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Impact of Primary Tumor Diameter and SUV_{max} on Pathological Lymph Node Involvement in Non-small Cell Lung Cancer

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ABSTRACT

Aim: The aim of our study was to determine the role of preoperative primary tumor diameter (PTD) and maximum standardized uptake (SUVmax) values on preoperative 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) in predicting regional lymph node (LN) involvement, lymphatic invasion (LI), vascular invasion (VI), and pleural invasion (PI) in patients with non-small cell lung cancer (NSCLC) who were operated without receiving neoadjuvant therapy.

Methods: A total of 70 patients diagnosed with NSCLC who underwent surgery after ^{18}F-FDG PET/CT but did not receive neoadjuvant therapy were retrospectively examined. The effects of PTD and SUV_{max} on postoperative LN involvement, LI, VI, and PI in patient groups below and above the determined threshold value on preoperative ^{18}F-FDG PET/CT were compared. Since an optimal cut-off value for specificity and sensitivity was not obtained with the receiver operating characteristic curve for both the PTD and SUVmax of the primary tumor, patients were grouped based on the median values for the two parameters.

Results: The median PTD was 32 mm. The median SUVmax of 12.55 was obtained, and patients were grouped according to these median values. No significant difference was found in the primary tumor diameters ≥32 mm and <32 mm in terms of pathological LN involvement (p=0.322), VI (p=0.122), LI (p=0.122) and PI (p=1.000). Again, no significant difference was found in the patient groups with SUVmax values of the primary tumor ≥12.55 and <12.55 regarding pathological LN involvement (p=0.621), VI (p=0.122), LI (p=0.122), and PI (p=1.000). A low positive correlation (p=0.000, r=0.447) was found between the PTD and SUVmax values.

Conclusion: ^{18}F-FDG PET/CT alone is not a reliable noninvasive method for predicting LN metastasis in patients with early-stage NSCLC for whom curative treatment is planned.

Keywords: Lung cancer, ^{18}F-FDG PET/CT, invasion, lymph node involvement

Introduction

Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. Approximately 40% of cases are metastatic upon diagnosis [1,2]. Curative treatment modalities (surgery, chemoradiotherapy) are chosen based on the stage of the remaining non-metastatic patients.

The precise staging of NSCLC, particularly preoperative identification of lymph node (LN) metastasis, is critical for treatment planning and prognosis determination.

LN metastasis is a significant prognostic factor in patients with NSCLC because it is associated with a worse prognosis. This is because LN metastases often indicate that the cancer has spread beyond the lung to other parts of the body.

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Patients with NSCLC who have larger tumors have an increased risk of LN metastasis. This is because larger tumors are more likely to invade the lymphatic system, which is a network of vessels containing white blood cells and other immune cells throughout the body.

LN metastasis can be determined by invasive or non-invasive methods. Non-invasive imaging methods, such as computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography-CT (^{18}F-FDG PET/CT), are widely used to identify involvement of the ipsilateral (N2) or contralateral mediastinal LNs (N3). Mediastinoscopy and endobronchial ultrasound-guided transbronchial needle aspiration are two invasive staging procedures that are frequently used after non-invasive staging results from CT and ^{18}F-FDG PET/CT scans. ^{18}F-FDG PET/CT using ^{18}F-FDG, a glucose analog shown to be useful in detecting malignancy, is an extremely important imaging method in the staging of NSCLC. Here, the maximum standardized uptake value (SUV_{max}) of the primary tumor and primary tumor diameter (PTD) can be used to predict the risk of nodal metastasis, and the threshold SUV_{max} value is between 2.5 and 4.0 [3].

Although invasive methods remain the gold standard for mediastinal nodal staging, they come with disadvantages, such as the risk of complications, delay in treatment, and high cost. Hence, the correct use of non-invasive mediastinal nodal staging will help in selecting patients who will benefit most from invasive staging and preventing unnecessary invasive procedures. However, in patients clinically staged as N0 (no nodal involvement) on preoperative ^{18}F-FDG PET/CT, the incidence of histologically proven occult nodal metastasis after surgery has been found to range between 8% and 58% in various stages [4,5].

