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Positron emission tomography/computed tomography (PET/CT) findings in lung nodules and masses: A single-center experience

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Abstract:

BACKGROUND AND AIM: Positron Emission Tomography/Computed Tomography (PET/CT) is utilized as a guide for sampling lung lesions and for staging lung cancer. In this study, we examined the importance of mass size and Standardized Uptake Value maximum (SUV_{max}) values in predicting cancer in lesions identified on PET/CT.

METHODS: We analyzed PET/CT results from patients diagnosed with newly discovered lung cancer or those presenting lung lesions in other radiological imaging. The lesion's longest diameter and the areas with the highest SUV_{max} values were recorded. Lesion-nodule categorization, as well as benign-malignant differentiation and cancer subtypes, were separately examined with respect to diameter and SUV_{max} involvement.

RESULTS: Separate diameter and SUV_{max} cut-off values were determined for predicting cancer in lesions and nodules. For all lesions, the likelihood of malignancy increases when the size exceeds 27.5 mm and the SUV_{max} value surpasses 5.428 ($p < 0.001$, $p < 0.001$). Concerning nodules, the malignancy threshold lies at a size of 15.5 mm and an SUV_{max} value of 4.54 ($p < 0.001$, $p = 0.022$). It was observed that lesion size and SUV_{max} value in primary lung cancers were significantly higher than in metastatic lung cancers ($p = 0.002$, $p = 0.04$). SUV_{max} uptake was lower in small cell lung cancer (SCLC) lesions compared to non-small cell lung cancer (NSCLC) lesions ($p = 0.001$). The longest diameter was higher in adenocarcinoma than in squamous cell carcinoma ($p = 0.028$).

CONCLUSIONS: PET/CT plays a crucial role in staging patients diagnosed with lung cancer. In cases where cancer is suspected but diagnosis is challenging, PET/CT findings, along with the individual's risk factors, will aid in clinical decision-making.

Keywords:

Lung cancer, mass, nodule

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Introduction

Lung cancer is one of the most common and deadliest types of cancer. It is categorized into two distinct histological patterns: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Among all types, adenocarcinoma has become the most prevalent in recent decades. Screening programs have been implemented to enable the early detection of lung cancer.^[1]

Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (F-18 FDG PET/CT) is commonly used in various cancer types for staging, treatment evaluation and restaging. However, F-18 FDG accumulation can also occur in infectious diseases.^[2] Inflammation can lead to false positive results due to heightened glucose metabolism in inflammatory cells. Certain lung tumor types, such as bronchoalveolar carcinoma, neuroendocrine tumors, and mucinous forms, exhibit variable glucose metabolism and may display low-level glucose metabolism.^[3] Standardized Uptake Value maximum (SUV_{max}) is a semiquantitative value that reflects glucose metabolism. Increased glucose metabolism with a high SUV_{max} in the primary tumor is associated with poor prognosis.^[4] While FDG PET/CT has limited value in determining the T staging of NSCLC, it can differentiate between the tumor and tumor-associated atelectasis. FDG PET/CT improves diagnostic accuracy for nodal staging, which is crucial for determining the potential for curative surgery. For M staging, FDG PET/CT demonstrates higher sensitivity in detecting extrathoracic metastases.^[5]

In this study, we explore the relationship between lesion sizes, metabolic activities, histological patterns, and cancer stages using PET/CT images from patients with confirmed or highly suspected lung cancer at our clinic.

Materials and Methods

For this study, approval number 17 dated 05/01/2023 was obtained from the ethics committee. We conducted a retrospective review of the files of 697 patients who underwent PET/CT with a new diagnosis or pre-diagnosis of lung cancer between 2017 and 2022. Patients who underwent PET/CT imaging after receiving treatment (surgery, chemotherapy, radiotherapy) and those for whom sufficient clinical information was not accessible were excluded from the study. The sex,

