Original Article

Necrosis onstaging 18F FDG PET/CT is associated with worse progression-free survival in patients with stage IIIB non-small cell lung cancer

ABSTRACT

Objective: The presence of pathological necrosis in the tumor is known to be a factor indicating worse survival. Our study defined necrosis in staging 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) in patients with stage IIIB non-small-cell lung cancer (NSCLC) to investigate whether this is a poor prognostic marker.

Methodology: A total of 77 patients with NSCLC were evaluated. To evaluate necrosis on ^{18}F FDG PET/CT, we drew a region of interest (ROI) in the area showing visually very low/or no FDG uptake on PET and PET/CT fusion images. If SUVmax was less than blood pool SUVmax and showed significantly less attenuation [10 to 30 Hounsfield units (HUs)] than surrounding tissue on low-dose correlative CT with non-intravenous contrast, we defined it as necrotic (PETNECROSIS). We evaluated the relationship of SUVmax, tumor size, and $PET_{NECROSIS}$ with progression-free survival (PFS) using a Cox proportional hazard regression model.

Results: A PFS analysis was performed on 16 patients treated with standard chemoradiotherapy (CRT) regimen. Tumor size ≤42 mm versus >42 mm ($P = 0.044$, HR: 6.103, 95 CI%: 1.053–35.358) and $PET_{NECROSIS}$ presence/absence ($P = 0.027$, HR: 6.719, 95 CI%: 1.245–36.264) were independent predictors for PFS. Patients with tumor size ≤42 mm and $PET_{NECROSIS}$ absence were associated with higher 1-year PFS rate than patients with tumor size >42 mm and $PET_{NECROSIS}$ presence (86% vs. 63.5% $P = 0.005$ and 87.5% vs. 29%, $P = 0.001$, respectively).

Conclusion: $PET_{NECROSIS}$ is helpful to distinguish the patients who would suffer worse survival in stage IIIB NSCLC.

KEY WORDS: Fluorodeoxyglucose, non-small cell lung cancer, positron emission tomography, necrosis, survival

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INTRODUCTION

^{18}F-fluorodeoxyglucose (^{18}F FDG) shows glucose metabolism in the tissue. Tumo glucose metabolism in non-small cell lung cancer (NSCLC) has been shown to significantly affect the biological behavior of the tumor and a correlation between the maximum standardized uptake value (SUVmax) and tumor aggressiveness.[1-3] Decreased blood flow in the tumor leads to hypoxia.[4,5] Hypoxia is a predictor of radiotherapy (RT) and chemotherapy response. Low oxygen levels are known to reduce the distribution of chemotherapy, and hypoxic tissues are more resistant to RT.[6,7]

Tumo necrosis, a common feature of solid tumors, is considered a result of chronic ischemic damage that develops due to rapid tumor growth. Thus, it can be said that the degree of necrosis reflects the level of intra-tumor hypoxia.[8,9] The presence of necrosis in surgical material in various types of cancer is associated with poor prognosis, and personalized adjuvant chemotherapy has been recommended in patients with necrosis.[10-12] However, patients with lung cancer are often diagnosed at an inoperable stage. Showing the presence of necrosis on staging ^{18}F-FDG PET/CT may contribute to treatment management.Although the presence of necrosis on staging ^{18}F-FDG PET/CT was shown to be a poor prognostic predictor in patients with sarcoma and lymphoma,[13-15] we have found no studies on

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patients with NSCLC.

The purpose of our study was to investigate if the necrosis as identified on staging ^{18}F FDG PET/CT is a predictor of worse progression-free survival (PFS) in patients with stage IIIB NSCLC.

METHODOLOGY

Ethical approval: The Clinical Research Ethics Committee of our institute reviewed and approved this retrospective study (ref. no. 40465587-000-63, 2019/50). As this was a retrospective study where the data were de-identified, it was exempt by the institutional review board from the need for informed consent. All procedures performed in the studies involving human participants were by the Helsinki Declaration.

Patients and Study Design: Patients in whom ^{18}F FDG PET/CT imaging was performed with indications of lung mass/nodule characterization and lung cancer staging between November 2016 and December 2017 were included in the study. NSCLC diagnosis was histopathologically confirmed in all patients. We evaluated PET/CT images of 77 patients with NSCLC. We observed that 27 patients had $PET_{NECROSIS}$. However, we included only a limited group of patients in the PFS analysis. There are many reasons for this. We did not include 25 patients who refused or interrupted treatment ($n = 7$), died due to non-disease-related reasons ($n = 3$), and were lost to follow-up ($n = 15$). The remaining 52 patients included a heterogeneous group of patients with different stages and received different treatment protocols. We excluded 13 operable patients who had surgical treatment. Twenty-three of the remaining 39 patients had distant metastases at the time of diagnosis and received different treatment regimens, so we did not include them either. We included 16 patients with stage IIIB NSCLC (AJCC 7th edition).[16] Seven of these patients had $PET_{NECROSIS}$ [Figure 1].

