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Original

Correlation of [^{18}F]FDG PET activity with expressions of Ki-67 in non-small-cell lung cancer

Ilknur Kucukosmanoglu[1], Meryem Ilkay Eren Karanis[1], Yasar Unlu[1], Mustafa Erol[2]

[1]Department of Pathology, Konya City Hospital, Konya, Turkey
[2]Department of Nuclear medicine, Konya City Hospital, Konya, Turkey

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Abstract

Background: Lung carcinoma is the most commonly diagnosed cancer throughout the world and is the leading cause of cancer-related deaths. Non-small cell lung cancer (NSCLC) accounts for up to 80% of newly diagnosed lung cancer cases. This study aimed to investigate the relationship between Ki-67 proliferation index (PI) and the maximum standardized uptake value (SUVmax) obtained from [^{18}F]FDG PET/CT in NSCLCs and whether prognosis was predicted with SUVmax values.

Material and methods: This retrospective study included biopsy and resection materials of 41 patients, who were examined in the pathology laboratory of Konya Training and Research Hospital between January 2010 and December 2019, and diagnosed with NSCLC, and whose [^{18}F]FDG PET/CT images were present.

Results: There was no significant difference between histopathological subtypes in terms of age ($p = 0.077$), Ki-67 PI ($p = 0.454$), and SUVmax ($p = 0.143$). No correlation was observed between Ki-67 PI and SUVmax values obtained from [^{18}F]FDG PET/CT ($p = 0.338$, $r = 0.153$). There was no significant correlation between Ki-67 PI and tumor diameter ($p = 0.531$). The SUVmax value was found to be lower (12.78 ± 6.14) in tumors measuring ≤ 2.5 in diameter and higher (18.46 ± 7.81) in tumors measuring > 2.5 cm ($p = 0.027$). Metastases not proven histopathologically but detected in [^{18}F]FDG PET/CT were found to have no significant correlation with Ki-67 and SUVmax values ($p = 0.881$, $p = 0.837$).

Conclusions: This study showed that there was no significant relationship between Ki-67 PI and SUVmax value obtained from [^{18}F]FDG PET/CT in NSCLC tumors.

KEY words: non-small cell lung cancer; Ki-67; PET/CT

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Introduction

Lung carcinoma is the most commonly diagnosed cancer throughout the world and is the leading cause of cancer-related deaths. NSCLC accounts for up to 80% of newly diagnosed lung cancer cases [1–4]. Adenocarcinoma (AC) and squamous cell carcinoma (SCC) are two main histological subtypes of NSCLC. Compared to AC, SCC has a more destructive growth pattern and is associated with lower overall survival rates [3, 5]. The most important prognostic determinant is the stage of cancer at the time of diagnosis. Therefore, it is important to determine the extent of the disease, *i.e.*, staging at the time of diagnosis, for determining the most suitable treatment option and obtaining prognostic information in patients with newly diagnosed NSCLC. In particular, it is of great importance to accurately distinguish patients with potentially curable early-stage cancer, who may benefit from radical surgery, from those who are deemed to be non-operable and therefore addressed to chemotherapy, radiotherapy, or both [6]. Uptake of fluorine-18-fluorodeoxyglucose ([^{18}F]FDG) measured by integrated positron emission tomography/computed tomography (PET/CT) is a widely used non-invasive diagnostic test. Functional abnormalities can be detected by PET, even before they become morphologically apparent in conventional imaging. Moreover, PET imaging is also utilized for detecting fibrosis, the presence of edema, and viable tumor cells after treatment. The most commonly employed tracer for the evaluation of lung cancer is [^{18}F]FDG [4, 6, 7]. The [^{18}F]FDG PET/CT measures the SUV of a pulmonary nodule, *i.e.*, the glucose avidity of the tumor. The [^{18}F]FDG PET/CT

