410.221 (range:13-3068.7), median maximum standardized uptake value (SUVmax) of primary tumor was found 16.2 (range:7.9-58.1), in lung

cancer patients. There is no statistically significant correlations between serum anti-p53 Ab level and tumor size, serum anti-p53 Ab level and TLG, serum anti-p53 Ab level and SUVmax (p=0.595, p=0.218 and p=0.884, respectively) (Table 3).

Table 3. Correlation between p53 and age, p53 and tumor size, p53 and TLG, p53 and SUVmax

	r value	*p* value
Age	-0.185	0.140
Tumor size	-0.068	0.595
TLG	-0.156	0.218
SUVmax	-0.019	0.884

Median serum anti-p53 Ab level was 3.4 ng/mL. Mean follow up time was 13 months (range between 1-58 months). The median survival duration was 14 months and the 2-year survival rate was 31%. Median survival rate was 13 months and 2-year survival rate was 36% in 33 patients whose serum anti-p53 Ab levels were ≤ 3.4 ng/mL. Median survival rate was 15 months and 2-year survival rate was 28 % in 32 patients whose serum anti-p53 Ab levels were >3.4 ng/mL (Table 4). It has been found that there is no effect of serum anti-p53 Ab level whether >3.4 ng/mL or ≤ 3.4 ng/mL on the patient survival rate (p=0.652) (Figure 1). There was no statistically significant relationship between histopathologic subtype of tumor and whether serum anti-p53 Ab level < 3.4 or >3.4 (p=0.550). There was no statistically significant correlation between age and serum anti-p53 Ab level (p=0.957, r=0.004).

Table 4. Survival rates of lung cancer patients according to p53 values

	Median survival rates (month)	2 year survival rates (%)	*p* value
P53 value*			
≤3.4	13	36	0.65
>3.4	15	28	

*Median p53 value was 3.4 in lung cancer patients in our study and therefore survival analysis was done according to this value.

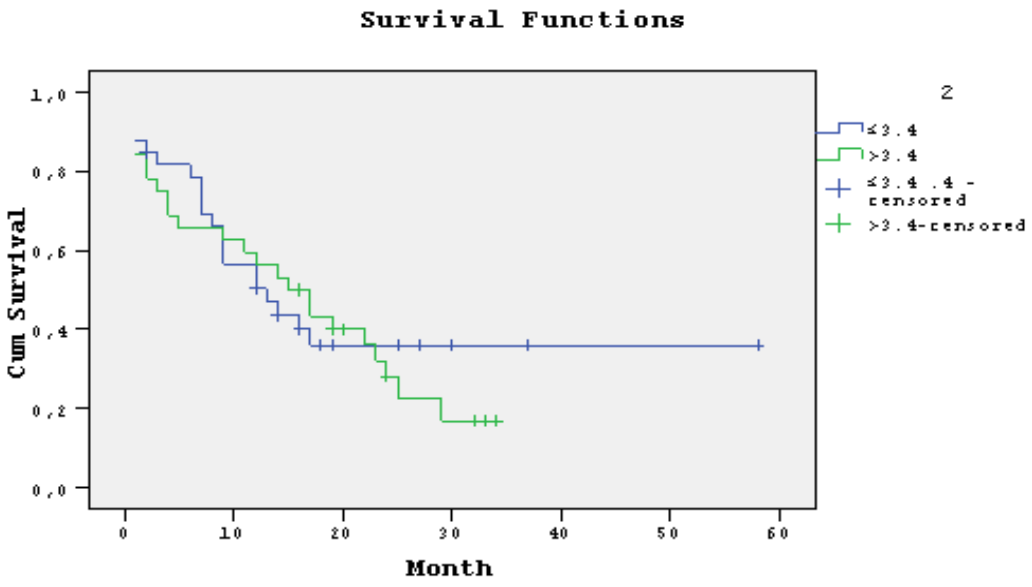


Figure 1. Survival curves for lung cancer patients according to the serum anti p-53 Ab levels.

In 3 of healthy volunteers serum anti-p53 Ab levels were found high in according to median serum anti-p53 value of healthy volunteers (median serum anti-p53 Ab level:3.07 ng/mL; these healthy volunteers serum-p53 Ab levels: 25.72 ng/mL, 52 ng/mL and 43.35 ng/mL) . One of the volunteers had almost 45 years of smoking history. Thorax CT was performed to that volunteer. There could not be found any mass or nodule. However an emphysema was detected. But thorax CT was not performed another two volunteers.

