Original Article
Mol Imaging Radionucl Ther 2022;31:104-113 DOI:10.4274/mirt.galenos.2022.24650

The Prognostic Value of ^{18}F-FDG PET/CT Metabolic Parameters in Predicting Treatment Response Before EGFR TKI Treatment in Patients with Advanced Lung Adenocarcinoma

İlerlemiş Akciğer Adenokarsinomu Olan Hastalarda EGFR TKI Tedavisi Öncesi Tedavi Yanıtını Öngörmede ^{18}F-FDG PET/BT Metabolik Parametrelerinin Prognostik Değeri

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Abstract

Objectives: This study makes a retrospective examination of exploring the prognostic value of ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) related metabolic-volumetric variables, nutritional status, and immune and inflammatory markers on progression-free survival (PFS) and overall survival (OS) in advanced adenocarcinoma patients with positive epidermal growth factor receptor (EGFR) mutations undergoing EGFR tyrosine kinase inhibitor (TKI) therapy.

Methods: A retrospective examination was made of patients diagnosed with lung adenocarcinoma who underwent ^{18}F-FDG PET/CT imaging for staging maximum four weeks before starting treatment, between January 2015 and July 2020. Included in the study were 68 patients identified histopathologically to have locally advanced/metastatic EGFR mutation-positive adenocarcinoma, and who underwent EGFR TKI therapy. The laboratory data of the patients, obtained 15 days before imaging performed for PET/CT staging, were evaluated.

Results: Metabolic tumor volume, modified Glasgow prognostic score and locally advanced disease were identified as independent prognostic parameters for PFS (p=0.004, p=0.029, p=0.016, respectively). A univariate Cox regression analysis revealed albumin/alkaline phosphatase and tumor size to be significant parameters for prognosis (p=0.033, p=0.043, respectively). A multivariate Cox regression analysis revealed that none of the parameters were predictive or OS.

Conclusion: The parameters of ^{18}F-FDG PET/CT, especially the volumetric parameters, were found to be strong prognostic factors with statistical significance for predicting PFS. We believe that these parameters are important prognostic markers that should be evaluated together in the management and follow-up of patients with EGFR mutation-positive adenocarcinoma.

Keywords: ^{18}F-FDG PET/CT, lung cancer, adenocarcinoma, EGFR, progression-free survival, overall survival

Öz

Amaç: Çalışmamızda, epidermal büyüme faktörü reseptörü (EGFR) tirozin kinaz inhibitörü (TKI) tedavisi gören pozitif EGFR mutasyonları olan ileri adenokarsinom hastalarında progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) üzerindeki ^{18}flor-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) ile ilişkili metabolik-hacimsel değişkenlerin, nutrisyonel durumunun ve immün ve enflamasyon belirteçlerin prognostik değerini retrospektif bir incelemesini yapmaktadır.

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Received: 04.10.2021 **Accepted:** 10.02.2022

Yöntem: Ocak 2015 ile Temmuz 2020 tarihleri arasında küçük hücreli dışı akciğer kanseri tanısı alan ve tedavi almadan en fazla dört hafta önce evreleme için ^{18}F-FDG PET/BT görüntülemesi yapılan hastalar geriye dönük olarak incelendi. Histopatolojik olarak adenokarsinom EGFR mutasyonu saptanan lokal ileri/metastatik TKI tedavisi alan 68 hasta çalışmaya dahil edildi. Hastaların PET/BT evrelemesi için yapılan görüntülemeden 15 gün önce alınan laboratuvar verileri değerlendirildi.

Bulgular: Metabolik tümör hacmi, modifiye Glasgow prognostik skoru ve lokal ileri hastalık, PFS için bağımsız prognostik parametreler olarak tanımlandı (sırasıyla; p=0,004, p=0,029, p=0,016). Tek değişkenli Cox regresyon analizi, albümin/alkalin fosfataz ve tümör boyutunun prognoz için önemli parametreler olduğunu ortaya koydu (sırasıyla; p=0,033, p=0,043). Çok değişkenli Cox regresyon analizi, hiçbir parametrenin OS için öngörücü olmadığını gösterdi.

