PAPER DETAILS

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Baseline 18F FDG PET/CT imaging in NSCLC: Possible utility in predicting strong-positive PD-L1 expression

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ABSTRACT

Purpose: To assess whether 18F FDG PET/CT imaging can predict non-small cell lung cancer (NSCLC) patients with strong PD-L1 expression (≥50%).

Methods: This retrospective study analyzed 149 NSCLC patients who had undergone baseline 18F FDG PET/CT imaging from June 2021 to May 2024. We recorded age, sex, smoking history, histopathology, TNM stage, metastasis, and PD-L1 expression levels. PET/CT parameters such as SUVmax, SUVmean, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were recorded. Patients were dichotomized based on two PD-L1 expression thresholds, as measured by immunohistochemistry: higher or lower than 1% (<1%, n = 62 versus ≥1%, n = 87) and higher or lower than 50% (<50%, n = 100 versus ≥50%, n = 39).

Results: No significant results were found for the comparison of PD-L1 negative (<1%) and positive (≥1%) patients. The <50% and ≥50% groups were similar in terms of all examined characteristics and PET/CT parameters except for TLG, which was significantly higher among patients with strong PD-L1 expression. ROC analysis revealed an area under curve of 0.606 (95% CI: 0.508–0.705, p = 0.049) for the discrimination of patients with and without strong PD-L1 expression, yielding 89.7% sensitivity, 30% specificity, and 45.6% overall accuracy.

Conclusion: This study identified TLG as a potential predictor for NSCLC patients with strong PD-L1 expression (≥50%) based on 18F FDG PET/CT imaging, despite low accuracy. High sensitivity and negative predictive value suggest a role as a supportive tool in screening.

Keywords: 18F-fluorodeoxyglucose, positron emission tomography, programmed death-ligand-1, non-small cell lung cancer

ÖZET

Amaç: Çalışmamızın amacı, inisyal F-18 FDG PET/BT'nin güçlü programlı ölüm ligandı 1 (PD-L1) (≥%50) ekspresyonu gösteren küçük hücreli dışı akciğer kanseri (KHDAK) hastalarını öngörmedeki rolünün değerlendirilmesidir.

Yöntemler: Haziran 2021-Mayıs 2024 tarihlerinde F-18 FDG PET/BT görüntülemesi yapılan 149 KHDAK hastaları retrospektif değerlendirildi. Yaş, cinsiyet, sigara anamnezi, histopatoloji, TNM evresi, metastaz durumu ve PD-L1 ekspresyon seviyeleri kaydedildi. Akciğer lezyonlarının SUVmax, SUVmean, metabolik tümör hacmi (MTV) ve toplam lezyon glikolizi (TLG) PET/BT parametreleri kaydedildi. Hastalar, immünohistokimya ile belirlenen PD-L1 seviyelerine göre PD-L1 ekspresyonları %1'den düşük ve yüksek (<%1, n = 62'ye karşılık ≥%1, n = 87) olan hastalar ve PD-L1 ekspresyonları % 50'den düşük ve yüksek (< %50 , n = 100'e karşılık ≥%50, n = 39) olan hastalar şeklinde gruplandı.

Bulgular: PD-L1 <%1 ve ≥%1 hasta gruplarının PET parametreleri arasında anlamlı farklılık izlenmedi. PD-L1 <%50 ve ≥%50 gruplarının karşılaştırılmasında ise ≥%50 PDL ekspresyonu olan hastaların primer lezyonlarına ait TLG değerleri anlamlı derecede daha yüksek bulundu. ROC analizinde TLG'nin bu iki grup hastayı %89,7 duyarlılık, %30 özgüllük ve %45,6 doğruluk ile ayırt edebildiği gösterildi.(EAA: 0,606, %95 CI: 0,508-0,705, p = 0,049)

Sonuç: Bu çalışma, düşük doğruluk oranına rağmen, F-18 FDG PET/BT görüntülemeden elde edilen TLG değerinin güçlü PD-L1 ekspresyonu (≥%50) gösteren KHDAK hastaları için potansiyel bir belirleyici olduğunu göstermektedir. Yüksek duyarlılık ve negatif öngörü değeri, bu hasta grubunu ön görmede destekleyici bir araç olarak rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: 18F-florodeoksiglukoz, pozitron emisyon tomografisi, programlanmış ölüm ligand-1, küçük hücreli dışı akciğer kanseri