Two of the patients (in LC group) included in the study had cancer history before. The disease free period was over 10 years. Both of the patients were in complete remission and follow up. One of them was colon cancer and the other was renal cell carcinoma. While serum anti-p53 Ab level was 52.49 ng/mL in patient with colon cancer, it was 3.45 ng/mL in patient with renal cell carcinoma.

There were statistically significant difference of serum anti-p53 Ab levels between male and female patients in LC and NAPN groups (p=0.030 and p=0.021, respectively) but in healthy volunteers group there was not statistically significant difference of serum anti-p53 Ab levels between male and female patients (p=0.436) (Table 5). When evaluated seperately there were not statistically significant difference of serum anti-p53 Ab levels between smoker and nonsmoker patients in LC, NAPN and healthy volunteers group (p=0.568; p=0.297; p=0.565, respectively) (Table 6).

Table 5. Comparision of serum anti-p53 Ab levels between male and female patients in LC, NAPN and healthy volunteers groups.

	Male n (%) (serum anti-p53 Ab level-ng/mL)	Female n (%) (serum anti-p53 Ab level-ng/mL)	*p value*
Patients Groups			
LC	58 (89.2) (11.29±24)	7 (10.8) (2.28±1.1)	*0.03
NAPN	27 (57.4) (14.79±26)	20 (42.6) (7.56±19)	*0.021
Healthy Volunteers	26 (76.5) (7.22±12)	8 (23.5) (2.8±0.8)	0.436

Table 6. Comparision of serum anti-p53 Ab levels between smoker and nonsmoker patients in LC, NAPN and healthy volunteers groups.

Smoking status	LC n (%) (serum anti-p53 Ab level-ng/mL)	NAPN n (%) (serum anti-p53 Ab level-ng/mL)	Healthy Volunteers n (%) (serum anti-p53 Ab level-ng/mL)
Smoker	58 (89.2) (1.19±25)	10 (21.3) (9.8±17)	9 (26.5) (10.77±17)
Nonsmoker	7 (10.8) (3.09±1)	37 (78.7) (12.3±25)	25 (73.5) (4.53±8)
p value	0.568	0.297	0.565

DISCUSSION

Some tumor markers are used for diagnosis and patient follow up in certain types of cancers. But there is no current tumor marker for lung cancer and only imaging methods are used for this purpose. But using of this imaging modalities are limited because of radiation exposure. Suspicious lesions which detected in thorax CT are evaluated with ^{18}F-FDG PET/CT. This method give chance of anatomical and metabolic evaluation of lesion. But some studies about tumor-associated antibodies have been done with the aim of increasing