Sonuç: ^{18}F-FDG PET/BT parametreleri, özellikle volümetrik parametreler, PFS'nin öngörülmesi için istatistiksel anlamlılığı olan güçlü prognostik faktörler olarak bulundu. Bu parametrelerin EGFR mutasyon pozitif adenokarsinomlu hastaların yönetimi ve takibinde birlikte değerlendirilmesi gereken önemli prognostik belirteçler olduğuna inanıyoruz.

Anahtar kelimeler: ^{18}F-FDG PET/BT, akciğer kanseri, EGFR, progresyonsuz sağkalım, genel sağkalım

Introduction

Non-small cell lung cancer (NSCLC), triggered by the activation of epidermal growth factor receptor (EGFR) mutations, accounts for approximately 10% of all NSCLC cases (1). Tyrosine kinase inhibitor (TKI) therapy is the first-line treatment for metastatic NSCLC with an EGFR mutation (2). EGFR signaling regulates the pathways of glucose metabolism in EGFR-mutated cancer cells, and EGFR TKIs reduce lactate production and glucose consumption (3). TKIs have been associated with longer progression-free survival (PFS) than chemotherapy in advanced NSCLC with EGFR mutations (2,4). The approved agents for TKI therapy include first-generation EGFR TKIs, erlotinib and gefitinib, and second-generation EGFR TKI, afatinib. The objective response rates to these agents in randomized clinical trials range from 56-74%, and the median time to progression is 9-13 months (5,6,7).

Recently, simple and accessible biomarkers related to systemic inflammation and nutritional status have been developed for predicting prognosis in various cancers (8). While the modified Glasgow prognostic score (mGPS), which is based on serum C-reactive protein (CRP) and albumin (ALB) concentrations, is considered a prognostic factor for most cancers (9), the prognostic nutritional index (PNI), which is calculated on the basis of ALB and total lymphocyte count, is more useful for predicting overall survival (OS) (10).

Lactate dehydrogenase (LDH) is another serum enzyme that is mainly involved in the conversion of pyruvate to lactate, and that has been linked to tumor metabolism (11). Several studies have established elevated LDH levels in various types of cancer, including NSCLC (12,13).

Immune and inflammatory responses have a characteristic significance for developing tumors in the body. Homeostasis and inflammation are among the numerous physiological and pathological pathways in which platelets are involved. There have been many studies associating an elevated platelet count with poor prognosis for various solid cancers, including those of the lung (14). The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are systemic inflammatory markers, play a prognostic role in many malignancies, such as malignant melanoma, esophageal cancer, prostate cancer, diffuse large B-cell lymphoma, breast cancer, nasopharyngeal cancer and NSCLC (15). There have also been many recent publications reporting the systemic immune-inflammation index (SII), which is based on platelet, lymphocyte and neutrophil counts, to be another important prognostic marker for various cancers (16).

^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is an imaging method that is used to diagnose and stage lung cancer and is based on the elevated glucose metabolism of tumor cells with increased expression of glucose transporter protein and hexokinase activity. In addition to diagnosis and staging, ^{18}F-FDG-PET is being increasingly used to assess treatment response and to predict outcomes (17). Some studies recommend early assessment with ^{18}F-FDG PET/CT as a criterion in the modification of tumor response during treatment (18,19). The volumetric parameters; metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been used to reflect the disease burden and tumor aggressiveness in NSCLC (20). The standardized uptake value (SUV) is a semi-quantitative determination of the normalized concentration of radioactivity, and maximum SUV (SUV_{max}) is the most widely applied parameter in clinical practice (21).

This study is conducted to explore the prognostic value of inflammatory markers and metabolic- and volume-based parameters related to ^{18}F-FDG PET/CT on treatment response assessment and outcome prediction, while also establishing the prognostic value of these parameters in adenocarcinoma patients with EGFR mutations.