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Lung cancer is the leading cause of cancer-related death, accounting for 18.0% of total cancer deaths. Approximately 85% of all lung cancers are non-small cell lung cancer (NSCLC) (1), and until recently, the standard treatment of these malignancies involved cytotoxic chemotherapeutics (2). The (programmed death protein) PD-1 receptor is an immune checkpoint inhibitor (ICIs) expressed on activated B and T cells, which physiologically functions in the down-regulation of excessive immune responses. Binding of PD-1 to its programmed death ligands (PD-L1) on tumor cells suppresses T cell activity, allowing potentially immunogenic tumors to evade the immune responses (3). The administration of ICIs which target and block the binding of PD-1 and its ligand PD-L1 (referred to as PD-1/PD-L1 inhibitors) stimulates antitumor immune activity (4). Nowadays, targeted agents and immunotherapy have become the preferable options in the treatment of metastatic NSCLC since they achieve good treatment response and improve survival; however, treatment efficacy can vary significantly depending on various factors (5,6).

One such factor is accepted to be PD-L1 expression. Although the impact of PD-L1 expression on treatment response remains debatable, recent studies indicate superior response to PD-1/PD-L1 inhibitors in the presence of higher levels of PD-L1 expression (7). As such, the US Food and Drug Administration (FDA) has approved the use of multiple anti-PD-L1 agents, including pembrolizumab, Atezolizumab and Cemiplimab in advanced NSCLC with strong PD-L1 expression (≥50% of tumor cells) (8). In relation, NCCN guidelines recommend treatment with ICIs to be based primarily on the presence and expression levels of PD-L1, as determined by immunohistochemistry (IHC) (9). Identifying tumor PD-L1 expression by IHC requires high-quality tissue samples, which are obtained via invasive procedures. These procedures cause patient discomfort and the obtained material may be inadequate to evaluate PD-L1 due to several factors, such as limited cellularity (10). Therefore, new methods allowing the prediction of PD-L1 expression level could be crucial to improve or expedite management decisions.

18F fluorodeoxyglucose positron emission tomography/computed tomography (18F FDG PET/CT) is a non-invasive imaging modality that can portray the metabolic status of cancerous lesions. A relationship between PD-L1 expression and high glucose metabolism has already been described as a result of studies examining PET/CT results in patients with NSCLC (11,12). Therefore, the aim of this study was to investigate whether 18F FDG PET/CT imaging can be used to predict PD-L1 expression in NSCLC, especially with respect to identifying patients with strong PDL1 expression (≥50%).

Methods

Study Design

NSCLC patients who underwent baseline 18F FDG PET/CT imaging from June 2021 to May 2024 in the Department of Nuclear Medicine of our institution were analyzed retrospectively. Inclusion criteria were: pathologically-proven new-onset NSCLC, having complete data records for baseline 18F FDG PET/CT before operation or biopsy, and having undergone detection of PD-L1 expression levels by IHC. Exclusion criteria were being diagnosed with small cell lung cancer, previously receiving antitumor therapy or undergoing surgery before 18F FDG PET/CT, being diagnosed with NSCLC demonstrating epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or C-ROS oncogene 1 (ROS1) aberrations, and a history of any other malignancy.

Age, sex, smoking habit (pack/year), histopathology, TNM stage, clinical stage, primary tumor site, nodal involvement, metastasis, operation history, IHC result of PD-L1 expression levels, metabolic and volumetric parameters derived from 18F FDG PET/CT were recorded. Stage of cancer was determined according to 8th TNM classification for lung and pleural tumors (13).

Patients with PD-L1 expression <50% were determined as group 1, and patients with strong positive (≥50%) PD-L1 expression were determined as group 2 patients.

This study was approved by the University of Health Sciences Turkey, Cam and Sakura City Hospital Ethics Committee. (Decision no: E-96317027-514.10-241607520 date: 03.04.2024) All diagnostic and therapeutic procedures had been performed in accordance with the local national guidelines and the Declaration of Helsinki. All patients had received appropriate information and provided informed consent to undergo the procedures.

Pathological evaluation

Staining with the SP263 assay (Ventana Medical Systems) was performed on formalin-fixed paraffin-embedded tumor tissue sections. Tumors were scored in terms of the tumor proportion score (TPS), which represents the percentage of viable tumor cells showing partial or complete membranous PD-L1 staining. Tumor PD-L1 expression was defined by TPS cut-off values: PD-L1 negative (TPS < 1%), PD-L1 positive (TPS ≥ 1%) or PD-L1 strong positive (TPS ≥ 50%).