Correspondence to: Ilknur Kucukosmanoglu, Department of Pathology, Konya City Hospital, 42020 Akabe, Karatay, Konya, Turkey
e-mail: ilknurkukrer@hotmail.com

imaging is known to be useful in (i) determining the clinical behavior of a pulmonary nodule with an uncertain histopathological diagnosis and (ii) demonstrating mediastinal lymph node metastasis and distant metastasis [1]. Uptake of [^{18}F]FDG is associated with the proliferative activity of the tumor in lung cancers and is an independent prognostic factor [8]. Glucose metabolism in cancer tissues measured by [^{18}F]FDG PET/CT is an important biomarker for the characterization of lung cancer. Special care is recommended when using PET/CT in the investigation of patients with diabetes and in possible inflammatory processes [4]. Despite recent advances in personalized medicine, lung cancer still has a poor prognosis. Analyses of the predictive biomarkers are important to maximize the benefit of treatment [2, 3, 9].

Evaluation of tumor proliferation as a morphology-based measure of tumor growth kinetics has a long-standing background. The PI analysis of the Ki-67 antigen, one of the proliferation-related antigens, is frequently used for this purpose. Ki-67 was first developed by Gerdes et al. [10] in 1983. Ki-67 is a DNA-binding nuclear protein that proliferates throughout the cell cycle but is not expressed in quiescent (G0) cells [2, 11, 12]. It is a well-known powerful biomarker with significant prognostic value in breast cancers, gastrointestinal system tumors, and neuroendocrine tumors [2]. Tumor cell proliferation comprehensively describes the aggression and biological behavior of a tumor, which may provide additional tips for treatment selection. Meta-analyses of numerous studies on resected early-stage NSCLC suggest that high Ki-67 values are associated with poor prognosis, shorter disease-free survival, and shorter recurrence-free survival [2, 4, 13]. However, the Ki-67 assessment in NSCLC has not been successfully included in routine reporting yet. Several studies reported a correlation between FDG uptake and Ki-67 proliferation in lymphomas, head and neck tumors, and NSCLC [9]. This study aimed to investigate the correlation between the Ki-67 proliferation index (PI) and SUVmax values obtained from [^{18}F]FDG PET/CT in NSCLC cases.

Material and methods

This retrospective study included biopsy and resection materials of 41 patients (38 males and 3 females), who were examined in the pathology laboratory of Konya Training and Research Hospital between January 2010 and December 2019, and diagnosed with NSCLC, and whose [^{18}F]FDG PET/CT images were present. Age, gender, treatment, and other information were obtained from hospital records. Formalin-fixed paraffin-embedded (FFPE) tissue specimens were used in the study. Five-micron-thick sections obtained from the paraffin blocks were stained with hematoxylin and eosin (H&E). These H&E stained preparations taken from the archive were re-examined under a light microscope by a single pathologist to confirm the diagnoses. Ki-67 immunohistochemical (IHC) staining preparations (clone: MIB-1) of these cases were also present. Ki-67 PI of the cases was re-calculated by the same pathologist. During the evaluation, the area of most intense staining (hot spot) was identified at small magnification. In the area of most intense staining, 500 tumor cells were counted at high magnification (x400) and positive-stained cells were expressed as a percentage (Fig.1). All patients with pulmonary nodules identified by imaging methods underwent [^{18}F]FDG PET/CT for diagnosis or staging within 10 days before the biopsy. These [^{18}F]FDG PET/CT scans were blindly re-evaluated by an experienced nuclear medicine specialist. The protocol was as follows: A fasting condition for at least six hours and prohibition of intravenous glucose infusion was applied before [^{18}F]FDG injection. Blood glucose levels were measured using a fingerstick blood sugar test and confirmed to be 180 mg/dL before [^{18}F]FDG injection. The PET/CT scan was performed 60 minutes after intravenous injection of 0.12 mCi/kg [^{18}F]FDG. Then, PET scans were then taken at seven to eight-bed positions and at two-minute intervals for each position. During the PET/CT scan, all patients were in the supine position. Non-contrast CT scanning began at the orbitomeatal line and progressed to the upper thigh (30 mAs, 130 kV, 5 mm slice thickness), and PET imaging followed immediately over the same body region. The CT data were used for attenuation correction and anatomical localization of the lesions. PET/CT fusion images were obtained in transaxial, sagittal, and coronal planes. SUVmax of the lesions was obtained from transaxial images (Fig. 2).

