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Original Article

The role of PET/CT in determining egfr mutation and ALK rearrangement in patients with lung adenocarcinoma

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Abstract

Aim: The aim of the present study is to evaluate the role of tumor FDG uptake in a non-invasive method and the use of positron emission tomography / computed tomography (PET/CT) in estimating epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements in cases of adenocarcinoma of the lung.

Material and Methods: A total of 115 patients with the diagnosis of an adenocarcinoma of the lung that underwent F-18 FDG PET/CT for staging and whose EGFR mutation and ALK rearrangement status were analyzed were retrospectively analyzed. The association of the PET parameters (SUVmax, SUVmean, MTV and TLG) of primary tumor with the molecular profile was analyzed.

Results: EGFR mutations (EGFR+ group) and ALK rearrangements (ALK+ group) were found in 15 (13%) and 10 (8.7%) of 115 patients; and 90 patients (78.3%) had no EGFR mutation or ALK rearrangement (EGFR/ALK-). EGFR mutations were found to be significantly higher among the never-smoked group (p=0.009). No significant association was identified between the SUVmean, MTV and TLG values and EGFR mutations; however, patients with a low SUVmax value were found to have a significantly higher rate of EGFR mutation (p=0.034). No statistically significant differences were found between the ALK+ and ALK- group in terms of age, sex, cigarette smoking status, tumor stage, or PET parameters.

Conclusion: Our study results suggest that a low SUVmax value in lung adenocarcinomas is associated with EGFR mutation, although the diagnostic efficacy is not high.

Keywords: Adenocarcinoma; non-small cell lung cancer; epidermal growth factor receptor mutation; anaplastic lymphoma kinase rearrangement; PET/CT; SUVmax

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for almost 85% of all lung cancers with the most common histological type being adenocarcinomas (1). There have been numerous studies providing an understanding of the pathogenesis of lung cancer, and to identify the optimum treatment approach, and significant developments have been made recently, particularly at a genomic level. Some of the more recent developments have been the identification of the epidermal growth factor receptor (EGFR) mutation and an anaplastic lymphoma kinase (ALK) rearrangement detected in tumor tissue, determining the response to targeted therapy in NSCLC. EGFR mutations are seen in adenocarcinomas, young individuals, women, non-smokers and individuals of Asian origin, while ALK rearrangements are seen more frequently in adenocarcinomas, young individuals and non-smokers (2,3). The EGFR gene chromosome is localized in 7p12-13, and is part of the tyrosine kinase family which includes also cell membrane receptors. EGFR mutations, by causing structural changes in the tyrosine kinase domain, result in ligand-independent continuous intracellular signal transductions, and are the target area of such tyrosine kinase inhibitors (TKI) as gefitinib and erlotinib (4,5). On the other hand, patients diagnosed with ALK rearrangements respond to TKI's such as crizotinib (6). The progression-free survival of such patients is longer, when they are treated using TKI, compared to treatments containing classical chemotherapeutics. Accordingly, performing molecular tests is suggested in patients with advanced stage NSCLC (7,8).

However, molecular tests are based on the evaluation of tumor tissue obtained using invasive methods, and obtaining an adequate tumor tissue sample may not

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always be possible. A fluorine-18 2-fluoro-2-Deoxy-d-glucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) is a non-invasive method commonly used for the diagnosis and staging of lung cancer. EGFR signal transduction organizes a metabolic glucose pathway in mutant lung cancer cells, and TKIs targeting EGFR decrease glucose consumption and lactate production (9). Furthermore, WZ4002 (specific inhibitor of EGFRT790M) and crizotinib have been demonstrated to decrease FDG uptake in mutant tumors (10). These findings suggest the possibility of using FDG uptake in a PET study as a non-invasive predictor of EGFR mutations and ALK rearrangements. However, the association of FDG uptake and EGFR mutation has been reported as controversial in the literature (11-20) and there is a limited number of data on the association of FDG affinity and ALK rearrangements (13,21,22). The aim of the present study is to evaluate the contribution of tumor FDG affinity to the prediction of EGFR mutations and ALK rearrangements.