18F FDG PET/CT imaging procedure

Scans and image reconstructions were carried out based on EANM guidelines for tumor imaging (v2.015) (14), and images were acquired with an Ingenuity TF 64 scanner (Philips Medical Systems, OH, USA). In order to ensure a serum glucose level of <150 mg/dL prior to the administration of 18F FDG, patients were routinely instructed to fast for 6 hours before scheduled scanning. Patients were transferred to a secluded room after injection. Following the 50-minute rest, the patient was taken for imaging which started with a low-dose whole-body CT set at: 113 mAS, 120 kV and 4-mm section thickness, and obtained data were utilized in the correction of attenuation. The PET imaging began immediately in the caudocranial direction on the same field of view (transverse, 3 min per bed). Finally, maximum intensity projection and cross-sectional (transaxial, coronal, sagittal) projections were utilized to assess both corrected and non-corrected PET and CT images.

Imaging Assessment

Two nuclear medicine physicians blinded to clinical, radiologic, and pathological data assessed the images. To normalize the FDG uptake in the lung tumor, three spherical ROIs, each 3 cm in diameter, were placed in the right lobe of the liver, which demonstrated uniform FDG uptake, and the mean value (L SUVmean) was calculated. A volume of interest (VOI) was positioned around the primary lung tumor on attenuation-corrected FDG PET/CT images using automated contouring with manual adjustments to ensure the lesion was fully captured in the axial, sagittal, and coronal planes. The SUVmax, or maximum standardized uptake value, was determined as the highest SUV from a single voxel within the VOI, while the SUVmean represented the average SUV concentration within the VOI. Metabolic tumor volume (MTV), with a threshold of 40% of the SUVmax in the VOI, was recorded, and total lesion glycolysis (TLG) was calculated by multiplying MTV by SUVmean. Finally, the ratio of the tumor SUVmax to L SUVmean was calculated to produce the Normalized SUV.

Statistical Analysis

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Analytical results showing $p < 0.05$ values were accepted as being statistically significant. For the normality check, the Shapiro-Wilk test was used. Descriptive statistics were presented with mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables, while frequency (percentage) values were used for categorical variables. Between-groups analysis of continuous variables was performed using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were analyzed with chi-square tests or the Fisher's exact test or its Freeman-Halton extension. The prediction performance of PET findings to determine PD-L1 expression was assessed using receiver operating characteristic (ROC) curve analysis. Optimal cut-off points were defined using the Youden index. Spearman correlation coefficients were calculated to evaluate directional relationship between continuous variables.

Results

We included 149 patients (127 males and 22 females) into the study, mean age was 63.93 ± 9.56 (range 37 - 87) years. PD-L1 expression was positive (≥1%) in 87 (58.39%) patients and was strongly positive (≥50%) in 39 (26.17%) patients. Patients were dichotomized based on being defined as PD-L1 negative (<1% expression, n = 62) or positive (>1% expression, n = 87), and also based on ≥50% PD-L1 expression, those with strong expression (n = 39) and without (n = 100).

When we compared PD-L1 negative (<1%) and positive groups (≥1%), we found that the groups were similar in terms of age, sex, pathology, smoking status, T stage, N stage, M stage, clinical stage, metastasis site, laterality (affected side), affected lobe, SUVmean, SUVmax, MTV, TLG, liver SUVmean and normalized SUV (**Table 1**). The only significant difference in this comparison was the smoking pack-years, which was lower in the positive group (p = 0.032).

Table 1: Summary of patient and tumor characteristics, PET findings with regard to PD-L1 expression positivity