age, longest diameter, and SUV_{max} involvement of the largest lesion, along with any cancer staging, of the remaining 467 patients were recorded. Patients were categorized into groups: benign, small cell lung cancer (SCLC), squamous cell lung carcinoma, lung adenocarcinoma, large cell lung carcinoma, unclassified NSCLC, and lung metastasis. Lesions smaller than 3 cm were classified as nodules and were also examined to determine a cut-off value for distinguishing between malignant and benign lesions (lowest diameter 5 mm, largest diameter 29 mm). The criteria for considering a lesion as benign were the absence of nodule progression during at least one year of radiological follow-up or the presence of benign features in the pathological result. Patients diagnosed with small cell lung cancer were staged as having limited-stage or extensive-stage disease, while those diagnosed with non-small cell lung cancer were evaluated according to the Tumor, Node, Metastasis 8th Edition (TNM-8) staging system.

F-18 FDG PET/CT imaging

Following a six-hour fasting period, patients underwent F-18 FDG PET/CT imaging. Blood glucose levels of all patients were assessed before F-18 FDG injection. F-18 FDG, in a dose of approximately 300-450 mBq based on body weight, was intravenously injected to patients if their blood glucose levels were below 180 mg/dL. Images were acquired 60 minutes after F-18 FDG injection using a PET/CT scanner (Siemens, BiographmCT, Germany) with 1-2 minutes of acquisition for each the 5-8 bed positions. The images were evaluated both visually and semiquantitatively. SUV_{max} values and dimensions of the lung lesions were documented, with the longest diameter of the lesion being used for statistical analysis.

Statistical analysis

Descriptive statistics were expressed as frequency, percentage, mean, and standard deviation. The normality of numeric variables was tested using the Shapiro-Wilk test. Mean differences between two normally distributed groups were compared using Student's t-test, while the Mann-Whitney U test was applied for comparisons involving data that was not normally distributed. Comparisons among more than two groups were tested using Kruskal-Wallis Variance Analysis (post hoc: Dunn). The efficacy of SUV_{max} and diameter measurements data was evaluated by calculating the area under the curve (AUC), with the receiver operating characteristic (ROC) curve assessing the device's performance across a range

Table 1: General features

	n	Mean±SD	%
Sex			
Female	89		19.1
Male	378		80.9
Age		61.19±12.43	
The longest diameter (mm)		45.90±31.28	
SUV _{max}		10.08±9.10	
Diagnosis			
Benign	145		31
SCLC	56		12
Squamos cell lung cancer	88		18.8
Lung adenocarcinoma	123		26.3
Unclassified NSCLC	11		2.4
Metastasis	33		7
Other lung cancers	6		1.3
Large cell lung cancers	5		1.1
Cancer Stagement			
Limited stage SCLC	19		
Extensive stage SCLC	37		
Stage 1 NSCLC	19		
Stage 2 NSCLC	17		
Stage 3 NSCLC	69		
Stage 4 NSCLC	122		

SD:Standard deviation, SUV_{max}: Standardized Uptake Value maximum, SCLC: Small cell lung cancer, NSCLC: Nonsmall cell lung cancer

of sensitivity and specificity values to determine optimal performance. The ROC curve was utilized to select the best cut-off points associated with appropriate cancer sensitivity and specificity. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 21.0 software package. P<0.05 was considered statistically significant.

Results

Of the 467 patients, 80.9% were male (n=378) and 19.1% were female (n=89). The mean age of the patients was 61.19 (±12.43) years. The diameter of the longest lesions measured in PET/CT was 45.9 mm (±31.28 mm), and the mean SUV_{max} value in lesions measured on PET/CT was 10.08 (±9.1). The mean SUV_{max} value measured on PET/CT was 2.91 for benign lesions and 14.73 for malignant lesions. After all examinations were concluded, the most common diagnosis was benign conditions (n=145, 31%).