Materials and Methods

Patients diagnosed with NSCLC who underwent ^{18}F-FDG PET/CT imaging for staging max four weeks before starting treatment between January 2015 and July 2020 were reviewed retrospectively. Subsequently, 68 patients who were found histopathologically to have locally advanced/metastatic EGFR mutation-positive adenocarcinoma and who underwent EGFR TKI therapy were included in the study. Patients were staged based on the TNM classification, according to the 8th edition staging system recommended by the International Association for the Study of Lung Cancer. The final surveillance program will be conducted in December 2020. Excluded from the study were: 1-) Patients with diagnoses other that concurrent cancer; 2-) Patients who underwent surgery or received any treatment (e.g. chemotherapy, radiotherapy) before imaging; 3-) Patients with missing hospital records; 4-) Patients without ^{18}F-FDG uptake at the site of the primary tumor; 5-) Patients with unknown status of EGFR gene mutation; and 6-) Patients who were followed up by an external center. In our retrospective study, the informed consent form was not documented, it was prepared in accordance with the local Clinical Practices guide and the current legislation, approval for the use of the patient data for publication was obtained from University of Health Sciences Turkey, Dr. Suat Seren Chest Diseases and Surgery Hospital Institutional Ethics Committee (approval no: 49109414-604.02).

Assessments

Age, gender and laboratory data [complete blood count, LDH, CRP, alkaline phosphatase (ALP), ALB obtained 15 days before ^{18}F-FDG PET/CT imaging was retrieved from the electronic hospital records. The NLR, PLR, CRP-to-ALB ratio, and serum ALB-to-serum ALP ratio were calculated. The formulas used to calculate the SII and PNI were as follows: SSI = platelet count × neutrophil count/lymphocyte count; PNI = 10 × serum ALB level + 0.5 × lymphocyte count. PNI score was recorded as 0 if PNI ≥45, and 1 if PNI was <45; mGPS was recorded as 0 if CRP was ≤10 mg/L, one if CRP was >10 mg/L and ALB ≥35 g/L, and 2 if CRP was >10 mg/L and alb <35 g/L. The recorded parameters related to ^{18}F-FDG PET/CT imaging included the longest diameter (mm) of the primary mass, MTV (cm^3), TLG (g/mL × cm^3), SUV_{max} and SUV_{mean}.

Positron Emission Tomography/Computed Tomography Protocol

Imaging was performed in a Philips Gemini TF 16-slice combined PET/CT scanner, with the same scanner used for all patients. Following a min 6 hours of fasting, 8-15 mCi ^{18}F-FDG (2.5 MBq/kg body weight) was administered intravenously and the time between intravenous injection and scans was 60±5 minutes. The patient did an intravenous contrast agent. The first CT images (140 kV, 100 mAs, 5 mm sections) and then PET images were acquired. Attenuation-corrected emission data were obtained using non-contrast-enhanced data, extrapolated to 511 keV. PET images were acquired through emission scanning for 1.5 min per bed position, and a wholebody scan from skull vertex to the proximal thigh using 9 or 10 bed positions. The images were reconstructed with iterative algorithms over a 128x128 matrix.

Image Analysis

Hybrid images of the ^{18}F-FDG PET/CT data were analyzed independently by two nuclear medicine specialists. The pattern and degree of primary mass uptake were evaluated and located. A 3D isocontour region of interest was drawn automatically on the lesion with the primary mass uptake in all three planes. While calculating the SUV_{max}, SUV_{mean} and the MTV included in the volume of interest, the area related to the 40% threshold was calculated automatically. TLG was calculated by multiplying MTV by the SUV_{mean}.

EGFR Mutation Assessment

Tissue samples acquired from paraffin-embedded specimens were collected in 1.5 mL vials, and DNA was extracted using a DNA Sample Preparation Kit (Cobas, Roche Molecular Systems, USA) and reverse transcription-polymerase chain reaction was performed. All procedures were conducted according to the manufacturer's instructions (Cobas EGFR Mutation Test v2, Roche Molecular Systems, USA).

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics (Version 26.0. Armonk, NY: IBM Corp.) and MedCalc Statistical Software version 16.4.3 (MedCalc Software BV, Ostend, Belgium; https://www.medcalc.org; 2016) software packages. Descriptive statistics were expressed as the unit number (n), percentage (%), mean ($\bar{x}$), standard deviation, standard error, median (M), minimum (min) and max values. The performance of prognostic markers in predicting recurrence and survival was evaluated by a receiver operating characteristic curve (ROC) analysis. The survival times of the patients were compared using the log-rank (Mantel-Cox) test of the Kaplan-Meier analysis, based on the optimum cut-off point for the markers found significant in the ROC analysis. Univariate and multivariate Cox regression analyses were used to determine the factors affecting PFS and OS. p values of <0.05 were considered statistically significant.