MATERIAL and METHODS

Patients

A total of 115 patients who were diagnosed histopathologically with lung adenocarcinoma, who underwent F-18 FDG PET/CT for staging purposes between December 2011 and August 2018, and whose EGFR mutation and ALK rearrangement status were analyzed via molecular methods were included in this retrospective study. In order to avoid partial volume effect, we included tumors larger than 1 cm in our study.

FDG PET/CT Imaging Procedure

Following a fasting period of at least six hours, 260-370 MBq F-18 FDG was injected intravenously (i.v.) into patients with a blood sugar of less than 200 mg/dL. One hour after the injection, images of the patients were taken from between the vertex and thigh using a PET/CT scanner (Biograph high-definition 16-slice CT, Siemens Healthcare®, Erlangen, Germany). The CT images (5 mm section thickness, 130 keV, 120 mA) were obtained first, followed by PET images (1.8 min/per bed), and both the PET and CT images were uploaded to three-dimensional work stations where the CT images were used for attenuation correction and anatomical correlation purposes.

All PET/CT images were evaluated independently by two experienced nuclear medicine specialists. Sections featuring the primary tumor in the lung identified by PET/CT were visually determined and a 3D-region of interest (ROI) was drawn. In ROI, the SUV value of the pixel of the maximum standardized uptake value (SUV) was determined as SUVmax. The 50% SUVmax value defined as reasonable (23) in Phantom studies, and used frequently in previous studies (24,25,15), was accepted as the threshold value. Automated contouring was applied to the threshold values to include pixels of equal or higher values, and the SUV mean, metabolic tumor volume value (MTV) was obtained. The total lesion glycolysis (TLG) was calculated by multiplying the MTV and SUVmean values.

EGFR mutation analysis

The EGFR mutation analysis of the 18–21 exons (Exon 18 Kodon 719, Exon 20 Codon 768, Exon 20 Codon 790, Exon 21 Codon 858-861 Mutation, Exon 19 Deletion Analysis) from the genomic DNA's of the tumor cells were analyzed using the pyrosequencing method, based on real-time DNA sequencing.

ALK rearrangement analysis

Immune histochemical and florescence in situ hybridization (FISH) methods were used to detect ALK rearrangements. A FISH (Abbott-Vysis LSI ALK) Break Apart Rearrangement Probe was used, as the currently accepted optimum method. Using the FISH method, the 5′ and 3′ ends of the related genes were labeled with florescent markers, after which, changes, such as the separation of the 5′ and 3′ ends and the loss of the 5′ end, were evaluated under an immune florescent microscope in a dark medium. The test was accepted positive for an ALK rearrangement, when separate green and red signals and/or single red (residual 3′) signals (Break apart signals) were observed on at least 15% of the evaluated cells.

Statistical analysis

The patients were divided into three groups: EGFR mutation positive (EGFR+); ALK rearrangement positive (ALK+); and EGFR mutation or ALK rearrangement positive (EGFR/ALK+). The age, sex, cigarette smoking status and cancer stage (1-3A=early stage, 3B-4=advanced stage) were defined according to the 8th Edition. To define the FDG affinity of the tumor, the SUVmax, SUVmean, MTV and TLG of the primary tumor were measured by an F-18 FDG PET/BT.

The Groups were evaluated independently to determine any association between the variables and the EGFR mutation or ALK rearrangement status (EGFR+ and EGFR-, ALK+ and ALK-, EGFR/ALK+ and wild type). A Fisher's exact test was used for categorical parameters, while a Mann-Whitney U-test was used for continuous variables. A receiver operating characteristic (ROC) curve was used to identify the ratio reflecting the highest sensitivity and specificity for the continuous variables that were found to be significant. A p value of <0.05 was considered statistically significant.

Our retrospective analysis was conducted in line with Helsinki declaration ethical standards.