Table 2: Determination of the relationship between cancer and the parameters by ROC analysis (all lesions)

Test result variable(s)	Sensitivity	Specificity	AUC (95% CI)	SE	p
The longest diameter >27.5 mm	0.835	0.785	0.863 (0.826–0.899)	0.019	<0.001
SUV _{max} >5.42	0.904	0.861	0.935 (0.909–0.961)	0.013	<0.001

ROC: Receiver operating characteristic, AUC: Under the curve, CI: Confidence interval, SE: Standard error, SUV_{max}: Standardized Uptake Value maximum

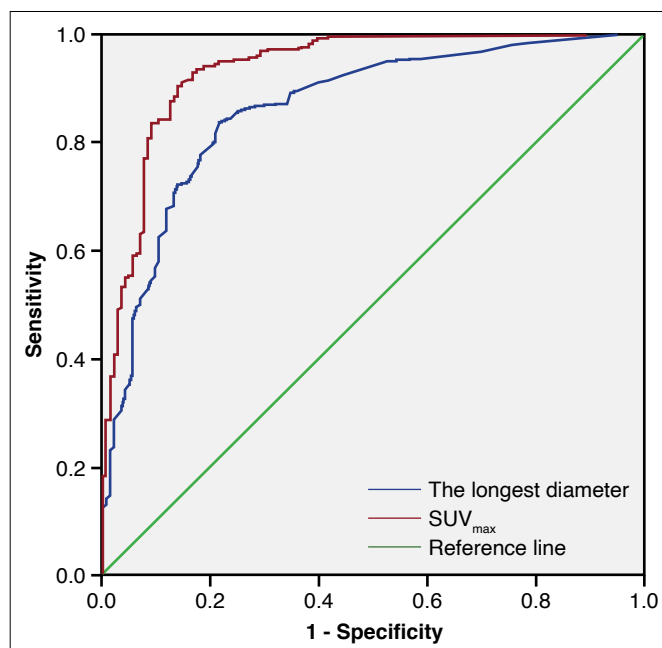


Figure 1: Determination of the relationship between cancer and the parameters by ROC analysis (all lesions)

ROC: Receiver operating characteristic, SUV_{max}: Standardized Uptake Value maximum

Among malignant conditions, the most frequent diagnosis was lung adenocarcinoma (n=123, 26.3%) (Table 1).

Lesions in all patients were compared based on their benign and malignant status. Using a cut-off value of 27.5 mm for the longest diameter, it was observed that it could distinguish between benign and malignant lesions with 83% sensitivity and 78% specificity (p<0.001). With a cut-off value of 5.42 for SUV_{max}, it was seen that it could differentiate between benign and malignant lesions with 90% sensitivity and 86% specificity (p<0.001) (Fig. 1, Table 2).

When comparing only the benign-malignant features of nodules, it was found that the probability of malignancy increased at 15.5 mm and above, with a sensitivity of 77.8% and a specificity of 57.6%. With the SUV_{max} cut-off value determined as 4.54, the sensitivity increased to 88.9%, and the specificity increased to 87.3% (p<0.001, p=0.022, respectively) (Fig. 2, Table 3).

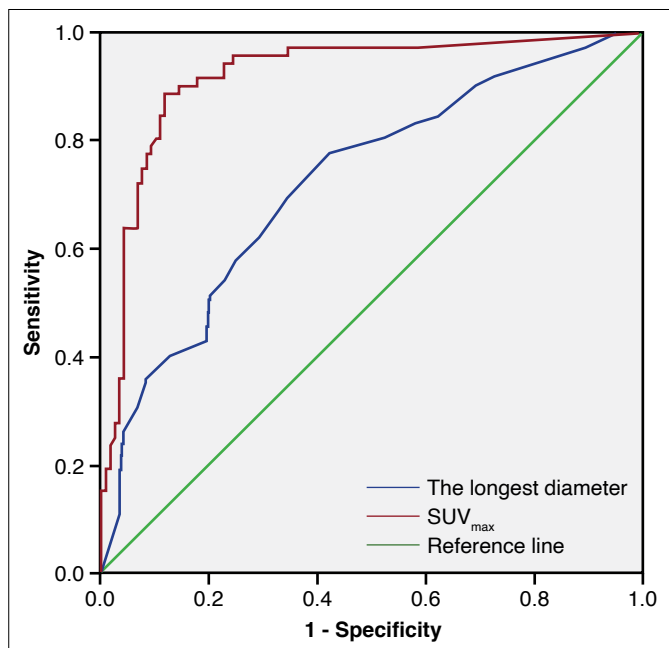


Figure 2: Determination of the relationship between cancer and the parameters by ROC analysis (nodules only)
 ROC: Receiver operating characteristic, SUV_{max}: Standardized Uptake Value maximum

The PET/CT features of primary lung cancers and metastatic lung cancers were compared. It was observed that the lesion size and SUV_{max} value in primary lung cancers were statistically significantly higher than in metastatic lung cancers (p=0.002, p=0.04, respectively) (Table 4).

