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Relationship Between The 18F-FDG Uptake with Ki-67 and P53 Expression in Patients with Lung Cancer: A Clino-Pathologic Study

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Abstract

Background: There have been some relationship between Ki-67 and P53 expression and the standardized uptake value (SUVmax) of the primary lesion during positron emission tomography-computed tomography (PET-CT) in lung cancers.

Methods: The staining density of Ki-67 and p53 expression in 31 cases were diagnosed with non-small cell carcinoma (NSLCL) and 13 cases were diagnosed with small cell carcinoma (SCLC) have been investigated..

Results: Ki-67 % was significantly correlated with SUVmax values in patients with lung cancer in all subtypes (adenocarcinoma, squamous and small cell lung cancer) but the regression analysis was more prominent in adenocarcinoma and squamous cell carcinoma. Squamous cell carcinoma group had significantly correlated Ki 67 levels with overall survival (OS), and p53 levels had significantly correlated with progression free survival (PFS) and OS. Adenocarcinoma and small cell lung carcinoma patients did not have any significant correlation between the Ki 67, p53 and OS as well as PFS.

Conclusions: There is a strong correlation between the SUVmax and pathologic staining of Ki 67 and p53. Squamous cell lung carcinoma subtype is highly expressed p53 and Ki 67 with might predicted by SUVmax and these findings are significantly correlated with oncologic outcomes. .

Keywords: Ki 67, p53, SUV max, Lung cancer

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Introduction

Lung cancer is the 2nd most common malignancy in both of men and women. It is also the most common cause of cancer related deaths.[1] Nearly 85% of lung cancers were diagnosed as large cell carcinoma, adenocarcinoma (AC), and squamous cell carcinoma (SCC) classified as non-small cell lung carcinoma (NSCLC). One third of the newly diagnosed NSLC patients were diagnosed at advanced stages (Stage IIIA or IIIB), and they are not suitable for surgical treatment. The 5-year survival rate of these patients is 16%.[2,3]

In last 3 decades, through advances in biology, various genetic and molecular determinants have been created in order to detect the prognosis of cancer patients. The most widely used one among them in recent period is 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (PET/CT). The maximum standardized uptake value (SUVmax) in fluorodeoxyglucose positron emission tomography reflects the glucose metabolic activity of a tumor. As a result of increase of membrane glucose transporter proteins (GLUT-1 and GLUT-3) and intracellular enzymes ensuring the glycolysis (hexokinase and fluorodeoxyglucose) in malign cells, FDG is transported into cells utilizing glucose, phosphorylated by hexokinase, stays as FDG-6-phosphate within the cell. It cannot be metabolized any more, and allows the PET imaging by accumulating in cell. Imaging the FDG accumulation is related with clinic-pathologic prognostic factors such as expression of the level of membrane glucose transporters such as GLUT-1 and GLUT-3, differentiation of tumor cells, the stage of the tumor, and its growth rate.[4,5 18] Through the level of F-FDG-uptake on PET value in lung cancers, the direct relationship between tumor growth and metastasis is shown.[6-8] At the same time, the correlation of survival of the NSCLC patients with independent prognostic factors can be determined.[9]

It has been determined in various studies that examining the Ki-67 proliferation index in lung cancers is of prognostic importance.10 In some of the studies, the correlation between FDG uptake and Ki-67 proliferation has been presented in lymphomas and head-neck tumors.[11-13] In some of recent studies on NSCLC patients, it has been revealed that there is a positive correlation between SUVmax and Ki-67.[14-17] Nevertheless, in literature, there are only few studies indicating the correlation between FDG uptake and p53 expression of tumor in NSCLC patients.[18-20] For this reason, in this study, we examined if there is a correlation between the SUVmax values of non-operated lung cancer patients in advanced stage and K-67 proliferation index and p53 expression of these tumors.

Materials and Methods

The study involved formalin fixed paraffin embedded tissue sections of histopathologically diagnosed cases of SCC (n=13), AK (n=18) and SCLC (n=13) from the archives of Department of Pathology. The preperates stained with hematoxylin and eosin were re-evaluated to confirm the diagnoses. All these patients of age and sex, was also retrieved from the medical records of department.