RESULTS

A total of 115 patients including 78 males and 37 females with a mean age of 59.7±10.7 years and with a histopathological diagnosis of a lung adenocarcinoma were included in the present study. The number of ever smokers and never smokers was 87 (75.7%) and 28 (24.3%), respectively. The majority of patients (71.3%) were in an advanced stage (3B–4) at the time of diagnosis. Among the patients, 11 were Stage 1A, 3 were Stage 1B, 2 were Stage 2A, 9 were Stage 2B, 8 were Stage 3A, 17 were

Stage 3B, 7 were Stage 3C and 58 were Stage 4. The mean values were calculated as SUVmax 16.9±10.0, SUVmean 10.9±6.2, MTV 23.1±46.4 mL and TLG 255±502 g, when all 115 patients were evaluated in terms of PET parameters. EGFR mutations and ALK rearrangements were analyzed in all 115 patients. EGFR mutations (EGFR+ group) and ALK rearrangements (ALK+ group) were found to be positive in 15 (13%) and 10 (8.7%) patients, respectively. No EGFR mutation or ALK rearrangement (EGFR/ALK-, wild type group) was detected in 90 (78.3%) patients. No patient was found to be simultaneously EGFR and ALK positive. The findings are summarized in Table 1. The most common mutation was in exon 21 (n=6, 40%), followed by exon 19 (n=5, 33%) among the EGFR+ patients.

Association between the parameters and EGFR mutation

The EGFR+ group included 7 (46.7%) female and 8 (53.3%) male patients with a mean age of 65.3±9.6 years, of which 8 (53.3%) were never smokers, while 6 (40%) had early-stage disease. The mean values of the PET parameters in the 15 EGFR positive patients were as follows: SUVmax 12.2±7.0, SUVmean 8.2±4.9, MTV 17.5±27.2 mL and TLG 151±282 g.

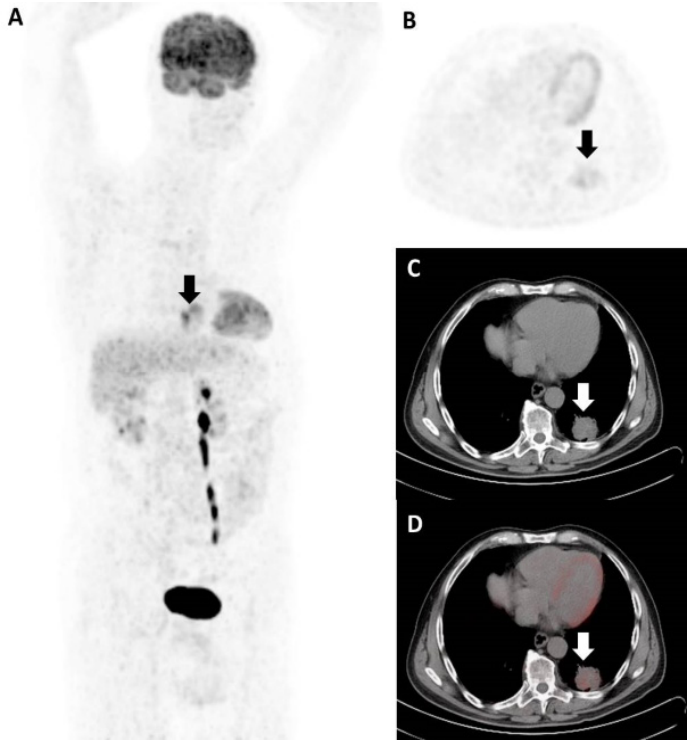

Figure 1. MIP (A), PET (B), CT (C) and fusion (D) images of a 73-year-old man with a diagnosis of stage 1B lung adenocarcinoma are shown. The PET parameters of the primary tumor (arrows) were found to be as follows: SUVmax: 8.8, SUVmean: 4.1, MTV: 22.8 mL, and TLG: 93.5 g. EGFR mutation was positive and ALK rearrangement was negative in the case, with a SUVmax <10 and no history of cigarette smoking

Statistical analysis revealed no significant difference between the EGFR+ and EGFR- groups in terms of sex, tumor stage, and SUVmean, MTV and TLG values, while EGFR mutations tended to be seen relatively more frequently in women and when early stage adenocarcinomas were found. The mean age of the EGFR+ group was significantly higher than that of the EGFR- group (65.3±9.6 vs 58.9±10.7 years; p=0.031). The EGFR mutations were found to be significantly higher in never smokers (53.3% vs 20.0%; p=0.009). The SUVmax values were found to be significantly lower in the EGFR+ group, compared to the non-mutant group (12.2±7.0 vs 17.6±10.2; p=0.034). A ROC analysis revealed 10 as the optimal cut-off value of SUVmax, which had a sensitivity of 82% and a specificity of 53.3% in differentiating the EGFR+ group from the non-mutant group (AUC:0.67; 95% CI: 0.51-0.83).