		PD-L1 expression		p
	Total (n=149)	Negative, <1% (n=62)	Positive, ≥1% (n=87)	
Age	63.93 ± 9.56	64.45 ± 9.94	63.56 ± 9.32	0.578†
Sex				
Male	127 (85.23%)	55 (88.71%)	72 (82.76%)	0.438§
Female	22 (14.77%)	7 (11.29%)	15 (17.24%)	
Pathology				
Adenocarcinoma	94 (69.63%)	43 (74.14%)	51 (66.23%)	0.424§
SCC	41 (30.37%)	15 (25.86%)	26 (33.77%)	
Smoking	118 (86.13%)	53 (91.38%)	65 (82.28%)	0.203§
Pack year	40 (20 - 50)	40 (30 - 55)	30 (15 - 50)	**0.032‡**
T stage				
T1	11 (7.38%)	6 (9.68%)	5 (5.75%)	0.746§
T2	29 (19.46%)	11 (17.74%)	18 (20.69%)	
T3	47 (31.54%)	18 (29.03%)	29 (33.33%)	
T4	62 (41.61%)	27 (43.55%)	35 (40.23%)	
N stage				
N0	14 (9.40%)	8 (12.90%)	6 (6.90%)	0.190§
N1	22 (14.77%)	5 (8.06%)	17 (19.54%)	
N2	39 (26.17%)	17 (27.42%)	22 (25.29%)	
N3	74 (49.66%)	32 (51.61%)	42 (48.28%)	
M stage				
M0	59 (39.60%)	27 (43.55%)	32 (36.78%)	0.508§
M1	90 (60.40%)	35 (56.45%)	55 (63.22%)	
Clinical stage				
Stage I & II	8 (5.37%)	5 (8.06%)	3 (3.45%)	0.409¶
Stage III	51 (34.23%)	22 (35.48%)	29 (33.33%)	
Stage IV	90 (60.40%)	35 (56.45%)	55 (63.22%)	
Metastasis site (1)				
Other lung	9 (6.04%)	6 (9.68%)	3 (3.45%)	0.164#
Distant lymph node	32 (21.48%)	14 (22.58%)	18 (20.69%)	0.940§
Liver	14 (9.40%)	4 (6.45%)	10 (11.49%)	0.450§
Bone	45 (30.20%)	16 (25.81%)	29 (33.33%)	0.421§
Brain	27 (18.12%)	9 (14.52%)	18 (20.69%)	0.454§
Adrenal gland	25 (16.78%)	9 (14.52%)	16 (18.39%)	0.688§
Side				
Right	95 (63.76%)	40 (64.52%)	55 (63.22%)	1.000§
Left	54 (36.24%)	22 (35.48%)	32 (36.78%)	
Affected lobe (1)				
Superior	86 (57.72%)	34 (54.84%)	52 (59.77%)	0.665§
Middle	8 (5.37%)	4 (6.45%)	4 (4.60%)	0.719#
Inferior	58 (38.93%)	25 (40.32%)	33 (37.93%)	0.901§
SUVmean	6.6 (5.1 - 9.6)	6.45 (5.2 - 9.1)	7.0 (4.9 - 9.9)	0.439‡
SUVmax	11.6 (8.4 - 16.8)	11.2 (8.6 - 16.6)	12.4 (8.3 - 16.9)	0.492‡
MTV	42.8 (17.1 - 74.3)	43.2 (12.8 - 74.4)	42.4 (20.0 - 74.0)	0.831‡
TLG	325.22 (87.48 - 600.21)	332.61 (72.96 - 593.60)	325.22 (103.60 - 628.00)	0.641‡
Liver SUVmean	1.9 (1.6 - 2.2)	1.8 (1.6 - 2.2)	2.0 (1.7 - 2.2)	0.115‡
Normalized SUV	6.33 (4.47 - 8.80)	6.38 (4.22 - 9.42)	6.26 (4.48 - 8.80)	0.942‡

Descriptive statistics were presented with mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.
(1) Patients may have more than one of the defined categories.
† Student's t test, ‡ Mann Whitney U test, § Chi-square test, # Fisher's exact test, ¶ Fisher-Freeman-Halton test

The comparison of patients with and without strong PD-L1 expression (≥50%) revealed that the TLG values of the primary lesion were significantly higher among patients with strong PD-L1 expression (p = 0.049) (**Table 2**). A representative image from a patient is provide in **Figure 1**. There were no significant differences between these groups in terms of age, sex, pathology, smoking status, smoking pack year, T stage, N stage, M stage, clinical stage, metastasis locations, side, affected lobe, SUVmean, SUVmax, MTV, liver SUVmean, and normalized SUV (**Table 2**).