The relationship between PTD and LN metastases in clinical staging and the proper selection of treatment methods has been investigated in many previous studies. Some studies have revealed a close relationship between these two factors, suggesting that PTD could be used to predict positive LN metastases [6,7]. However, others have concluded that there is no such specific correlation between these two factors [8,9]. It is believed that combining the PTD and SUV_{max} values may provide a more sensitive method for detecting pathological LN metastasis.

In this study, we aimed to determine the role of the PTD and SUV_{max} in preoperative ^{18}F-FDG PET/CT in predicting regional LN involvement, lymphatic invasion (LI), vascular invasion (VI), and pleural invasion (PI) in patients with NSCLC who were operated on without neoadjuvant therapy.

Methods

The computer registration system of our hospital was reviewed, and the archive file records of 70 patients who were diagnosed with NSCLC at the medical oncology clinic between October 2014 and February 2023 and who underwent surgery (segmentectomy, lobectomy, bilobectomy, pneumonectomy) after 18F-FDG PET/CT without receiving neoadjuvant therapy were retrospectively examined. The effects of PTD and SUV_{max} on postoperative LN, lymphatic, vascular, and PI in patient groups below and above the determined threshold value on preoperative ^{18}F-FDG PET/CT were compared. Since an optimal cut-off value for specificity and sensitivity was not obtained with the receiver operating characteristic (ROC) curve for both the PTD and SUV_{max} of the primary tumor, patients were grouped based on the median values for the two parameters.

The demographic and clinical characteristics of the patients included in the study are presented in Table 1. Parameters such as PTD and SUV_{max} in preoperative 18F-FDG PET/CT and histopathological diagnosis of the tumor in postoperative pathology reports, LN involvement, LI, VI, and PI were recorded. The effects of PTD and SUV_{max} on pathological LN involvement, LI, VI, and PI were compared between patient groups below and above the determined threshold value. The median follow-up period was 30.4 (0.17-112.7).

This study was planned and conducted in accordance with Good Clinical Practices and the Declaration of Helsinki, and it was approved by the Ethics Committee of Aydın Adnan Menderes University Hospital (approval no: E-53043469-050.04.04-346879, date: 11.05.2023).

Table 1. Demographics and clinical characteristics of all patients

		n	%
Gender	Male	60	85.7
	Female	10	14.3
Age	Median (min-max)	68 (48-91)	
Smoking	Never	5	7.1
	Current or ex-smoker	65	92.9
Smoking duration (pack years)	Median (min-max)	40 (0-100)	
ECOG	0	28	40.0
	1	42	60.0
Localization	Right	47	67.1
	Left	23	32.9
Surgery	Segmentectomy	7	10.0
	Lobectomy	52	74.3
	Bilobectomy	3	4.3
	Pneumonectomy	8	11.4
Histological type	SCC	38	54.3
	Adeno	32	45.7
Adjuvant chemotherapy	Did not receive	22	31.4
	Received	48	68.6
Adjuvant radiotherapy	Did not receive	60	85.7
	Received	10	14.3

ECOG: Eastern Cooperative Oncology Group, SCC: Squamous cell cancers, Min-max: Minimum-maximum

Statistical Analysis

Data were summarized using descriptive statistics, such as mean, standard deviation, median, minimum, maximum, frequency, and ratio. The distribution of variables was assessed using the Kolmogorov-Smirnov test. Independent quantitative data were analyzed using independent sample t-tests and Mann-Whitney U tests. The chi-square test was employed for qualitative independent data, with the Fisher's test used when conditions for the chi-square test were not met. ROC curve analysis was performed to maximize the sensitivity, specificity, and accuracy for assessing the cut-off value for PTD and SUV_{max}. A p value of less than 0.05 was considered statistically significant. Statistical Package for the Social Sciences 22.0 software was used for the analyses.

Results

For the PTD and SUV_{max} values of the primary tumor, since a cut-off value could not be obtained with the ROC curve with optimal specificity and sensitivity, patients were divided into 2 groups based on the median values.

There was no significant difference in age between patients with a PTD of ≥32 mm and <32 mm (p=0.073). In the group with ≥32 mm, the male gender was found to be more predominant (p=0.040) (Table 2).