Table 1. Laboratory and demographic data of patients

Characteristic	Total
Patients, n	115
Age, mean ± SD	59.7 ± 10.7
Sex	
Woman, n (%)	37 (32.2)
Man, n (%)	78 (67,8)
Smoking status	
Ever smoker, n (%)	87 (75.7)
Never smoker, n (%)	28 (24.3)
Tumour stage	
Stage I – IIIa, n (%)	33 (28.7)
Stage IIIb – IV, n (%)	82 (71.3)
Mutation status	
EGFR (+), n (%)	15 (13.0)
ALK (+), n (%)	10 (8.7)
EGFR or ALK (+), n (%)	25 (21.7)
FDG PET/CT	
SUV max, mean ± SD	16.9 ± 10.0
SUV mean, mean ± SD	10.9 ± 6.2
MTV, mean ± SD	23.1 ± 46.4
TLG, mean ± SD	255 ± 502

Association of the parameters and ALK rearrangement

The ALK+ group was composed of 4 women (40.0%) and 6 men (60.0%), among whom 5 were never smokers (50.0%) and 1 (10.0%) was early stage. The mean age of the entire group was 55.7±8.8 years. The mean PET parameter values of the 10 ALK positive patients were SUVmax 17.6±4.6, SUVmean 11.5±3.3, MTV 16.2±11.4 mL and TLG50 186±147 g. Statistical analysis revealed no statistically significant difference in sex, cigarette smoking status, tumor stage or PET parameters (SUVmax, SUVmean, MTV and TLG) between the ALK+ group and ALK- group.

Table 2. Differences of the variables between the groups

	EGFR			ALK			EGFR/ALK		
	+ (n=15)	- (n=100)	P	+ (n=10)	- (n=105)	P	+ (n=25)	- (n=90)	P
Age	65.3 ± 9.6	58.9 ± 10.7	**0.031**	55.7 ± 8.8	60.1 ± 10.9	0.222	61.5 ± 10.3	59.3 ± 10.9	0.354
Sex									
Woman	7 (46.7)	30 (30.0)	0.239	4 (40.0)	33 (31.4)	0.725	11 (44.0)	26 (28.9)	0.225
Man	8 (53.3)	70 (70.0)		6 (60.0)	72 (68.6)		14 (56.0)	64 (71.1)	
Smoking status									
Ever smoker	7 (46.7)	80 (80.0)	**0.009**	5 (50.0)	82 (78.1)	0.062	12 (48.0)	75 (83.3)	**0.001**
Never smoker	8 (53.3)	20 (20.0)		5 (50.0)	23 (21.9)		13 (52.0)	15 (16.7)	
Tumour stage									
Stage I-IIIa	6 (40.0)	27 (27.0)	0.361	1 (10.0)	32 (30.5)	0.277	7 (28.0)	26 (28.9)	1.000
Stage IIIb-IV	9 (60.0)	73 (73.0)		9 (90.0)	73 (69.5)		18 (72.0)	64 (71.1)	
FDG PET/CT									
SUV max	12.2 ± 7.0	17.6 ± 10.2	**0.034**	17.6 ± 4.6	16.8 ± 10.4	0.361	14.3 ± 6.6	17.6 ± 10.6	0.269
SUV mean	8.2 ± 4.9	11.3 ± 6.3	0.052	11.5 ± 3.3	10.9 ± 6.5	0.413	9.5 ± 4.6	11.3 ± 6.6	0.306
MTV	17.5 ± 27.2	23.9 ± 48.7	0.395	16.2 ± 11.4	23.7 ± 48.4	0.442	17.0 ± 21.9	24.8 ± 51.1	0.865
TLG	151 ± 282	270 ± 526	0.074	186 ± 147	261 ± 523	0.316	165 ± 234	280 ± 552	0.438

Categorical variables are shown as n (%), continuous variables are shown as mean ± SD in the table. Fisher exact test was used for categorical parameters and Mann-Whitney U test was used for continuous parameters since all of them were nonparametric. Significant values (P<0.05) are presented in bold