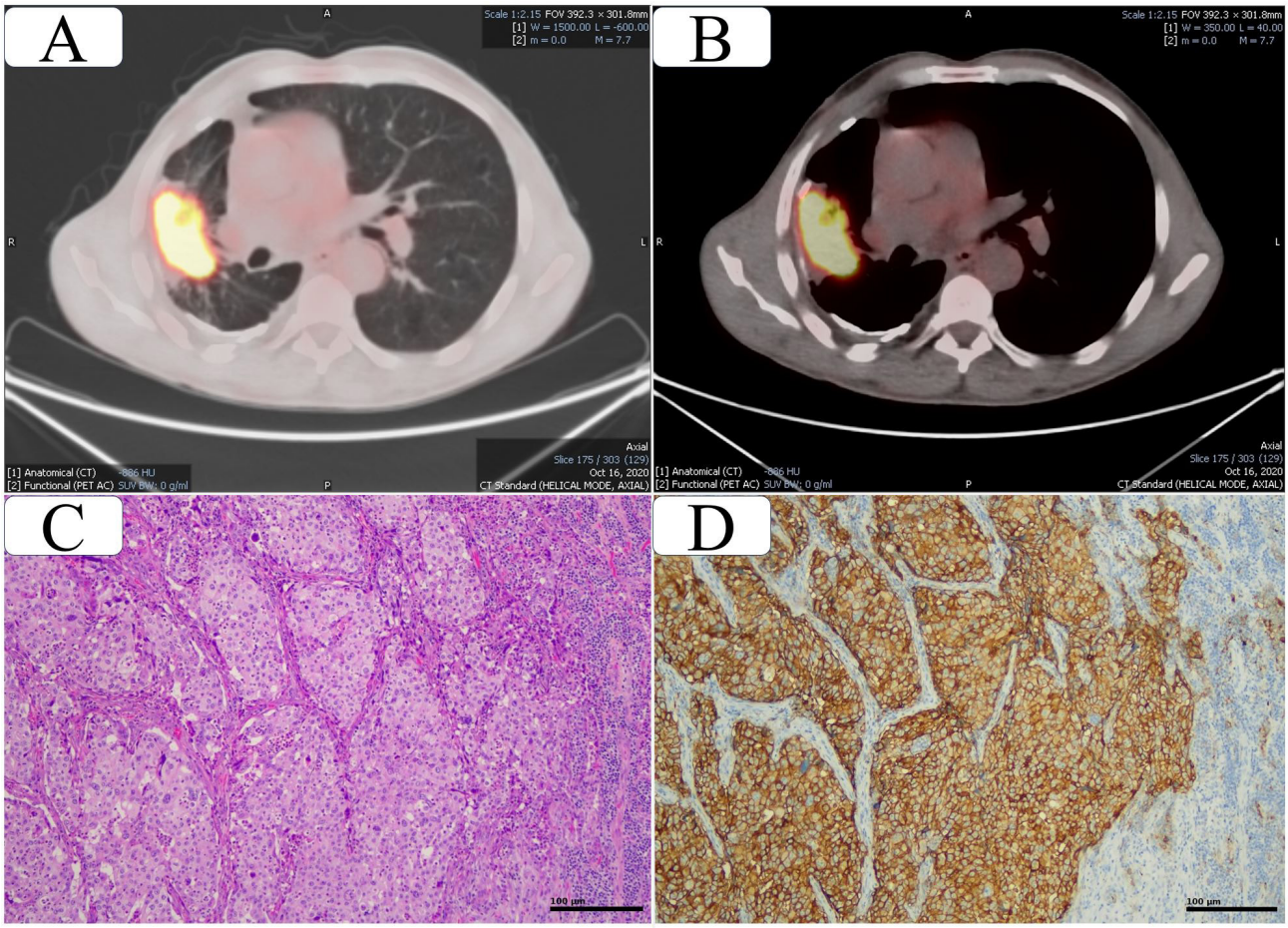

Figure 1: Representative images of 18F fluorodeoxyglucose positron emission tomography/computed tomography (18F FDG PET/CT) and immunohistochemical staining (IHC) of a non-small cell lung cancer (NSCLC) patient with high programmed death ligand-1 (PD-L1) expression (≥50%). (A, B) The axial fused pretreatment 18F FDG PET/CT images show values derived from the primary lung tumor: maximal standardized uptake value (SUVmax) of 15.9 g/ml, metabolic tumor volume (MTV) of 44.7 cm^3, and total lesion glycolysis (TLG) of 447. (C) Tumor infiltration areas showing strong PD-L1 positivity (H&E, x100). (D) Strong PD-L1 positivity observed in the tumor (x100).