The number of patients who smoked (p=0.164), the smoking duration (p=0.506), Eastern Cooperative Oncology Group (ECOG) status (p=0.329), tumor localization (p=0.203), and histological subtype (p=0.150) did not significantly differ between the groups. The number of patients who received adjuvant chemotherapy was significantly higher in the group with a PTD of ≥32 mm (p=0.000). There was no significant difference in the number of patients who received adjuvant radiotherapy (p=0.495, Table 2).

Age was not significantly different (p=0.073) in the groups of patients with SUV_{max} values ≥12.55 and <12.55 for the primary tumor. Regarding gender distribution, male sex was more predominant (p=0.040) in the group with SUV_{max} ≥12.55 (Table 3).

No significant differences were observed between the groups in the number of patients who smoked (p=0.643), duration of smoking (p=0.948), ECOG status (p=0.626), tumor localization (p=0.203), or histological subtype (p=0.055). In the group with a primary tumor SUV_{max} value ≥12.55, the number of patients who received adjuvant chemotherapy was significantly higher (p=0.002). Adjuvant radiotherapy was not significantly different between the number of patients who received it (p=1.000) (Table 3).

Pathological LN involvement (p=0.322), VI (p=0.122), LI (p=0.122), and PI (p=1.000) were not significantly different between the two groups according to PTD (Table 4).

Regarding the SUV_{max} values of the primary tumor, no significant difference was found between the two groups in terms of the pathological LN involvement (p=0.621), VI (p=0.122), LI (p=0.122) and PI (p=1.000) (Table 5).

A low positive correlation was observed between the PTD and SUV_{max} values (p=0.000, r=0.447) (Figure 1).

Table 2. Demographic and clinical characteristics of patients according to tumor diameter

		Tumor diameter <32 mm				Tumor diameter ≥32 mm				p	
		Mean±SD			Median	Mean±SD			Median		
Age		67.43	±	8.68	69 (48-88)	67.97	±	10.48	68 (43-91)	0.073	t
Gender	Male	27		77.1%		33		94.3%		***0.040***	x^2
	Female	8		22.9%		2		5.7%			
Smoking	Never smoked	4		11.4%		1		2.9%		0.164	x^2
	Smoked	31		88.6%		34		97.1%			
Smoking duration (pack years)		38.09	±	18.23	40.00	40.43	±	22.31	35.00	0.506	m
ECOG	0	16		45.7%		12		34.3%		0.329	x^2
	1	19		54.3%		23		65.7%			
Localization	Right	21		60.0%		26		74.3%		0.203	x^2
	Left	14		40.0%		9		25.7%			
Histological type	Squamous carcinoma	16		45.7%		22		62.9%		0.150	x^2
	Adenocarcinoma	19		54.3%		13		37.1%			
Adjuvant chemotherapy	Did not receive	18		51.4%		4		11.4%		***0.000***	x^2
	Received	17		48.6%		31		88.6%			
Adjuvant radiotherapy	Did not receive	29		82.9%		31		88.6%		0.495	x^2
	Received	6		17.1%		4		11.4%			

t: Independent samples t-test, m: Mann-Whitney U test, x^2: Chi-square test, ECOG: Eastern Cooperative Oncology Group, SD: Standard deviation

Table 3. Demographic and clinical characteristics of patients by SUVmax value

		SUVmax value <12.55				SUVmax value ≥12.55				p	
		Mean±SD			Median (min-max)	Mean±SD			Median (min-max)		
Age		65.7	±	9.7	67 (43-88)	69.7	±	9.1	70 (48-91)	0.073	t
Gender	Male	27		77.1%		33		94.3%		***0.040***	x^2
	Female	8		22.9%		2		5.7%			
Smoking	Never smoked	3		8.6%		2		5.7%		0.643	x^2
	Smoked	32		91.4%		33		94.3%			
Smoking duration (pack-years)		37.1	±	16.4	40 (0-70)	41.4	±	23.5	40 (0-100)	0.948	m
ECOG	0	15		42.9%		13		37.1%			x^2
	1	20		57.1%		22		62.9%		0.626	
Localization	Right	21		60.0%		26		74.3%		0.203	x^2
	Left	14		40.0%		9		25.7%			
Histological type	Squamous carcinoma	15		42.9%		23		65.7%		0.055	x^2
	Adenocarcinoma	20		57.1%		12		34.3%			
Adjuvant chemotherapy	Did not receive	17		48.6%		5		14.3%		***0.002***	x^2
	Received	18		51.4%		30		85.7%			
Adjuvant radiotherapy	Did not receive	30		85.7%		30		85.7%		1.000	x^2
	Received	5		14.3%		5		14.3%			

t: Independent samples t-test, m: Mann-Whitney U test, x^2: Chi-square test, ECOG: Eastern Cooperative Oncology Group, SD: Standard deviation, Min-max: Minimum-maximum, SUVmax: Maximum standardized uptake