Results

Patient Characteristics

Among the 68 patients with advanced EGFR-mutated adenocarcinoma were 40 (58.8%) female and 28 (41.2%) male patients, with a median age of 64.5 (31.0-85.0) years. 43 (63.2%) patients of 68 were non-smoker. Of the patients with advanced adenocarcinoma, 15 (22.1%) were classified as locally advanced and 53 (77.9%) as metastatic. Of the total, five (7.3%) patients had mutations in exon 18, 47 (69.1%) in exon 19, and 16 (23.5%) in exon 21. For EGFR TKI, 27 (39.7%) patients underwent afatinib therapy, 35 (51.5%) erlotinib therapy and six (8.8%) gefitinib therapy. During the follow-up, 66.2% of the patients experienced local or metastatic relapse and 13 (19.1%) died from disease progression. Patient characteristics are presented in Table 1.

^{18}F-FDG PET/CT Parameters

Of 68 patients with advanced EGFR mutation adenocarcinoma, the median SUV_{max} value was 9.81 (3.50-38.10), the median MTV value was 25.66 (1.66-461.12), and the median TLG value was 158.19 (5.88-1826.04). The metabolic and volumetric parameters of the patients, as well as their immune and inflammatory parameters, are presented in Table 1.

Progression-free Survival Analysis

The median PFS was 13.9 (1.9-99.8) months overall. When the continuous variables were evaluated on the ROC curve drawn to determine progression, the analysis results revealed that the parameters with a significant area under the curve (AUC) values were MTV 0.725 [95% confidence interval (CI): 0.630-0.826, p=0.001], TLG 0.728 (95% CI: 0.606-0.828, p<0.001) and NLR 0.653 (95% CI: 0.528-0.765, p=0.019), which were predictive of progression (Table 2). MTV >7.04, TLG >78.68, NLR >4.73, an mGPS score of two and metastatic disease had statistically significantly high sensitivity and specificity in predicting of progression (Table 2). Optimum values were determined for MTV, TLG and NLR for use in the determination of progression, and patients were divided into groups based on these values. A Kaplan-Meier analysis revealed MTV, TLG, NLR, gender and locally advanced disease to be significant parameters, and further showing that PFS was significantly shorter in patients with MTV >7.04, TLG >78.68 and NLR >4.73 than in those with low values of these parameters (p=0.001, p=0.003, p=0.001, respectively). Metastatic patients had a shorter PFS than locally advanced patients (p=0.003); and those with an mGPS score of two were found to have a shorter PFS than those with a score of 0 (p=0.009) (Table 3). The univariate Cox regression analysis

Table 1. Patient characteristics

Characteristics	n (%)	
Gender		
Female	40 (58.8)	
Male	28 (41.2)	
Age (years)		
Mean ± SD	63.2±11.2	
M (min-max)	64.5 (31.0-85.0)	
Stage		
Local advanced stage	15 (22.1)	
Metastatic	53 (77.9)	
Pharmaceutical group		
Afatinib	27 (39.7)	
Erlotinib	35 (51.5)	
Gefitinib	6 (8.8)	
Exon 18	5 (7.3)	
Exon 19	47 (69.1)	
Exon 21	16 (23.5)	
Relapse		
No	23 (33.8)	
Yes	45 (66.2)	
Survival		
Alive	55 (80.9)	
Ex	13 (19.1)	
mGPS score		
0	33 (51.5)	
2	33 (48.5)	
PNI score		
<45	26 (38.2)	
>45	42 (61.8)	
	Mean ± SD	**M (min-max)**
Progression-free survival	19.9±17.5	13.9 (1.9-99.8)
Overall survival	25.7±19.1	21.9 (2.9-99.8)
SUV_{max}	10.87±5.71	9.81 (3.50-38.10)
SUV_{mean}	5.89±3.28	5.33 (1.20-20.50)
MTV	60.57±90.75	25.66 (1.66-461.12)
TLG	294.14±362.41	158.19 (5.88-1826.04)
LDH	225.1±79.8	208.0 (117.0-475.0)
CRP/ALB	8.05±13.59	2.21 (0.13-70.47)
ALB/ALP	0.047±0.021	0.047 (0.021-0.174)
NLR	5.08±5.56	3.33 (1.00-29.20)
PLR	238.27±190.65	192.48 (37.37-1385.00)
Size (cm)	4.14±1.82	4.00 (1.30-10.50)
SII	1587.2±1825.5	1008.4 (253.4-9956.0)
PNI	46.28±10.04	48.00 (8.50-80.60)