Five micron thick serial sections were obtained from the paraffin embedded blocks belonging to the selected suitable preparations fixed with formalin to study p53 and Ki-67 immunohistochemical (IHC) examinationon positively charged slide. The p53 and Ki-67 (clone 4C4.9 A00087, ScyTec, 1:100 dilution) primary antibodies were investigated with IHC examination in the sections. The biotin-free, HRP multimer-based, hydrogen peroxide substrate and 3,3'-diaminobenzidine tetrahydrochloride (DAB) chromogen containing ultraView™ Universal DAB Detection Kit (Catalog number 760-091, Ventana Medical Systems, Tucson, AZ) and a full automated immunohistochemistry staining device (Ventana Bench Mark XT, Ventana Medical Systems, Tucson, AZ) were used as the IHC staining system. The whole IHC staining process including deparaffinization and antigen revealing procedures were performed at the Bench Mark XT and fully automated IHC staining device. Only the primary antibodies p53 and Ki-67 were manually placed as drops and incubated at 37°C for 30 minutes. The sections were counterstained with Mayer's hematoxylin. Known positive controls were also stained simultaneously.

Progression-free survival (PFS) was defined as the time between the diagnosis and disease progression, whichever occurred first. Overall survival (OS) was calculated as the time between the diagnosis and death or last follow-up.

Assesment of Immmunostaining

The reels were first observed at low magnification for deter-

mining the areas of highest and lowest expression of Ki-67, and designated as Highest Score (HS) and Lowest Score (LS), respectively. These areas were further analyzed at a single high power field (HPF, 400 magnification) and the staining scores were determined. Average of staining score in a whole reel was defined as Average Score (AS). Ki-67 expression was defined as the percent of Ki-67-positive tumor cells divided by the total number of tumor cells within one HPF, and were divided into four grades (0, < 1%; 1, 1-10%; 2, 11-30%; 3, > 30%) 19 Intensity of staining was scored as the following: 0 (no staining), 1+ (weak staining), 2 + (intermediate staining), 3 + (strong staining). The percentage of positive cells was scored as 0 (0%), 1 (1% to 9%), 2 (10% to 49%), and 3 (50% to 100%) for p53.21 All IHC results were evaluated by 2 pathologists who were blind to the FDG PET results.

PET/CT imaging

PET/CT imaging has been performed within 2 weeks after surgery/biopsy.

Patient Preparation

When they came for PET/BT imaging, the written consent of the patients were obtained, and their blood glucose levels were measured via glicometer. If the blood glucose level was lower than 200 mg/dl, then injection of approximately 10±2.6 mCi (7-15 mCi [259-555 MBq]) F-18 FDG IV was made by opening appropriate vascular access.

After FDG injection, they were taken into private rooms in order for them to take a rest for 45-60 minutes at semi-supine position. After asking them for emptying their bladders, the PET/CT imaging was performed via Siemens Biograph mCT device in whole body protocol.

CT Imaging

For attenuation correction and anatomic correlation, the CT imaging was performed at low dose CT parameters from head to toe.

PET Imaging

Right after the CT imaging, whole-body PET imaging was performed from head to femoral distal. PET ımaging was performed for 1.8 minutes for each bed position, 13-18 minutes in total for 7-10 bed positions. On 24 of the cases, the regional late PET/CT imaging was implemented.

Quantification

Besides visual evaluations, also the quantitative evaluations are available with PET images.* A semi-digital value is utilized in clinic studies for this purpose. The most widely used one is the standardized uptake value (SUV).

For anatomic localization, CT images were utilized in interpreting the FDG-PET images and, by determining the relevant region other than physiological involvement regions from the lesion indicating the increased, FDH involvement in proportion to background activity, the standardized maximum uptake value (SUVmax) was calculated by using TRUE V software in work station computer according to the formula below.

SUVmax value was calculated according to this formula:

SUVmax:	Radioactivity concentration in tissue in relevant region [µCi/g (Bq/g)]
	Dose of injected radioactivity [µCi (Bq)] / Body weight [g]

Reporting

FDG-PET/CT images of all of the patients were obtained from the digital archive. PET/CT images were evaluated by at least 1 nuclear medicine expert.

Treatment

All patients diagnosed with adenocarcinoma were analyzed for EGFR and ALK mutations, and then wild type tumors had been treated with chemotherapy as pemetrexed based either cisplatin or carboplatin depend on renal functions. All patients diagnosed with squamous cell carcinoma patients treated with chemotherapy as docetaxel based either cisplatin or carboplatin depend on renal functions, if there was a contraindication for taxane treatment gemcitabine based treatment were administered. All small cell lung carcinoma treated according to our clinics protocol by cisplatin-etoposide, if renal functions were abnormal, carboplatin used instead of cisplatin.

Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version 17 software (SPSS Inc., Chicago, IL, USA). For the continuous variables, parametric test conditions were first tested. The Shapiro–Wilk test was used to determine whether the continuous variables were normally distributed. Descriptive statistics were shown as mean+standard deviation or median + IR (minimum– maximum) where appropriate. Degrees of association between continuous variables were calculated by Spearman's correlation analysis. Parameters were considered to be significant if p value was less than 0.05.