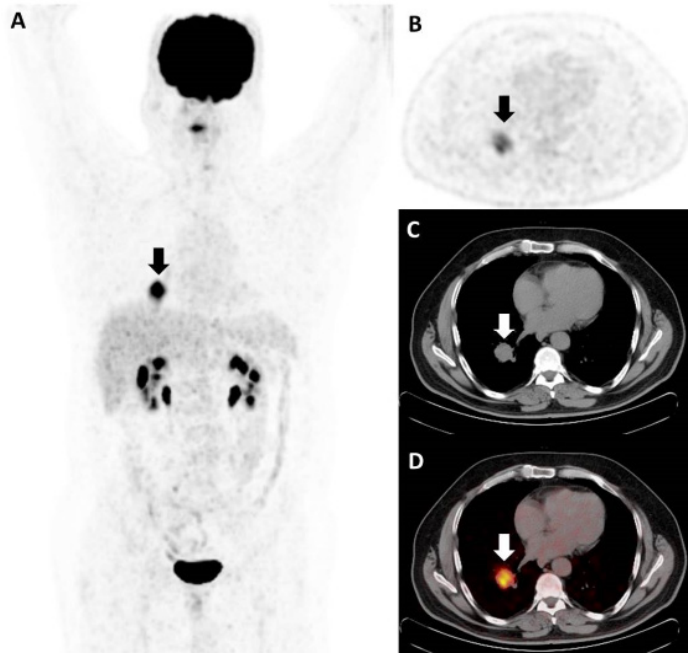

Figure 2. The SUVmax, SUVmean, MTV and TLG values of the primary tumor (arrows) in the MIP(A), PET(B), CT(C) and fusion (D) images of a 67-year-old male case with a diagnosis of stage 1A adenocarcinoma were found to be 17.2, 7.7, 16.2 mL, and 124.7 g, respectively. EGFR mutation and ALK rearrangement were negative in the case with a SUVmax >10 and 50 pack/year history of cigarette smoking

Comparison of EGFR/ALK+ and EGFR/ALK- (wild type) groups in terms of variables

The number of patients detected to have EGFR mutations or ALK rearrangements (EGFR/ALK+) was 25, while the number of patients in the EGFR/ALK- (wild type) group was 90. No statistically significant difference was found between the two groups in terms of sex, tumor stage or PET parameters (SUVmax, SUVmean, MTV and TLG). EGFR mutations and ALK rearrangements were found to be significantly higher in never smokers (52.0% vs 16.7%; p=0.001) and the possible predictive factor was considered to be the presence of EGFR mutation-positive patients in the EGFR/ALK+ group.

Differences of the variables between the groups are shown in Table 2. Clinical characteristics and PET parameters of two sample cases are shown in Figures 1 and 2.

DISCUSSION

The EGFR gene belongs to the tyrosine kinase family, which is one of cell membrane receptors. Tyrosine kinase inhibitors have been demonstrated to have a significant therapeutic effect and to prolong progression-free survival in patients with EGFR mutations or ALK rearrangements (6,26,27). Accordingly, a molecular analysis is recommended as the standard method for the management of advanced stage NSCLC patients. It is not possible, however, to carry out molecular studies in

every center, and several challenges can be encountered, such as in obtaining an adequate tumor tissue sample or the intolerance of the patient to invasive methods (i.e., coagulation abnormalities or severe cardiopulmonary insufficiency). Previous studies showed that patients with an unknown EGFR mutation status selected based on clinical factors who underwent TKI treatment responded better to first-line chemotherapy with improved progression-free survival (26,28,29). Therefore, alternative non-invasive methods such as F-18 FDG PET/CT are now being considered in addition to clinical factors when selecting patients who are considered likely to benefit from TKI treatment.