SD: Standard deviation, min: Minimum, max: Maximum, mGPS: Modified Glasgow prognostic score, PNI: Prognostic nutritional index, SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ALB: Albumin, ALP: Alkaline phosphatase, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, PLR: Platelet-to-lymphocyte ratio

Table 2. ROC analysis results of prognostic markers according to recurrence and survival status					
Recurrence status	**AUC (95% CI)**	**p**	**Cut-off value**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
MTV	0.725 (0.630-0.826)	0.001	>7.04	95.56 (84.9-99.5)	43.48 (23.2-65.5)
TLG	0.728 (0.606-0.828)	<0.001	>78.68	73.33 (58.1-85.4)	60.87 (38.5-80.3)
N/L	0.653 (0.528-0.765)	0.019	>4.733	35.56 (21.9-51.2)	100.0 (85.2-100.0)
Survival status					
MTV	0.715 (0.594-0.817)	0.007	>41.02	69.23 (38.6-90.9)	75.00 (61.6-85.6)
TLG	0.701 (0.578-0.805	0.017	>384.8	61.54 (31.6-86.1)	80.36 (67.6-89.8)
LDH	0.678 (0.554-0.787)	0.031	>222	69.23 (38.6-90.9)	69.09 (55.2-80.9)
CRP/ALB	0.729 (0.607-0.829)	0.007	>3.956	76.92 (46.2-95.0)	72.73 (59.0-83.9)
PNI	0.776 (0.658-0.868)	0.001	≤41.3	76.92 (46.2-95.0)	83.64 (71.2-92.2)

ROC: Receiver operating characteristic curve, AUC: Area under curve, CI: Confidence interval, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ALB: Albumin, PNI: Prognostic nutritional index, CI: Confidence interval

for systemic inflammation, and nutritional and volumetric parameters identified PLR, SII and tumor size was predictive of PFS (p=0.001, p=0.001, p=0.007, respectively) (Table 3). The Multivariate Cox regression analysis, in turn, identified MTV, mGPS and stage as independent prognostic factors for PFS (p=0.004, p=0.029, p=0.016, respectively) (Table 4). Among the volumetric parameters, MTV was determined to be a representative volumetric parameter; and among the general patient characteristics, age and gender had no statistically significant effect on PFS.

Overall Survival Analysis

The median OS was 21.9 (2.9-99.8) months. Among the general patient characteristics, age and gender had no statistically significant effect on OS.

When the continuous variables were evaluated on the ROC curve drawn according to survival, the parameters with a significant AUC values were MTV 0.715 (95% CI: 0.594-0.817, p=0.007), TLG 0.701 (%95 CI: 0.578-0.805, p=0.017), LDH 0.678 (%95 CI: 0.554-0.787, p=0.031), CRP/ALB 0.729 (95% CI: 0.607-0.829, p=0.007) and PNI 0.776 (95% CI: 0.658-0.868, p=0.001), which were predictive of survival MTV >41.02, TLG >384.8, LDH >222, CRP/ALB >3.956, and PNI >41.3 had statistically significantly high sensitivity and specificity in predicting survival (Table 2).