Results

In this investigation, 44 patients diagnosed with locally advanced or metastatic stage lung cancer were studied, with a mean age 64 years old. In the study 41 patients were men and remaining 3 patients were women. Characteristics of the study population were summarized in the table-1.

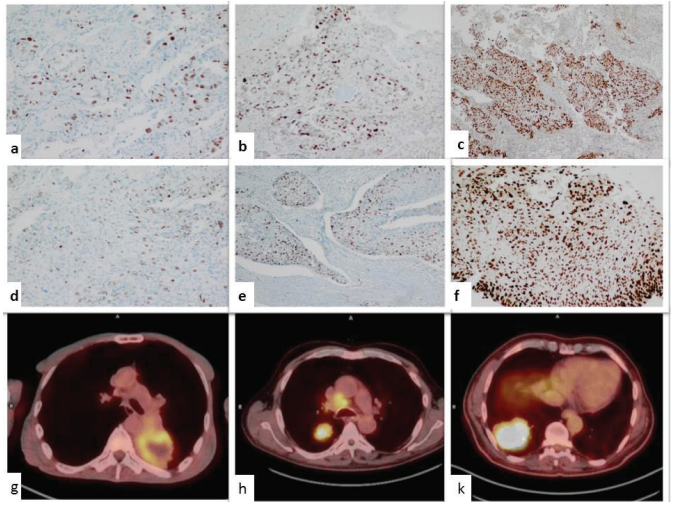

Figure 1:
a. Adenocarcinoma was observed low Ki-67 proliferation index (x100)
b. Adenocarcinoma was observed moderate staining for p53 (x200)
c. Adenocarcinoma was observed strong staining for p53 (x100)
d. Squamous cell carcinoma was observed low Ki-67 proliferation index (x200)
e. Squamous cell carcinoma was observed moderate staining for p53 (x200)
f. Squamous cell carcinoma was observed strong staining for p53 (x100)
g. Adenocarcinoma with a SUVmax of 4.8 in the right lower lobe
h. Adenocarcinoma with a SUVmax of 9.6 in the right lower lobe superior
k. Squamous cell carcinoma with a SUVmax of 14.4 in the right lower lobe

Adenocarcinoma were diagnosed in 18 patients, squamous cell carcinoma was diagnosed in 13 patients and small cell lung cancer were diagnosed in 13 patients. All patients treated with chemotherapy with or without radiation therapy according to their stage. PET- CT was performed before the treatment and tissue biopsy was done from the lung mass. The mean SUVmax value was 11.2 (5.1-24.9), Ki-67% score was 39(11-85) and p53% score was 54 (5-92) in study population. When we compared the Ki-67, p53 and SUVmax values according to the tumor type, Ki-67 % was 34 (11-75) in non-small cell lung cancer and 50 (26-85) in small cell lung cancer (p=0.009), p53 was 50.9 (5-90) vs 64 (34-92) respectively and p=0.043. SUVmax value was 11.2 (5.1-24.9) vs 11.4 (6-17) respectively and P=0.8.

Table 1. General Characteristics of Study Population.

Characteristics	Study Population n=44 (IR/SD)
Age, years	64 (40-85)
Glucose, mg/dL	80 (15)
Hemoglobin, gr/dl	12 (9-16)
Creatinine, mg/dl	0.78 (0.65-1.1)
Albumin, gr/dL	3.2 (3.2-5)
WBC(10^3)	9000 (6000-12000)
PLT (10^3)	185.000(105000-450000)
AST gr/dl, sd	35 (20-120)
ALT gr/dl, sd	28 (18-140)
Body Mass Index	22 (18-31)
Ki 67, %	39
P53, %	54
NSCLC	
Stage 3	14
Stage 4	17
SCLC	
Limited Stage	4
Extensive Stage	9
Overall survival, months	8.7
Progression free survival, months	6

WBC: white blood cell, PLT: Platelet count, NSCLC: Non small cell lung cancer, SCLC: small cell lung cancer, Liver function tests: AST and ALT, CK: creatine kinase

We found a significant correlation between the SUVmax values with Ki67% and p53% values, p=0.0001 (Pearson Correlation was 0.83) and p=0.0001 (Pearson Correlation was 0.81),

respectively.

In the regression analyses, there was a significant relation in value uptake SUVmax with Ki-67 % and p53 % (R square was 0.72, p=0.003 and 0.027, respectively). For the pathologic subgroup of the lung cancer, adenocarcinoma, squamous and small cell lung cancer were analyzed again.