Table 2: Summary of patient and tumor characteristics, PET findings with regard to strong (≥50%) PD-L1 expression

	PD-L1 expression		p
	<50% (n=110)	≥50% (n=39)	
Age	63.94 ± 9.83	63.92 ± 8.89	0.994†
Sex			
Male	93 (84.55%)	34 (87.18%)	0.892§
Female	17 (15.45%)	5 (12.82%)	
Pathology			
Adenocarcinoma	74 (71.84%)	20 (62.50%)	0.433§
SCC	29 (28.16%)	12 (37.50%)	
Smoking	83 (83.00%)	35 (94.59%)	0.143§
Pack year	35 (20 - 50)	40 (30 - 50)	0.323‡
T stage			
T1	11 (10.00%)	0 (0.00%)	0.150§
T2	23 (20.91%)	6 (15.38%)	
T3	33 (30.00%)	14 (35.90%)	
T4	43 (39.09%)	19 (48.72%)	
N stage			
N0	13 (11.82%)	1 (2.56%)	0.164§
N1	13 (11.82%)	9 (23.08%)	
N2	29 (26.36%)	10 (25.64%)	
N3	55 (50.00%)	19 (48.72%)	
M stage			
M0	45 (40.91%)	14 (35.90%)	0.719§
M1	65 (59.09%)	25 (64.10%)	
Clinical stage			
Stage I & II	7 (6.36%)	1 (2.56%)	0.636§
Stage III	38 (34.55%)	13 (33.33%)	
Stage IV	65 (59.09%)	25 (64.10%)	
Metastasis site (1)			
Other lung	8 (7.27%)	1 (2.56%)	0.447#
Distant lymph node	25 (22.73%)	7 (17.95%)	0.691§
Liver	9 (8.18%)	5 (12.82%)	0.523#
Bone	34 (30.91%)	11 (28.21%)	0.910§
Brain	18 (16.36%)	9 (23.08%)	0.488§
Adrenal gland	17 (15.45%)	8 (20.51%)	0.633§
Side			
Right	69 (62.73%)	26 (66.67%)	0.806§
Left	41 (37.27%)	13 (33.33%)	
Affected lobe (1)			
Superior	62 (56.36%)	24 (61.54%)	0.709§
Middle	5 (4.55%)	3 (7.69%)	0.432#
Inferior	45 (40.91%)	13 (33.33%)	0.520§
SUVmean	6.4 (4.9 - 9.1)	8.2 (5.3 - 10.8)	0.073‡
SUVmax	11.0 (8.2 - 16.2)	13.6 (9.4 - 19.4)	0.052‡
MTV	41.65 (12.8 - 73.2)	43.7 (25.0 - 105.3)	0.142‡
TLG	317.53 (79.05 - 592.90)	462.33 (182.32 - 838.32)	**0.049‡**
Liver SUVmean	1.9 (1.6 - 2.2)	2.0 (1.7 - 2.4)	0.336‡
Normalized SUV	6.09 (4.19 - 8.21)	7.39 (4.92 - 10.00)	0.082‡

Descriptive statistics were presented with mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables.
(1) Patients may have more than one of the defined categories.
† Student's t test, ‡ Mann Whitney U test, § Chi-square test, # Fisher's exact test.

ROC analysis revealed that TLG had 89.74% sensitivity, 30.00% specificity, 31.25% positive predictive value and 89.19% negative predictive value (45.64% overall accuracy) in discriminating patients with and without strong (≥50%) PD-L1 expression. The area under the ROC curve of TLG was 0.606 (95% CI: 0.508 - 0.705, p = 0.049) (**Table 3, Figure 2**)

Table 3: Performance of PET findings to predict strong positive (≥50%) PD-L1 expression, ROC curve analysis

	Cut-off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95% CI)	p
SUVmean	>7.9	53.85%	66.36%	63.09%	36.21%	80.22%	0.597 (0.491 - 0.703)	0.073
SUVmax	>13.2	53.85%	68.18%	64.43%	37.50%	80.65%	0.605 (0.501 - 0.708)	0.052
MTV	>18.1	89.74%	32.73%	47.65%	32.11%	90.00%	0.579 (0.481 - 0.678)	0.142
TLG	>87.0	89.74%	30.00%	45.64%	31.25%	89.19%	0.606 (0.508 - 0.705)	**0.049**
Normalized SUV	>8.4	41.03%	77.27%	67.79%	39.02%	78.70%	0.594 (0.493 - 0.695)	0.082

ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence interval

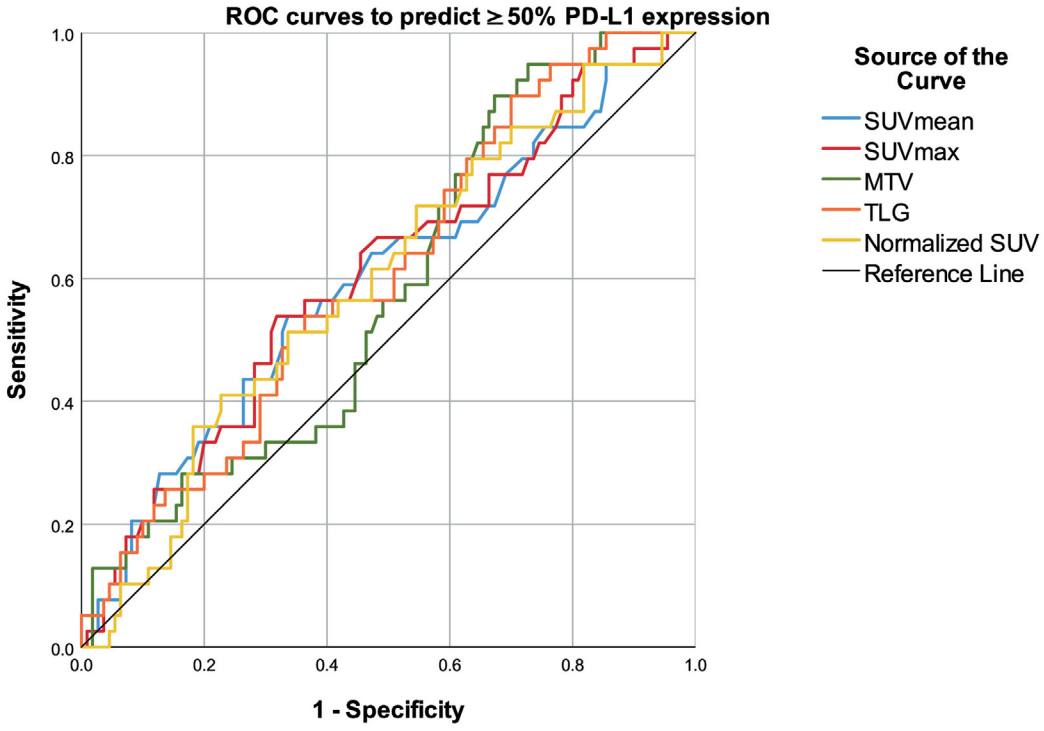

Figure 2: ROC curves of PET findings in the prediction of strong positive (≥50%) PD-L1 expression

Discussion

PD-1/PD-L1 inhibitors have become a crucial component of the treatment of advanced NSCLC without EGFR, ALK or ROS1 aberrations, either as a monotherapy or in combination with other immunotherapy/chemotherapies (15). Before initiating treatment, PD-L1 expression levels are assessed to predict which patients will respond to PD-1/PD-L1 inhibitors. Although the use of cut-off values to identify patients with high probability of therapeutic response is controversial, the FDA approved the use of multiple anti PD-L1 agents in a group of advanced NSCLC patients with strong PD-L1 expression (≥50%), suggesting that this threshold carries substantial clinical significance (7,8). Our analysis to assess the utility of 18F FDG PET/CT parameters in determining PD-L1 expression revealed that TLG was significantly higher among patients who were strongly positive for PD-L1 (as measured by IHC). Despite the very low overall accuracy (45.64%) determined by ROC analysis, the high sensitivity and negative predictive value show that elevated TLG values (defined as values greater than 87) might be utilized as supportive data in the identification of patients with ≥50% PD-L1 expression.