Table 4. Relationship between tumor size and microscopic tumor spread in pathological samples

		Tumor diameter <32 mm		Tumor diameter ≥32 mm		p	
		n	%	n	%		
Pathological N factor	N0	24	72.7%	20	57.1%	0.322	x^2
	N1-3	11	33.3%	15	42.9%		
Venous invasion	Absent	14	42.4%	8	22.9%	0.122	x^2
	Present	21	63.6%	27	77.1%		
Lymphatic invasion	Absent	14	42.4%	8	22.9%	0.122	x^2
	Present	21	63.6%	27	77.1%		
Pleural invasion	Absent	23	69.7%	23	65.7%	1.000	x^2
	Present	12	36.4%	12	34.3%		

x^2: Chi-square test

Discussion

Our study showed that the preoperative PTD and SUV_{max} on ^{18}F-FDG PET/CT were insufficient to predict pathological LN involvement in patients with NSCLC.

In clinical stage 1A patients, the prevalence of LN metastasis is low, and because of high false-positive rates, the role of ^{18}F-FDG PET/CT is limited [10,11]. Additionally, a study has shown that the utility of ^{18}F-FDG PET/CT in predicting LN metastasis in subsolid lesions significantly decreases, with a sensitivity of 11.1%, specificity of 86.1%, and accuracy of 81.9% for LN staging in patients with subsolid adenocarcinomas (AC) with a PTD ≤3 cm [12].

This study showed that the incidence of LN metastasis in lung cancer increased with tumor size. Seok et al. [13] found that when patients were split into six groups based on tumor diameter: ≤0.5, 0.6-1, 1.1-1.5, 16-2.0, 2.1-2.5, and 2.6-3 cm, the rates of LN metastasis were 0%, 0%, 7%, 14%, 27%, and 31%. However, our study has shown similar results in terms of PTD among patients with NSCLC.

^{18}F-FDG PET/CT is a valuable tool in oncology practice because it can be used to measure increased glucose metabolism in tumor cells. This is because tumor cells typically have a higher metabolic rate than normal cells, and they take up more glucose to fuel their growth. A SUV_{max} >2.5 is generally used as a cut-off value for malignancy. This indicates that lesions or tissues

with an SUV_{max} >2.5 are more likely to be cancerous than those with an SUV_{max} 2.5. However, some benign conditions can also cause high ^{18}F-FDG uptake, and there are some cancers that may have an SUV_{max} below 2.5.

Tuberculosis, obstructive pneumonia, anthracosis, or immune reactions resulting from granulomatous inflammation can lead to false-positive results. Low-grade malignancies can also result in false negatives [14,15]. However, it is important to note that using a higher SUV_{max} cut-off value can also increase the false positive rate. This means that more patients will be identified as having metastasis even if they do not actually have metastasis. This can lead to unnecessary additional testing and procedures.

Some authors have claimed that using a higher SUV_{max} than the traditional 2.5 can increase the accuracy of metastasis presence. This is because a high SUV_{max} is more likely to indicate malignant tissue. However, it is important to note that no single SUV_{max} value is universally accurate for all cancer types. The optimal cut-off value varies depending on the specific type of cancer, tumor location, and other factors [16].