The Kaplan-Meier analysis for survival showed OS to be significantly shorter in patients with MTV >41.02, TLG >384.8, LDH >222 and CRP/ALB >3.956 than in those with low values of these parameters (p=0.001, p=0.002, p=0.040, p<0.001, p<0.001, p=0.001, respectively) (Table 4). A multivariate Cox regression analysis for systemic inflammation, and nutritional and volumetric parameters identified ALB/ALP and tumor size as significant parameters (p=0.033, p=0.043, respectively) (Table 4). The multivariate Cox regression analysis demonstrated that none of the parameters were predictive or OS (Table 4).

Discussion

This study found MTV, a volumetric parameter of ^{18}F-FDG PET/CT performed for staging in 68 patients with advanced EGFR-mutated adenocarcinoma, to be an independent prognostic factor for PFS. We further identified the scoring method for mGPS according to CRP and ALB levels as another significant prognostic factor for PFS. ROC analysis results revealed MTV, TLG and NLR to have statistically high sensitivity and specificity in predicting progression. We believe that these parameters are important prognostic markers that should be evaluated together in the treatment management and follow-up of patients with EGFR mutation-positive advanced adenocarcinomas.

EGFR mutations play a decisive role in the systematic treatment of NSCLC. The treatment of EGFR-mutated NSCLC has improved significantly in recent years, with EGFR-TKIs being the primary therapy for patients with advanced EGFR-mutated NSCLC (22,23). Previous studies have clearly demonstrated the dramatic response of patients with advanced adenocarcinoma to treatment with EGFR TKIs (gefitinib, erlotinib and afatinib). The presence of somatic mutations in the EGFR gene is deemed the best predictor of the response to TKIs (5,24). Gefitinib, erlotinib, afatinib and osimertinib have significantly prolonged the PFS of patients with untreated advanced EGFR-mutated NSCLC, although discussions of the optimal sequence are continuing (25). Patients who are to benefit from EGFR TKI therapy should be selected carefully to avoid such critical side effects as interstitial lung disease (26).

The variation in the survival of patients with advanced adenocarcinoma is associated with multiple factors (EGFR mutations, metabolism changes, serum markers and gender). ^{18}F-FDG PET/CT is a promising method and may reveal specific differences in metabolism in contrast to

Table 3. Univariant analysis of factors affecting progression-free survival					
	Recurrence		Estimate progression-free time (m)	Estimate proportion surviving at the 1/3 year	p value
	Present	Absent			
	n (%)	n (%)	Mean ± SE		
MTV					
≤7.04	2	10	79.873±12.27	100/75	**0.001[k]**
>7.04	43	13	21.20±2.45	62.7/49.9	
TLG					
≤78.68	12	14	48.73±9.522	78.6/45.3	**0.003[k]**
>78.68	33	9	19.47±2.53	63.2/7.0	
NLR					
≤4.73	29	23	37.02±6.03	79.4/49.8	**0.001[k]**
>4.73	16	0	14.55±3.74	37.5/6.3	
Gender					
Female	24	16	36.53±6.70	100/55.9	**0.187[k]**
Male	21	7	22.64±3.98	59.4/14.3	
Stage					
Local advanced stage	6	9	56.18±11.87	83.3/31.3/0.0	**0.003[k]**
Metastatic	39	14	20.98±2.78	93.3/52.3/43.6	
mGPS score					
0	20	15	36.65±6.56	80.7/33	0.009[k]
2	25	8	19.54±3.42	57/9.2	
Multivariate analysis of factors affecting progression-free survival					
	Odss ratio	**95% CI for Odss ratio**			
		Lower bound	**Upper bound**	**p**	
SUV_{max}	0.995	0.946	1.046	0.839[c]	
SUV_{mean}	0.98	0.897	1.071	0.654[c]	
LDH	0.998	0.994	1.002	0.379[c]	
CRP/ALB	1.014	0.998	1.031	0.095[c]	
ALB/ALP	0.001	0	7938.969	0.392[c]	
PLR	1.002	1.001	1.003	0.001[c]	
Size (cm)	1.225	1.057	1.419	0.007[c]	
SII	1	1	1	0.001[c]	
PNI	0.966	0.932	1.001	0.059[c]	
Age	1.01	0.985	1.035	0.437[c]	
MTV	11.474	2.191	60.096	0.004	
TLG	0.675	0.286	1.595	0.371	
NLR	0.617	0.216	1.764	0.367	
Stage	3.313	1.251	8.771	0.016	
mGPS score	1.496	1.042	2.146	0.029	
PLR	1.002	0.999	1.004	0.231	
Size (cm)	1.127	0.938	1.354	0.202	
SII	1	1	1	0.686	