EGFR mutations are encountered most frequently with adenocarcinoma among the types of NSCLC, being particularly more commonly among Asians, women, and never smokers (30,31). EGFR mutations were found in 13% of the respondents in the present study, and this rate is similar to that reported in other Western countries (32,33,34,35). Consistent with the literature, EGFR mutations were found to be significantly higher in never smokers in the present study (p=0.009) and there was a tendency for EGFR mutations to be more common in women, although not statistically significant. The association between EGFR mutations and the FDG uptake of the primary tumor identified by a PET/CT has been evaluated in several studies, but with contradictory results. A statistically significant association between a low normalized primary tumor SUVmax (pSUVmax) value and EGFR mutations was found in a study by Mak et al. (11) evaluating 100 mostly white patients diagnosed with NSCLC. In another study including 100 patients with NSCLC, a low pSUV value was identified in multivariate analyses to be a significant predictor of EGFR mutation (12). In a study of 808 Chinese patients diagnosed with NSCLC, a significant association was found between the EGFR mutation and the low SUVmax value of primary tumor, of lymph node metastasis and of distant metastases (13). A multivariate analysis demonstrated that pSUVmax <7.0, female sex, non-smoker status, and adenocarcinoma were the predictors of EGFR mutations (13). In a study including 71 patients with Stage 4 adenocarcinoma, the SUVmax value of the metastasis (nodal and distant) rather than the primary tumor was found to be significantly lower in EGFR+ patients, compared to EGFR- patients, and a metastasis SUVmax of ≤7.2 was suggested to be a threshold level for the prediction of mutation status (14). Caicedo et al. (15) reported that EGFR+ patients demonstrated a lower FDG uptake, compared to EGFR- patients in their study of 102 patients with Stage 3–4 NSCLC. However, this difference was suggested to originate from the KRAS mutation that was present in some of EGFR- patients. In contrast, Ko et al., (16) in their study of 132 Stage 1–4 patients with an adenocarcinoma, the EGFR mutation was found to be significantly higher in patients with a higher pSUVmax (≥6) value. In another study including 77 Asian patients with Stage 3B–4 lung adenocarcinoma, those with a high FDG uptake (pSUVmax≥9.5) were suggested as carrying a higher rate of EGFR mutation (17). Nevertheless, there have also been studies suggesting no clinical role of FDG uptake in the prediction of EGFR mutation in NSCLC (18).

In this present study, the SUVmax, SUVmean, MTV and TLG values were used to evaluate the FDG affinity of the primary tumor. No significant association was found between the SUVmean, MTV and TLG values and EGFR mutation, although the rate of EGFR mutation was found to be significantly higher in patients with a low SUVmax value. There are literature data supporting the findings of the present study, although some advocate the opposite. The contradictory results are considered to originate mainly from the differences in patient population, especially in ethnic factors, the evaluation of only adenocarcinomas in some studies and all NSCLCs in others, the presence of subtypes in varying ratios and different tumor stages, and only adenocarcinomas being studied.

The ALK rearrangement, which is more common in adenocarcinoma, youngs and non-smokers, is seen in 1–4.9% of NSCLCs (36,37,38,39). An association has been identified between PET parameters and ALK rearrangement in a limited number of studies in the literature. Lv et al. (13) evaluated 223 patients with NSCLC (190 adenocarcinoma and 33 non-adenocarcinoma), both together and separately and found no significant association between the pSUVmax value and ALK rearrangement. In another study including 331 patients with an adenocarcinoma, ALK-positive patients were suggested to have higher pSUVmax values than the ALK-negative patients (21). In a study by Jeong et al. (22), of 221 patients with an advanced stage adenocarcinoma, a high pSUVmax value in the primary tumor was reported to be an independent predictor of ALK positivity. In this present study, 10 patients (8.7%) were found to be ALK rearrangement positive with no statistically significant difference in the age, cigarette smoking status, and PET parameters (SUVmax, SUVmean, MTV and TLG) between the ALK+ and ALK- groups. The findings of this present study are consistent with the study by Lv et al. (13) in terms of the association of pSUVmax and ALK rearrangement, but different to the study by Jeong et al. (22). This can be attributed to the fact that patients with an advanced stage adenocarcinoma were evaluated in the study by Jeong et al. (22), 53 patients with prior treatment were included and a relatively high rate of ALK positivity was found, compared to the present study (18.6% vs. 8.7%).

CONCLUSION

In conclusion, we suggest that a low SUVmax value in lung adenocarcinomas is associated with EGFR mutation, although the diagnostic efficacy is not high. Although our study has limitations such as limited number of patients, it is thought that it will contribute to literature because it includes adenocarcinoma alone and evaluates different PET parameters such as MTV and TLG, in addition to SUV. However, further prospective, large-scale studies are needed to confirm our findings.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Ethics committee approval was not obtained because of the retrospective design of the study. But our study was conducted in line with Helsinki declaration ethical standards.

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