Table 2 Comparison of Characteristics according to the tumor histology

	Non small cell carcinoma	Small cell carcinoma	P value
SUV max	11.2	11.4	0.08
Ki 67, %	34	50	0.009
P53, %	50.9	64	0.043
Overall survival, months	9	7.5	0.25
Progression free survival, months	5	4	0.42

In the adenocarcinoma group regression analyses showed that there was a significant correlation for SUVmax with Ki-67 % (Pearson Correlation was 0.96, p=0.0001) and p53 % (Pearson Correlation was 0.84, p=0.0001). In patient with squamous cell carcinoma, there were significant correlations between the SUVmax with Ki-67 % and p53 % (Pearson Correlation was 0.64, P=0.001 and Pearson Correlation was 0.69, P=0.0001 respectively). In small cell lung cancer group, there was a significant correlation with SUVmax and Ki-67 % (Pearson Correlation was 0.53, P=0.005) but there was no significant correlation with p35 % (Pearson Correlation was 0.27, P=0.066). When we investigated correlation of parameter with oncologic outcomes such as OS and PFS, Ki 67 was significantly correlated with OS (Pearson Correlation was 0.4, P=0.045) but not PFS as well as p53. Median OS was 9.9, 9 and 7.7 months respectively in adenocarcinoma, squamous cell carcinoma and small cell carcinoma and there were no significant differences between the group. Likewise, there were no significant differences between the groups for PFS (6, 5 and 4 months) (Summarized in table 3).

Our analyses showed that Ki-67 % was significantly correlated with SUVmax values in patients with lung cancer in all subtypes (adenocarcinoma, squamous and small cell lung cancer) but the regression analysis was more prominent in adenocarcinoma and squamous cell carcinoma. There was significant correlation between the SUVmax and p53 % values in adenocarcinoma and squamous cell carcinoma. Also in squamous cell carcinoma group had significantly correlated Ki 67 levels with OS (P=0.022), and p53 levels had significantly correlated with PFS (P=0.048) and OS (P=0.038). Adenocarcinoma and small cell lung carcinoma patients did not have any significant correlation between the Ki 67, p53 and OS as well as PFS.

Table 3 Pathologic characteristics and oncologic outcomes with SUV value.

Histologic type	Overall survival, months	Progression free survival, months	Ki 67%	P53	SUV ax
Adenocarcinoma	9.9	6	31	46.7	10.4
Squamous cell	9	5	39	56.7	12
Small cell	7.7	4	50	64.1	11.4

Squamous cell carcinoma group had significantly correlated Ki 67 levels with OS (P=0.022), and p53 levels had significantly correlated with PFS (P=0.048) and OS (P=0.038).

Discussion

It has been shown that FDG uptake is correlated with proliferation in lymphoma and head-neck cancers.[11] However, no relation with NSCLC could be detected at all. In our study, we examined if there is a correlation between the SUVmax values of non-operated lung cancer patients in advanced stage and K-67 proliferation index and p53 expression of these tumors. TNM phasing in cancer patients is a very important tool used by clinic oncologists in order to determine the prognosis. Despite the curative surgical resection, the relapse and survival may exhibit significant variation even among the patients in same pathological stage.8 In order to determine more aggressive behaviors of some tumors, estimation can be made by evaluating the proliferation markers. The most widely used proliferation marker used for this purpose is Ki-67. Ki-67 exists in the G1, S, G2 and M-phases of the cellular cycle. It doesn't exist in cells in the G0 phase. There is a strong correlation between various cellular proliferation indices and Ki-67 immunoreactivity. It has been reported to be related with poor prognosis by examining in various tumors. It has been determined to be a strong prognostic determinant in NSCLC.[12] In literature, there are studies examining the correlation of NSCLC patients' SUVmax values with the Ki-67 proliferation index of