k: Kaplan Meier test, log rank (Mantel-Cox), c: Cox regression-enter method, SE: Standard Error, CI: Confidence interval, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, mGPS: Modified Glasgow prognostic score, PNI: Prognostic nutritional index, SUVmax: Maximum standardized uptake value, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ALB: Albumin, ALP: Alkaline phosphatase, PLR: Platelet-to-lymphocyte ratio

Table 4. Univariate analysis of factors affecting overall survival					
	Dead	Alive	Estimate survival (m)	Estimate proportion surviving at the 1/3 year	p value
	n (%)	n (%)	Mean ± SE		
MTV					
≤41.02	4	41	2682,80±150,13	92/85.9	0.001[k]
>41.02	9	14	880.10±106.26	69.5/27.8	
TLG					
≤384.8	5	44	85.77±6.21	89.8/83.3	0.002[k]
>384.8	8	11	26.58±4.51	71.8/28.7	
LDH					
≤222	4	38	60.57±3.32	88.2/88.2	0.040[k]
>222	9	17	57.44±10.45	79.1/48	
CRP/ALB					
≤3.956	3	40	91.82±4.44	91.1/91.1	<0.001[k]
>3.956	10	15	21.52±2.10	73.2/15.2	
PNI					
≤41.3	10	9	19.07±2.7	62.6/0.0	<0.001[k]
>41.3	3	46	93.12±3.75	95.1/92.6	
Stage					
Local advanced stage	1	14	89.49±9.60	85.7	0.065[k]
Metastatic	12	41	47.05±5.10	79.2	
mGPS score					
0	2	33	93.32±4.45	92.7/92.7	0.001[k]
2	11	22	32.43±6.66	76.2/26.1	
Multivariate analysis of factors affecting overall survival					
	Odss ratio	95% CI for Odss ratio			
		Lower bound	Upper bound	p	
SUV_{max}	0.976	0.884	1.077	0.624[c]	
SUV_{mean}	0.956	0.806	1.134	0.602[c]	
LDH	1.003	0.998	1.009	0.258[c]	
ALB/ALP	0	0	0.028	0.033[c]	
NLR	1.017	0.928	1.115	0.72[c]	
PLR	1.001	0.998	1.003	0.674[c]	
Size (cm)	1.282	1.008	1.629	0.043[c]	
SII	1	1	1	0.29[c]	
Age	0.991	0.94.8	1.035	0.674[c]	
MTV	2.503	0.34	18.416	0.368	
TLG	0.357	0.042	3.057	0.347	
LDH	1.719	0.326	9.073	0.523	
Stage	3.003	0.343	26.249	0.32	
mGPS score	1.735	0.458	6.562	0.417	
Size (cm)	1.416	0.939	2.135	0.097	
ALB/ALP	0	0	449.598	0.088	
CRP/ALB	1.896	0.138	26.072	0.633	
PNI	0.431	0.064	2.888	0.386	

[k]: Kaplan Meier test, log rank (Mantel-Cox), [c]: Cox regression-enter method, SE: Standard Error, CI: Confidence interval, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, mGPS: Modified Glasgow prognostic score, PNI: Prognostic nutritional index, SUV_{max}: Maximum standardized uptake value, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ALB: Albumin, ALP: Alkaline phosphatase

conventional methods when selecting patients with a better prognosis. ^{18}F-FDG PET/CT has been increasingly identified as a prognostic biomarker for various malignancies in the assessment of early responses to treatment (27). Studies have shown that assessment with ^{18}F-FDG PET/CT in NSCLC can predict PFS and OS in patients treated with TKIs in the early period (18,28). In another study, early ^{18}F-FDG PET/CT was reported to predict the histopathological response in NSCLC patients treated with TKIs as neoadjuvant therapy (29).