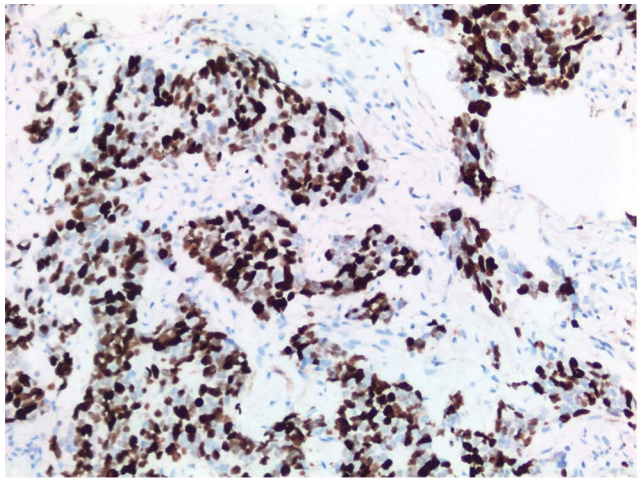

Figure 1. Ki-67 immunohistochemical staining, x 200 magnification (proliferation index: 75%)

The statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Chicago, IL, USA). The Shapiro-Wilk test was used for examining the continuous variables with normal and abnormal distributions, while the one-way analysis of variance (ANOVA) was used for the normally distributed continuous variables. The Kruskal-Wallis test was used for the abnormally distributed continuous variables. When the Kruskal-Wallis test indicated statistically significant differences, the causes of those differences were determined using a Bonferroni-adjusted Mann-Whitney U test. The continuous variables were presented as the mean ± standard deviation (SD). For all possible multiple comparisons, the Bonferroni adjustment was performed to control the type I errors. The Spearman correlation analysis was used to study the correlations between measurements. Statistical significance was considered at $p < 0.05$.

Approval was obtained from the ethics committee of KTO Karatay University for the study.

Results

The diagnosis was SCC in six (14.6%) of the cases, AC in 21 (51.2%), and NSCLC-not otherwise specified (NOS) in 14 (34.1%).

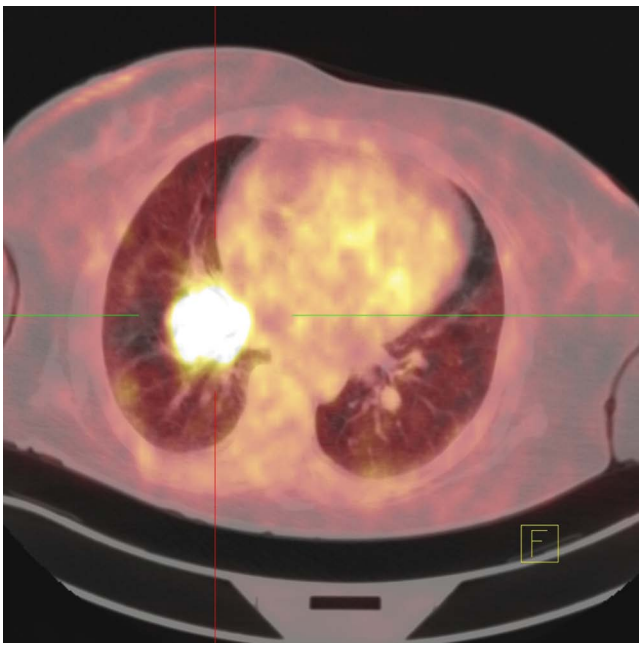

Figure 2. An [^{18}F]FDG PET/CT image of a patient with adenocarcinoma (SUVmax: 14.52)

The mean age was 60.19 ± 10.66 years in AC cases, 61.79 ± 8.11 years in NSCLC-NOS cases, and 69.33 ± 10.09 years in SCC cases. The mean Ki-67 PI was 33.86 ± 20.67 in AC, 49.57 ± 20.82 in NSCLC-NOS, and 34.00 ± 17.15 in SCC. The mean SUVmax value was 15.20 ± 6.34 in ACs, 17.85 ± 9.12 in NSCLC-NOS, and 18.99 ± 8.99 in SCC (Tab. 1). There was no significant difference between histopathological subtypes in terms of age, Ki-67 PI, and SUVmax.