those tumors. Moreover, Ki-67 proliferation index has been detected to be higher in squamous cell carcinomas in proportion to adenocarcinomas, slightly differentiated tumors, mildly differentiated and well-differentiated tumors. In study of Kaida et al. on 36 NSCLC patients, it has been found that there was a positive correlation between patients' SUVmax values and tumors' Ki-67 expression.[14] In study of Vesselle et al. on 178 NSCLC patients, the patients have been scanned via FDG-PET before the treatment.[15] The histological types of these tumors have been compared with Ki-67 proliferation index and SUVmax values. They have determined that there are lower FDG uptake and Ki-67 proliferation index in bronchoalveolar carcinomas in proportion to other tumor types. They have detected lower levels of FDG uptake in non-bronchoalveolar carcinomas in proportion to squamous cell carcinomas and large cell undifferentiated carcinoma. Moreover, there was a significant positive correlation between FDG uptake and Ki-67 scores. As a result of the study, they have stated that there was a significant difference between FDG uptake of NSCLC patients and sub-type, differentiation degree of these tumors and Ki-67 proliferation index in parallel with that. Vesselle et al. in another study on 39 potentially resectable early-phase NSCLC patients, have examined the correlation between FDG uptake and Ki-67 proliferation indexes of those tumors, tumor differentiation, and tumor diameters.[6] They have detected that there was a correlation between FDG uptake and Ki-67 expression and tumor differentiation, but no correlation between tumor diameter and SUVmax. In a study of Watanabe et al. they have investigated the correlation between FDG uptake and pathological tumor stage, proliferative activities determined by Ki-67 and cyclin D1, and p53, in clinical stage (c-stage) IA lung adenocarcinomas.[16] In that study, the contrast rate between FDG uptake tumor and contralateral lung was calculated. They have detected a significant correlation between Ki-67 staining score and contrast rate, and also. Zhou et al. have investigated the relationship between max standard uptake FDG ile p53, Ki-67, PCNA, vascular endothelial growth factor (VEGF), glucose transporter-1 (GLUT-1), and S-phase fraction (SPF) on 23 clinic-stage I NSCLC patients.[17] As a result of the study, they have shown that F-18 FDG uptake in NSCLC correlates well with the expression of p53, Ki-67, PCNA, VEGF, GLUT-1, and SPF. In a study of Araz et al. on metastatic lung cancer patients, they have investigated the relationship between the patients' SUVmax values and Ki-67, p53, transforming growth factor-□ (TGF-□) and lysyl oxidase (LOX) staining densities, and its role in metastasis.[18] As a result of the study, they have detected a significant relationship between metastatic adenocarcinomas' SUVmax values and p53 and LOX. On the other hand, no significant relationship has been detected between SUVmax values of metastatic SCC and SCLC patients and 4 immunohistochemical parameters. In our study, a positive correlation has been observed between NSCLC patients' SUVmax values and those tumors' Ki-67 and P53 expression. But no significant relationship could be detected between SCLC patients' SUVmax values and p53.

The p53 tumour suppressor protein is an important transcription factor in the arrangement of cellular cycle mechanisms. The p53 gene plays a critical role in maintaining controlled cell division and is the gene subjected to mutations in malignancies. As a result of mutation, p53 loses its normal functions, and alterations occur in production of p53 protein. p53 protein accumulates in nucleus of tumor cells, because it has longer half-life in proportion to wild-type p53.[21,23] The expression of p53 in tumors is less resistant to cisplatin, carboplatin, paclitaxel and gemcitabine.[24] The possible reason of that depends on transcription of some MDR genes in those tumors. 25 Duan et al. have implemented epidermal growth factor receptor (EGFR), p53 and excision repair cross complementing gene 1(ERCC1) expression to the tissues of 62 NSCLC patients through immunohistoshemical method.[20] In that study, they have investigated the correlation between chemotherapy that is resistant to tumor markers and FDG-PET SUVmax values. They have detected a positive correlation in tumor type, its differentiation, p53 and ERCC1 with SUVmax values. As a result of the study, they have proposed FDG-PET as a simple and good non-invasive method for predicting p53-related chemotherapy resistance in NSCLCs. In a study of Nakamura et al. on 30 resected NSCLC patients, they have investigated the correlation between FDG uptake and p53.[21] As a result of the study, they haven't detected any correlation between SUVmax and p53 expression. In a study of Sasaki et al. on 28 NSCLC patients, they have investigated the post-operative PDG-PET SUVmax values and tumor suppressor genes, Rb, p16, p27 and p53.[19] As a result of the study, they have observed higher SUVmax values in tumors where there were changes in tumor

suppressor genes in proportion to the ones there wasn't any change. They have asserted that the presence of abnormalities in tumor-suppressor genes accelerates the proliferation in tumor cells, and consequently increases the FDG uptake in lung tumors. In a study of Watanabe et al.[16] on Stage 1 adenocarcinomas, they haven't detected any correlation between FDG uptake and P53. But, in our study, a positive correlation was observed between SUVmax values of the NSCLC patients and those tumors' p53 expression.

Conclusion

Our analyses showed that Ki-67% and p53% values were significantly correlated with SUVmax values in patients with inoperable and metastatic patients with NSCLC (adenocarcinoma and squamous). Also there were significant correlation between the SUVmax and Ki-67 % values in SCLC.

Competing interests

The authors declare that they have no competing interests.

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