The PET/CT features of SCLC and NSCLC (squamous lung carcinoma, lung adenocarcinoma, large cell lung carcinoma, unclassified NSCLC) were compared. The average longest diameter lengths were similar, but SUV_{max} uptake was statistically lower in the SCLC group (p=0.516, p=0.001, respectively) (Table 5).

PET/CT features of squamous lung carcinoma and lung adenocarcinoma were compared. SUV_{max} averages were similar, while the longest diameter was higher in adenocarcinoma than in squamous cell carcinoma (p=0.208, p=0.028, respectively) (Table 6). Additionally, when compared in terms of stage, stage 2 and stage 3 observation rates were significantly higher in squamous cell cancer

patients, whereas the stage 4 observation rate was higher in adenocarcinoma cases (p=0.007) (Table 7).

PET/CT features of limited-stage and extensive-stage SCLC were compared. There was no difference in SUV_{max} but the largest diameter was higher in extensive-stage SCLC (p=0.216, p=0.007, respectively) (Table 8).

PET/CT features were compared according to different stages in the NSCLC group. While SUV_{max} uptake was lower in stage 1 patients compared to others, there was no statistical difference between the other stages. The longest radius gradually increased starting from stage 1, but there was no statistical difference between stage 3 and stage 4 (p<0.001, p<0.001, respectively) (Table 9).

Discussion

The use of PET/CT in patients diagnosed with lung cancer holds a significant place in staging. It is also valuable in guiding patients with lung lesions toward peripheral lesion sampling rather than more invasive procedures.^[6] Avoiding further invasive procedures can prevent unnecessary PET/CT scans and, consequently, unnecessary radiation exposure in some patients. Our study revealed that almost one-third of patients who underwent PET/CT were diagnosed with benign conditions. Therefore, appropriate radiological follow-up, especially in patients with pneumonia or complications, and pathological sampling through methods like bronchoscopy or endobronchial ultrasonography (EBUS) should be considered, particularly in high-risk malignancy cases.

As lung cancer is often associated with epigenetic changes, the risk of its occurrence increases with age. Higher prevalence of risk factors such as smoking habits and employment in heavy industries among males leads to an intensified risk in males.^[1] The fact that the mean age of the population in our study was 61.1, with approximately 80% of them being male, can be attributed to the elevated risk factors associated with lung diseases, particularly in advanced age.

Table 3: Determination of the relationship between cancer and the parameters by ROC analysis (nodules only)

Test result variable(s)	Sensitivity	Specificity	AUC (95% CI)	SE	p
The longest diameter >15.5 mm	0.778	0.576	0.724 (0.650–0.800)	0.038	<0.001
Suv _{max} >4.54	0.889	0.873	0.920 (0.877–0.963)	0.022	0.022

ROC: Receiver operating characteristic, AUC: Under the curve, CI: Confidence interval, SE: Standard error, SUV_{max}: Standardized Uptake Value maximum

Table 4: PET/CT comparison of primary lung cancer and metastatic lung cancer

	Metastatic lung cancer (n=33) Mean±SD	Primary lung cancer (n=289) Mean±SD	p
SUV _{max}	11.9±8.66	15.05±8.29	0.040
The longest diameter (mm)	41.00±28.30	58.22±30.27	0.002

P value was obtained from Student t test. PET/CT: Positron Emission Tomography/Computed Tomography, SD: Standard deviation, SUV_{max}: Standardized Uptake Value maximum

Table 5: PET/CT comparison of SCLC and NSCLC

	SCLC (n=56) Mean±SD	NSCLC (n=227) Mean±SD	p
SUV _{max}	12.41±5.78	15.63±8.17	0.001
The longest diameter (mm)	60.43±35.58	57.48±28.89	0.516