Several studies (28,29) to date have evaluated the significance of ^{18}F-FDG uptake in the prediction of EGFR mutations in NSCLC, some of which have focused on SUV_{max}, identifying low SUV_{max} as an independent predictor of EGFR mutations (30,31,32,33); while in another study, it was emphasized that a high SUV_{max} was a significant predictor of EGFR mutations (31). It has been suggested that these differences may be attributable to clinicopathological features, and so this study evaluated the metabolic and volumetric parameters from PET/CT with immune, inflammatory and nutritional parameters for assessing PFS and OS, and investigated the effects of these parameters on each other, with MTV and mGPS being identified as the most valuable prognostic parameters for PFS. Compared to other studies, we think that evaluating ^{18}F-FDG PET/CT volumetric-metabolic and immune-inflammatory parameters in patients with NSCLC is more effective in determining the prognosis of the disease.

A recent study emphasized the important role of the systemic inflammation and the immune status of patients in cancer progression. Immune suppression and systemic inflammation at the onset of the disease are associated with a poor prognosis (34), and NLR, PLR, and LDH are the most effective and easily accessible markers for assessing inflammation and immune status (15).

There have been many studies reporting the prognostic value of ^{18}F-FDG PET/CT based on metabolic parameters, not only in lung cancer treated with TKIs (35,36), but also in other lung cancers in general (37,38). Unlike SUV_{max}, MTV and TLG include metabolic load and disease extent, and thus can have a higher predictive value (39,40,41). Similar to our study, another study reported that ^{18}F-FDG PET/CT volumetric parameters reflect both metabolic and tumor burdens, and thus had higher prognostic value than the metabolic activity values obtained by PET/CT (42,43) and tumor size (44) in lung cancers. Volumetric parameters, such as MTV and TLG, have been extensively studied in recent years. The prognostic role of MTV and TLG was meta-analyzed in patients with NSCLC at different stages (44). Volume-based parameters exhibit advantages in the measurement of metabolic tumor burden. Parameters obtained ^{18}F-FDG PET/CT can be used to select patients at high risk of death and who may benefit from subsequent more aggressive treatments.

Furthermore, our study identified mGPS and NLR as significant prognostic factors for PFS. There have been other studies demonstrating that other available blood-based biomarkers, such as NLR, PLR and mGPS, reflect the inflammatory status associated with cancer, and can be used as prognostic factors in lung cancer (21,45). mGPS, which assesses both systemic inflammation and nutritional status, has been identified as a potential prognostic predictor of lung cancer, as evaluated in many studies (46,47). The utility of NLR as a predictor in cancer patients has not been well studied, although there is increasing evidence that molecular and cellular pathways involve inflammations that contribute to the proliferation, angiogenesis and metastasis of neoplastic cells (48,49). Moreover, circulating neutrophils release various inflammatory cytokines, including tumor necrosis factor-α and interleukin-6, leading to cancer progression (50). It may therefore be reasonable to claim that treatment with EGFR-TKI is more effective in EGFR-mutated NSCLC patients with low NLR than in those with high NLR. Our analysis also suggests that NLR may be associated with PFS in NSCLC patients.

Study Limitations

Our study had certain limitations. The study protocol could not be strictly controlled because to its retrospective nature, although a standard imaging protocol was followed for all patients, and there was no difference due to homogeneous clinical management.

Conclusion

The aim in this study was to determine the optimum prognostic factors for assessing treatment response in advanced EGFR-mutated adenocarcinoma patients treated with TKIs. ^{18}F-FDG PET/CT volumetric parameters were found to have statistical significance in predicting PFS. We believe that these parameters are important prognostic markers that should be evaluated together in the management and follow-up of patients with EGFR-mutated adenocarcinoma. ^{18}F-FDG PET/CT may be considered an appropriate guide when making treatment decisions.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Dr. Suat Seren Chest Diseases and Surgery Hospital Institutional Ethics Committee (approval no: 49109414-604.02).

Informed Consent: Consent was received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: N.A., Design: N.A., Data Collection or Processing: N.A., H.K., N.K., Analysis or Interpretation: N.A., H.K., Literature Search: N.A., M.A., N.K., Writing: N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study has received no financial support.

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