No correlation was found between Ki-67 PI, and SUVmax values obtained from [^{18}F]FDG PET/CT ($p = 0.338$, $r = 0.153$). The cutoff values for Ki-67 PI were determined as ≤ 10, 10–25, and ≥ 25. Similarly, there was no correlation with SUVmax ($p = 0.230$). There was no significant correlation between Ki-67 PI and tumor diameter ($p = 0.531$). The SUVmax value was found to be lower in tumors measuring ≤ 2.5 in diameter and higher in tumors measuring > 2.5 cm ($p = 0.027$) (Tab. 2).

Metastases not proven histopathologically but detected in [^{18}F]FDG PET/CT were found to have no significant correlation with Ki-67 and SUVmax values ($p = 0.881$, $p = 0.837$) (Tab.3).

Conclusions

In recent years, PET/CT has become a routinely used procedure for the assessment of lung cancer. Many studies suggested that [^{18}F]FDG PET/CT was superior to CT in terms of the accuracy of nodal (N) staging for lung cancer. Therefore, [^{18}F]FDG PET/CT is currently recognized as the most accurate imaging method for N staging of lung cancer. Nonetheless, there are also studies reporting that [^{18}F]FDG PET/CT gives false negative and false positive findings in lung cancer cases, including N staging.

In a retrospective analysis involving solid lung masses, a positive correlation was found between the size of a malignant tumor and SUVmax. Multivariate analysis demonstrated that the combination of high SUV and large lesion size describes a subgroup of patients with the poorest prognosis and a median survival rate of fewer than six months [1].

The most widely used tracer for the detection of lung cancer is [^{18}F]FDG, which provides valuable information for patient management, particularly for detecting nodal and metastatic involvement and evaluating response to treatment. Misleading data may be encountered while utilizing [^{18}F]FDG PET/CT in

Table 1. Relationship between histopathological type ,and SUVmax, Ki-67 and age

	AC (n = 21)	NSCLC, NOS (n = 14)	SCC (n = 6)	p-value
Age	60.19 ± 10.66	61.79 ± 8.11	69.33 ± 10.09	0.077
Ki-67 PI	33.86 ± 20.67	49.57 ± 20.82	34.00 ± 17.15	0.454
SUVmax	15.20 ± 6.34	17.85 ± 9.12	18.99 ± 8.99	0.143

AC — adenocarcinoma; NOS — not otherwise specified; NSCLC — non-small cell lung cancer; PI — proliferation index; SCC — squamous cell carcinoma; SUVmax — maximum standardized uptake value

Table 2. Relationship between diameter and SUVmax, Ki-67

	≤ 2.5 cm (n = 13)	> 2.5 cm (n = 28)	p-value
Ki-67 PI	36 ± 22.74	40.68 ± 20.66	0.531
SUVmax	12.78 ± 6.14	18.46 ± 7.81	0.027

PI — proliferation index; SUVmax — maximum standardized uptake value

Table 3. Relationship between metastasis and SUVmax, Ki-67

	Metastasis present	Metastasis absent	p-value
Ki-67 PI	39.67 ± 19.96	38.65 ± 23.38	0.881
SUVmax	16.87 ± 7.29	16.36 ± 8.52	0.837

PI — proliferation index; SUVmax — maximum standardized uptake value

the assessment of brain metastasis (due to high physiological [^{18}F]FDG uptake in the brain), tumor types characterized by low glucose intake (neuroendocrine tumors, lepidic pattern adenocarcinomas), and cases with concomitant inflammation (due to high FDG uptake of inflammatory cells). In recent years, new PET tracers have been designed to overcome these limitations and have been successfully used in cases with suspected secondary brain lesions. The information provided by PET/CT is valuable in the clinical management of patients with lung cancer [6].