diagnostic accuracy and early diagnosis [13]. Recent studies showed that tumor antigens causes spesific immun response in lung cancer patients. Anti- P53 Ab is most studied tumor antigen in this group. TP53 tumor suppresor gene mutations can induce an immune response and anti-p53 Ab can occur early in the carcinogenic process for some tumors[14]. Although detection frequency of serum anti-p53 Ab is low, specificity of p53 autoantibodies for cancer was found high in cohort studies. Lei at al [15] reported that anti-p53 antibody can be an assistant marker in diagnosing lung cancer, but the low sensitivity limits its use as a screening tool for lung cancer in 4414 subjected meta-analysis. Wu et al [9] do a scientific research about association of serum p53 protein and antibodies with malignant tumors ;case–control study was conduct in 569 patients with various types of malignant tumors and 879 healthy controls. They found that the rate of anti-p53 antibodies in patients with various malignant tumors was 14.59% compared with 1.02% in healthy controls. They suggest that serum p53 protein and antibody are associated with increased cancer risk and can be used as early serological markers in the diagnosis of malignancies tumors. Mattioni et al [16] was found that the presence of serum p53Abs was found to be associated with smoking level and lung function impairment, both risk factors of cancer development in 675 subjected multicenter study. However they did not observe the occurrence of lung cancer or other cancers in the follow-up of positive subjects in a median follow-up of 24 months. In our study; we found that there is no significant difference of serum anti-p53 Ab levels among healthy volunteers, LC patients, NAPN patients. Moreover the prognostic role of anti-p53 antibodies in lung cancer remains opposite and as some studies show an association with poor prognosis, others show no relation between survival and anti-p53 Abs [17]. Ciancino et al.[18] found that via fiberoptic bronchial biopsies of NSCLC patients; p53 negative patients had a in significantly higher survival rates than p53 positive patients. Lai et al [19] reported that, the anti-p53 Ab positive lung cancer patients had a worse prognosis than the anti-p53 Ab negative patients. In this study they found that median survival time 20 weeks in anti-p53 Ab positive patients and 41 weeks in anti-p53 Ab negative patients. When the median serum anti-p53 Ab level was taken as 3.4 ng / ml; It has been found that there is no effect of serum anti-p53 Ab level whether >3.4 ng/mL or ≤ 3.4 ng/mL on the patient survival rate (p=0.652). It is known that incidence of p53 gene mutations is higher in aggressive SCLC patients than NSCLC patients [20]. Zalcman et al [21] found that survival rates of serum anti p53 Ab positive patients is shorter than serum anti p53 Ab negative patients in their study with limited-stage small cell lung cancer patients. In literature higher incidence of p53 gene mutations are seen in SCLC patients than NSCLC patients. But in our study it was found that anti-p53 Ab levels were higher in NSCLC patients than SCLC patients (although there was not statistically significant) (Table 2). Yu et al [22] reported that serum -p53 Abs remarkably decreased after neoadjuvant chemotheraphy treatment and pre-neoadjuvant chemotheraphy low serum-p53 Abs correlated with high objective chemoresponse rate in 47 stage III NSCLC patients.

FDG-PET is routinely used non invasive imaging tecnique in worldvide by means of its capability for demonstrating high glucose activity in malignant tumors. Duan et al [23] evaluated that are there any relationship between the expressions of chemotherapy resistance related tumor markers and SUVmax value of tumor in ^{18}F-FDG PET/CT. And they have been showed that there is positive correlation between the expressions of p53 and SUVmax on FDG-PET in NSCLCs. So they reported that FDG-PET might be a simple and good non-invasive method for predicting p53-related chemotherapy resistance in NSCLCs. Distinctly, another study suggested that there was no association between p53 expression and FDG uptake in NSCLC patients [24]. In our study, there is no statistically significant correlations between serum anti-p53 Ab level and tumor size, serum anti-p53 Ab level and TLG. Interestingly in our study we found that median serum anti-p53 Ab levels in man patients was found higher than woman patients (Table2). It is thought that this condition may be related with cigarette smoking. Because in our study; 65.8% of man subjects and 11.4 % of woman subjects were cigarette smoker. Cigarette smoking ratio was highest in lung cancer patients (Table 1). However there was no statistically significant relationship between cigarette smoking and serum anti-p53 Ab levels in our study. Whereas we had been found statistically significant relationship between cigarette smoking and serum anti-p53 Ab levels in our preliminary study [25]. But we think that this condition may be related with patient number.

Hypoxia induces p53 protein accumulation and p53 dependent apoptosis in oncogenically transformed cells. Hypoxic tumors have more aggressive nature with compared to well-oxygenated ones and p53 mutations are seen more frequent in advanced stages of tumor development [26]. In our study there was no statistically significant difference for serum anti-p53 Ab level in LC and NAPN patients. This

situation may be related with hypoxic state of subjects It is claimed that overexpression of some angiogenic factors such as hypoxia inducible factor-1A may be a prediposing factors of lung fibrosis like sarcoidosis and overexpression of these factors may be responsible for FDG uptake in lung cancer [27]. For explaining this situation, new studies are required.

CONCLUSION

In our study there was no statistically significant difference of serum anti-p53 Ab levels between lung cancer patients and NAPN patients. Therefore we think that this antibody is not tumor spesific and serum anti-p53 Ab level measurement is not appropriate for lung cancer screening. Even though serum anti-p53 Ab is very important in carcinogenesis, we think that serum anti-p53 Ab level by itself is not important in lung cancer diagnosis and survival rate. There are multiple factors in carcinogenesis and this may be the reason of this situation. There is no known cut off serum value of anti-p53 Ab for lung cancer patients.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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