Many studies have shown that patients who failed first-line chemotherapy can benefit from PD-1/PD-L1 inhibitors, given that they have PD-L1 expression rates higher than 1% (16). The 50% cut-off value for PD-L1 expression was first identified in KEYNOTE-001, a phase 1 study of advanced NSCLC patients treated with pembrolizumab. In this study, PD-L1 expression in at least 50% of tumor cells was found to be associated with improved treatment response to pembrolizumab in advanced NSCLC patients (17). In another phase 3 trial including advanced NSCLC patients with a PD-L1 expression of ≥50%, pembrolizumab was associated with prolonged progression-free and overall survival as well as fewer adverse events compared to platinum-based chemotherapy (18), supporting the utility of quantifying PD-L1 expression. Similar results have also been reported with other PD-L1 inhibitors. For instance, Sezer et al. reported improved overall survival and progression-free survival with first-line cemiplimab monotherapy compared to platinum-double chemotherapy in patients with advanced NSCLC with a PDL of at least 50% (15). Other studies in advanced NSCLC patients with ≥50% PD-L1 expression have also demonstrated better clinical outcomes with first-line pembrolizumab (19,20). According to recent research, high PD-L1 expression is correlated with tumor angiogenesis, which may be an intracellular resistance mechanism for ICIs in patients with NSCLC. Researchers have proposed that this function has important consequences for the efficacy of ICIs, possibly demonstrating the need for the use of antiangiogenic drugs in conjunction with ICIs for first-line treatment of NSCLC patients exhibiting elevated PD-L1 expression, or as a second-line strategy when the tumor progresses (21). Data obtained from non-invasive 18F FDG PET/CT imaging might benefit the clinical management of the disease by potentially supporting the identification of individuals with a PD-L1 expression of ≥50%. Despite low discriminatory accuracy, the high negative predictive value particularly suggests that readily-obtained imaging data (shortly after diagnosis) can be useful to screen for candidates suitable (or unsuitable) for PD-1/PD-L1 inhibitor treatment.

The metabolic parameters acquired via 18F FDG PET/CT have been previously been associated with PD-L1 expression levels (11,12,22,23). However, there are remarkably limited investigations aiming to evaluate whether PD-L1 expression can be estimated with the radiomic features obtained from 18F FDG PET/CT (24). Xu et al examined patients with a PD-L1 expression of ≥50% (high expression) and reported that SUVmax and TLG values were significantly higher in patients with high expression (25), similar to our results. There are also several other studies that have described the possible use of radiomic data in the prediction of high PD-L1 expression (26,27). Li et al. reported convincing AUC scores for the prediction of PD-L1 expression (≥50%) with radiomic data, which were higher than the AUC for TLG values detected in our study (AUC: 0.606; 95% CI: 0.508 - 0.705). Of note, these differences between radiomic feature extraction and our results is not surprising since texture analysis can measure tumor heterogeneity of the entire tumor (27).

Prior research has established that patients with high TLG and high PD-L1 expression are recognized as having high risk, and these subjects have significantly worse overall survival. (28). Furthermore, it has been suggested that combining TLG and PD-L1 expression may produce a more accurate prognostic assessment for patients with NSCLC. (25) In our study, survival analysis could not be performed since these patients were not followed for a sufficiently long period.

Our comparison of PD-L1 negative (<1%) and positive (≥1%) groups did not reveal any notable differences between the groups and there were no relationships between PD-L1 expression and any of the 18F FDG PET/CT parameters. In contrast, several studies in the literature

have suggested that FDG uptake is significantly higher in PD-L1 positive patients relative to those defined to be negative (29,30). We believe that variations in patient characteristics and detection methods could explain these discrepancies in the literature.

This study has several limitations. First of all, this was a retrospective study and the sample size might be considered to be small, especially in terms of the distribution of patients with and without strong positivity for PD-L1. This difference in distribution is one of the factors that caused the exceedingly low accuracy detected for TLG despite very high sensitivity and negative predictive values. We believe future studies would benefit from including similar group sizes for patients with and without ≥50% PD-L1 expression, thereby improving the likelihood to clarify the utility of TLG measurements in this context. Secondly, since the follow-up period of the patients is short, survival analyses were not possible. Prospective studies with a larger number of patients are needed to determine the role of F 18 FDG PET/CT parameters in predicting PD-L1 expression levels among patients with NSCLC.

Conclusion

Our data shows that TLG, as measured by 18F FDG PET/CT, can predict NSCLC patients with strong positive (≥50%) PD-L1 expression owing to its high sensitivity. The high negative predictive value also suggests that TLG screening may be useful as a supportive tool in this context, despite the low overall accuracy which was caused by low specificity. Particularly since the use of multiple anti-PD-L1 agents has been approved for advanced NSCLC patients with ≥50% PD-L1 expression, there is a need for further research on this topic to improve the management and prognosis of the disease. Further studies on this subject with a larger patient population are needed to confirm our results.

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Conflicts of interest

The authors declare no competing interests

Ethics approval

This study was approved by the University of Health Sciences Turkey, Cam and Sakura City Hospital Ethics Committee. (Decision no: E-96317027-514.10-241607520 date: 03.04.2024)

Availability of data and material

All data is available

Authors' contributions

ÖVT: Concept design, data collection, analysis, literature search, writing

EA: data collection

NB: data collection, writing

SB: data collection

BEA: writing

MK: writing

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