P value was obtained from Student t test. PET/CT: Positron Emission Tomography/Computed Tomography, SCLC: Small cell lung cancer, NSCLC: Non-small cell lung cancer, SD: Standard deviation, SUV_{max}: Standardized Uptake Value maximum

Asymptomatic or mild symptoms of lung cancer in the initial disease stage unfortunately result in delayed diagnoses. Late hospital admissions are partly responsible for this delay, often due to the misattribution of symptoms such as cough and shortness of breath in smokers to smoking itself.^[7] In our SCLC patient group, extensive-stage disease was observed twice as frequently as limited-stage disease; among our NSCLC patients, the patient count increased with each progressive stage.

In lung lesions, the distinction between benign and malignant cases is clearly established through patho-

Table 6: PET/CT comparison of squamous cell lung cancer and lung adenocancer

	Squamous cell lung cancer (n=88) Mean±SD	Lung adenocancer (n=123) Mean±SD	p
SUV _{max}	16.22±8.09	14.82±7.9	0.208
The longest diameter (mm)	62.64±25.48	53.71±31.15	0.028

P value was obtained from Student t test. PET/CT: Positron Emission Tomography/Computed Tomography, SD: Standard deviation, SUV_{max}: Standardized Uptake Value maximum

Table 7: PET/CT comparison of stage distribution in squamous cancer and adenocancer

	Squamous cell		Adenocancer		p
	n	%	n	%	
Stage					
1.00	6	6.8	14	11.4	0.007
2.00	11	12.5	6	4.9	
3.00	35	39.8	30	24.4	
4.00	36	40.9	73	59.3	

P value was obtained from Pearson Chi Square test. PET/CT: Positron Emission Tomography/Computed Tomography

logical examination. However, within a limited patient subgroup, definitive pathological diagnosis may not be attainable, necessitating potential re-evaluation. In such instances, along with considering the patient's smoking history and family history of cancer, radiological images are employed. By definition, the primary distinguishing between masses and nodules is diameter; lesions larger than 3 cm are classified as masses, while those smaller are referred to as nodules.^[8] In our study, a diameter

Table 8: PET/CT comparison of SCLC images by staging

	Limited SCLC (n=19) Mean±SD	Extensive SCLC (n=37) Mean±SD	p
SUV _{max}	11.56±7.87	12.84±4.41	0.216
The longest diameter (mm)	49.68±44.74	65.95±29.01	0.007

P value derived from Mann Whitney U test. PET/CT: Positron Emission Tomography/Computed Tomography, SCLC: Small cell lung cancer, SD: Standard deviation, SUV_{max}: Standardized Uptake Value maximum

Table 9: PET/CT comparison of NSCLC images by staging

	Stage				p
	1 Mean±SD	2 Mean±SD	3 Mean±SD	4 Mean±SD	
The longest diameter (mm)	24.05±9.15 ^a	45.82±13.9 ^b	64.91±24.84 ^c	60.45±30.58 ^c	<0.001
SUV _{max}	9.40±5.78 ^a	13.94±6.22 ^b	16.90±8.46 ^b	16.18±8.16 ^b	<0.001

P value derived from Kruskal Wallis test. Within each row, different superscript letters indicate significant differences (p<0.05) according to the Dunn test. PET/CT: Positron Emission Tomography/Computed Tomography, NSCLC: Non-small cell lung cancer, SD: Standard deviation, SUV_{max}: Standardized Uptake Value maximum

greater than 27.5 mm was significantly associated with malignancy. Moreover, SUV_{max} uptake greater than 5.42 was found to be associated with malignancy. Since SUV_{max} can also increase in non-malignant conditions, relying solely on it for cancer diagnosis is insufficient. Therefore, as the level of involvement intensifies, additional pathological examinations should not be disregarded.

In the most recent report published by the Fleischner Society in 2017, recommendations for approaching nodules were presented. Particularly for solitary pulmonary nodules measuring 8 mm or larger, close follow-up or further examination is recommended to assess malignancy.^[9] Consequently, when examining nodules individually in our study, we observed an increased probability of malignancy when the diameter was 15.5 mm or greater or when the SUV_{max} value exceeded 4.54. We believe that establishing cut-off values in PET/CT studies for nodule assessment could potentially bring about changes in clinical practice.