Several studies have demonstrated that SUV can reflect different histopathological parameters in lung cancer and has a moderate correlation with Ki-67. This is not a surprising finding. Ki-67, which is a non-histone nuclear protein and is synthesized throughout the entire cell cycle, except the G0 phase, is responsible for cell proliferation. It is an established biomarker in lung cancer for predicting tumor behavior. Theoretically, SUV reflects metabolic activity and can therefore be associated with various proliferation biomarkers. On the other hand, metabolic activity has no direct correlation with proliferation since FDG is not a specific tracer of cellular proliferation [5, 13]. The PET parameters can also be used as biomarkers if they correlate with various histopathological findings that reflect the proliferation or other features of lung cancer. Pretreatment SUV is often used as a relative measure of [^{18}F]FDG uptake and is accepted as a prognostic factor for risk stratification in different malignancies; however, it does not reflect the heterogeneity of a tumor. Therefore, other PET parameters including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) reflecting metabolic volume and activity have been proposed as quantitative indices of tumor metabolism to eliminate this disadvantage of SUVmax. There is a need for further studies to identify any possible correlation between various PET parameters and histopathology in lung cancer [13].

Studies are demonstrating a positive correlation between Ki-67 PI and FDG uptake; however, the correlation was reported to be weak in these studies. On the other hand, a threshold value was determined for Ki-67 PI by authors who reported that there was a weak correlation between FDG uptake values and tumor cell proliferation. According to Spyratos et al. [14], the choice of cut-off depends on the clinical objective: if Ki-67 is used to exclude patients with slowly proliferating tumors from chemotherapeutic protocols, a cut-off value of 10% will help to avoid overtreatment. In contrast, if Ki-67 is used to identify patients sensitive to chemotherapy protocols, it is preferable to set the cut-off at 25% [5]. In conclusion, an optimal threshold still needs to be defined for Ki-67 PI and validated for lung cancer. Among studies published after 2000, no consensus seems to be present on the prognostic value of Ki-67 PI in neither univariate nor multivariate analyses. The reason for conflicting results from the studies may be attributed to the fact that different variables that may influence the prognostic effect of Ki-67 are included in the studies. Although many studies have shown the negative prognostic effect of high Ki-67, most of these studies are of retrospective design and involve heterogeneous patient groups receiving incomparable treatments and follow-ups [12].

Information related to cell proliferation can also be useful in understanding tumor behavior in addition to the histological classification of tumors. Proliferative activity was found to have a significant correlation with metastatic potential, recurrence, or general prognosis in lung cancer [15]. Standardization is required for IHC, particularly regarding the positivity threshold, to become a useful prognostic factor in clinical practice. Furthermore, the present findings should be confirmed by taking into account classical well-defined prognostic factors for survival in patients with lung cancer [11]. Whether Ki-67 PI and SUVmax values were prognostic biomarkers was investigated separately in previous studies whereas this study assessed Ki-67 and SUVmax values together and investigated the correlation between them. The literature review showed that several studies reported high Ki-67 PI as a poor prognostic parameter in lung cancers whereas there were also studies reporting that high FDG uptake was associated with the proliferative activity of the tumor and could be used as a poor prognostic parameter.

We believe that information on the Ki-67 biomarker indicating the proliferative activity of the tumor can be predicted by the FDG uptake of the tumor. However, correlation analysis revealed no correlation between these two parameters. There were speculations that the cut-off value for KI-67 PI was chosen to affect the p-value in several studies. According to the statistical analyses we performed for Ki-67 both without determining any cut-off value and determining a cut-off value, there was no significant correlation between the two parameters in both cases.

This study has several limitations. Firstly, it was conducted in a single hospital, with a small number of cases. Therefore, the results may not be representative of larger populations. Moreover, since the SUVmax value does not reflect the heterogeneity of a tumor, comparing other PET parameters such as MTV and TLG, which reflects metabolic volume and activity, with Ki-67 PI in future studies may be helpful to eliminate this disadvantage of SUVmax. Therefore, conducting similar prospective studies including a larger number of patients with more homogeneous distribution (such as near tumor diameter) may shed light on this issue.

Conflict of interest

The authors have no conflicts of interest to declare.

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