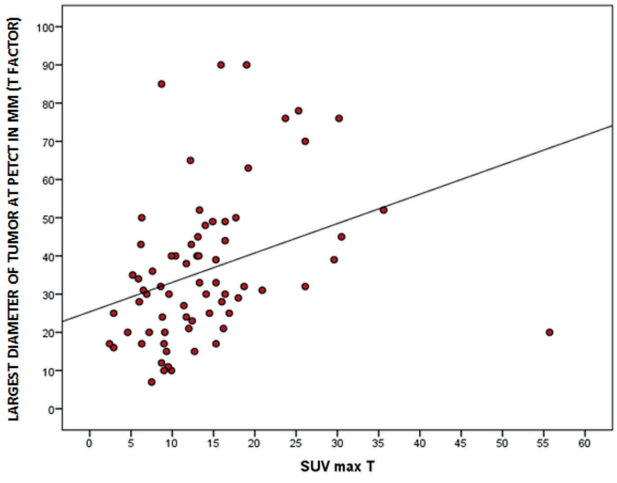

Figure 1. Positive correlation between primary tumor diameter and SUVmax value (p=0.000, r=0.447)
SUVmax: Maximum standardized uptake, PET/CT: Positron emission tomography/computed tomography

The SUV_{max} value was also a good indicator of tumor aggressiveness [17]. However, a study conducted in patients with resected stage 1 NSCLC found that the cellular components in the tumor varied widely and therefore did not correlate with 18F-FGD activity [18].

Tumor size and the presence of necrosis are other factors affecting a tumor's SUV_{max}. Previous studies have shown a positive correlation between PTD and SUV_{max} [19,20]. Similarly, in our study, a positive correlation was found between the PTD and SUV_{max}. However, there was no significant difference in pathological LN involvement between the two groups based on the SUV_{max} of the main tumor.

It is known that the likelihood of necrosis increases with tumor size, which is associated with a lower SUV_{max}. However, the relationship between SUV_{max} and necrosis was not evaluated in our study.

Tumor histologic type has also been identified to be associated with LN metastasis in patients with NSCLC. It is known that squamous cell cancers (SCC) have shorter doubling times and grow faster than AC, and therefore have higher glucose metabolism [21]. Moreover, glucose transporter-1 expression is higher in SCCs. Accordingly, previous studies have shown that SUV_{max} values are higher in SCC [22-24]. Kim et al. [25] found that the SUV_{max} was 10.8±4.4 for SCC and 8.8±3.2 for AC.

However, contrary to this, our study showed no significant difference in PTDs and SUV_{max} values according to histological subtype.

In studies involving patients with early-stage NSCLC, a high primary tumor SUV_{max} was found to be a strong indicator of lymphovascular invasion (LVI) and LN metastasis [23,26]. In a study conducted by Koksal et al. [27], it was found that the SUV_{max} of the tumor did not correlate with the nodal (N) stage, and the median SUV_{max} did not show a significant difference between groups with and without LN metastasis. Similarly, in our study, the tumor SUV_{max} was insufficient to predict pathological LN metastasis. Additionally, no significant relationship was observed between SUV_{max} and LVI or PI.

Table 5. Relationship between SUVmax and microscopic tumor spread in pathological samples

		Primary tumor SUVmax <12.55		Primary tumor SUVmax ≥12.55		p	
		n	%	n	%		
Pathological N factor	N0	23	65.7%	21	60.0%	0.621	x^2
	N1-3	12	34.3%	14	40.0%		
Venous invasion	Absent	14	40.0%	8	22.9%	0.122	x^2
	Present	21	60.0%	27	77.1%		
Lymphatic invasion	Absent	14	40.0%	8	22.9%	0.122	x^2
	Present	21	60.0%	27	77.1%		
Pleural invasion	Absent	23	65.7%	23	65.7%	1.000	x^2
	Present	12	34.3%	12	34.3%		

x^2: Chi-square test, SUVmax: Maximum standardized uptake

Study Limitations

The important limitations of our study are its non-randomized and retrospective nature. In addition, the small number of patients might have affected the study outcome. Therefore, we believe that prospective studies with large cohorts are needed to evaluate the utility of preoperative ^{18}F-FDG PET/CT in predicting LN involvement.

Conclusion

Ultimately, the decision to use a higher SUV_{max} cut-off value should be made on a case-by-case basis in consultation with a medical oncologist.

Footnote

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Hospital of Ethics Committee (approval no: E-53043469-050.04.04-346879, date: 11.05.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.A., B.D., S.B., Y.Y., Concept: A.A., S.B., Design: A.A., S.B., Data Collection or Processing: A.A., B.D., Analysis or Interpretation: A.A., B.D., S.B., Y.Y., Literature Search: A.A., B.D., Writing: A.A.

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