The SUV_{max} of adenocarcinoma with bronchoalveolar carcinoma is significantly lower when compared with other non-small cell lung cancer types.^[10] Aquino et al.^[11] demonstrated statistical significance in SUV_{max} values between all adenocarcinomas and squamous cell carcinoma, large cell and all adenocarcinomas, non-bronchoalveolar adenocarcinoma and squamous cell carcinoma, bronchoalveolar adenocarcinoma and non-bronchoalveolar adenocarcinoma, bronchoalveolar adenocarcinoma and large cell carcinoma, and bronchoalveolar adenocarcinoma and squamous cell carcinoma. However, no statistical difference was found between squamous cell carcinoma and large cell carcinoma or between large cell carcinoma and non-bronchoalveolar adenocarcinoma. In the study by Hu et al.,^[12] metabolic parameters such as SUV_{max} , metabolic tumor volume, and tumor lesion glycolysis were higher in squamous cell carcinoma than adenocarcinoma. SUV_{max} were not statistically significant between small cell carcinoma and adenocarcinoma or between small cell carcinoma and squamous cell carcinoma. Additionally, Sahiner et al.^[13] did not find a significant difference in SUV_{max} values between small cell lung cancer and non-small cell lung cancer. Despite these previous studies, in our study, SUV_{max} values of squamous cell carcinoma were slightly higher than those of adenocarcinoma, but this difference was not statistically significant. SUV_{max} values in non-small cell lung cancer were higher than SUV_{max} values in small cell lung cancer. Of the 56 patients with small cell carcinoma, 37 (66.1%) had extensive disease, while

191 of 227 (84.1%) had stage 3 and 4 disease in non-small cell lung carcinoma. The difference in SUV_{max} between small cell carcinoma and non-small cell carcinoma may be attributed to the percentage of patients in later stages.

In the study of Çalışkan et al.,^[14] the SUV_{max} value was statistically higher in squamous cell carcinoma compared to adenocarcinoma and small cell lung cancer. SUV_{max} values were similar across the stages of squamous cell carcinoma, adenocarcinoma, and small cell lung cancer. Postoperative upstaging significantly occurred more frequently in patients with adenocarcinoma with high SUV_{max} but not in patients with squamous cell carcinoma. Preoperative lymph node sampling may be necessary in patients with adenocarcinoma and high SUV_{max} values of the primary tumor.^[15] Tumor SUV_{max} did not differ according to the presence of lymph node involvement or distant metastases in patients with non-small cell lung cancer.^[16] In the Hu et al.'s^[12] study, metabolic parameters did not differ between the stages of small cell lung cancer. In our study, SUV_{max} values were similar between the limited and extensive stages of small cell lung cancer. However, in non-small cell lung cancer, SUV_{max} values were statistically different between stage 1 and the other stages. This difference may be attributed to the tumor diameter, with the mean longest diameter being 24.05 in stage 1, 45.82 in stage 2, 64.91 in stage 3, and 60.45 in stage 4. This could be because SUV_{max} values may be underestimated in smaller lesions, as previously mentioned by Sahiner et al.^[13]

Lung adenocarcinoma tends to be more peripherally located compared to squamous cell lung cancer. This peripheral location often results in later symptom onset due to its distance from the central airways.^[17] Similarly, we attribute the lower lesion diameter and cancer stage in our squamous cell cancer patients, as compared to lung adenocarcinoma, to the location of the tumor, the earlier occurrence of symptoms it causes, and the subsequent earlier hospital admission.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee (No: 17, Date: 05/01/2023).

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Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept – K.B.A., H.İ.A.; Design – K.B.A.; Supervision – K.B.A., N.D.; Materials – K.B.A., N.D., H.İ.A.; Data collection &/or processing – H.İ.A.; Analysis and/or interpretation – M.K., K.B.A.; Literature search – N.D.; Writing – K.B.A., M.K.; Critical review – H.İ.A.

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