Radiotherapy Technique and Chemotherapy Regimen: All operations were performed using a Varian Trilogy IX linear accelerator (Varian Medical Systems). Intensity-modulated radiotherapy (IMRT) was applied to all patients. Patients were simulated with their arms elevated using a T-bar. Radiotherapy planning computed tomography was performed in spontaneous breathing without using the breath-holding technique. Primary tumor and lymph nodes with short axes greater than 1 cm in CT were identified as gross tumor volume (GTV). We added 8 mm to the GTV in patients with adenocarcinoma and 6 mm to the GTV in patients with SCC to close the microscopic spread and establish a clinical target volume (CTV). Considering tumor movement, we added an inner edge (IM) to the CTV and created an internal target volume (ITV). Without a four-dimensional CT (4D-CT), we determined a 1 cm value of IM in all directions to encompass a complete breathing cycle. Five millimeters were added to the ITV, considering set-up errors to create a planning

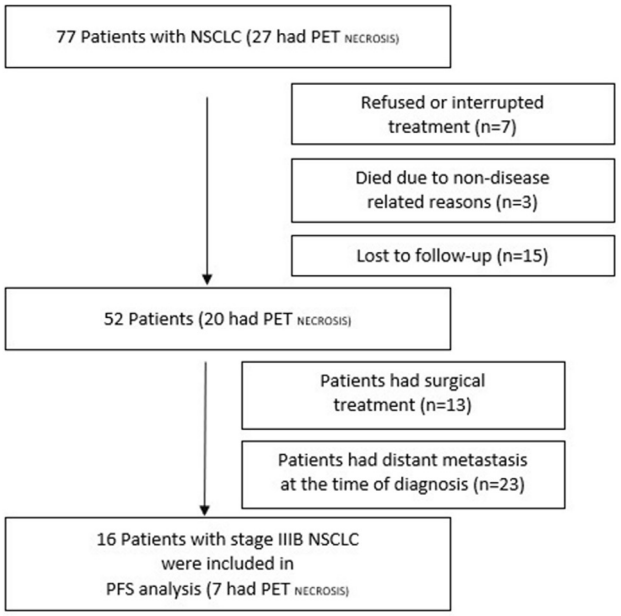

Figure 1: Patient selection diagram

target volume (PTV).[17] A median total radiotherapy dose of 68.4 (64.8-71.2) Gy with 1.8 Gy per fraction was given. All the patients received four weekly doses of carboplatin and paclitaxel concurrently with radiotherapy.

Patient Follow-up: The PFS was calculated from the date of diagnosis to the date of progression of the disease (new lesion or expansion of the previous existing lesion) or the date of recurrence or death associated with the disease. From the date of diagnosis to the last follow-up, the period was calculated in the patients who survived or in whom progression was not observed. The follow-up of the disease was conducted using conventional CT and ^{18}F-FDG PET/CT.

Conventional CT Procedures: All CT scans were operated using the same CT scanner (Discovery CT750HD, GE Healthcare, Wisconsin, USA). The patients were injected with 80–100 mL (1.35 mL/kg body weight) non-ionic iodinated contrast material at a rate of 3–4.0 mL/s, and scans were obtained after approximately 50 s. The scan parameters were tube voltage, 140 kVp dynamic switching in 0.5 ms, tube current between 40 and 60 mA. The images were taken during mid-inspiratory breath-hold.

^{18}F-FDG PET/CT Procedures: A PET/CT scanner Biograph mCT (Siemens Healthcare, Erlangen, Germany) was used. After at least 6 h of fasting, patients with a blood glucose level of <200 mg/dL were administered an FDG injection at an approximate dose of 3.7 MBq/kg. After a median of 63 min [min-max 54–79 min], imaging was performed in the supine position with arms up. PET imaging was adjusted to 2 min per bed position. Low-dose CT parameters: voltage, 120 kV; CARE dose 4D mA tube current; slice thickness, 5.00 mm.

18F FDG PET/CT Image Analyses: Siemens Healthhineers Syngo via VB30 workstation, MM Oncology, post-processing unit was used for the analyses. All analyses were conducted through consensus by one nuclear medicine specialist (OK) with 9 years of PET/CT experience and a radiation oncologist (GE) with 10 years of experience. The maximum standardized uptake value normalized to body mass (SUVmax) and the tumor size were evaluated.

Tumor Necrosis on ^{18}F-FDG PET/CT Evaluation: We drew a region of interest (ROI) in the area showing visually very low/or no FDG uptake on PET and PET/CT fusion images. If the SUVmax value we measured in ROI was less than the blood pool SUVmax and had significantly lower attenuation from the surrounding tissue in non-intravenous contrast-enhanced low-dose correlative CT, we defined this area as necrotic ($PET_{NECROSIS}$). On non-intravenous contrast-enhanced low-dose correlative CT, low-attenuation areas were identified with Hounsfield units (HUs) between 10 and 30 units.[14,18,19] Size-adjustable oval-shaped ROIs were used. We drew the ROI with the maximum size from which we would obtain a value of SUVmax lower than the aorta. Lung cavities are gas-filled spaces, seen as lucency or low-attenuation area, within pulmonary consolidation, a mass, or a nodule distinguished from $PET_{NECROSIS}$.[20] $PET_{NECROSIS}$ was decided by the consensus of two physicians [Figure 2].

Statistical analysis

Continuous variables were expressed as median (min-max) and mean with standard deviation (SD). Variables were compared using either Student's t-test in parametric and Mann–Whitney U tests in non-parametric, depending on the normality of the distribution. The receiver operating characteristic (ROC) statistics of ^{18}F FDG PET/CT parameters were estimated, threshold values providing the optimal sensitivity and specificity were determined, and those with a $P < 0.05$ were included in the univariate analysis. Univariate and multivariate analyses were performed using the Cox model to assess the relationship between survival and ^{18}F FDG PET/CT parameters. The multivariate Cox proportional hazards regression model included any variable with $P < 0.2$ in the univariate model. The full model included all the variables we studied for multivariate analyses, and the final model was constructed using the backward stepwise procedure. The survival curves for PFS were created using the Kaplan–Meier method. The differences between groups were investigated using the log-rank test. All analyses were performed using SPSS v. 22 (SPSS, Inc., Chicago, IL), and a two-tailed $P < 0.05$ was considered significant.

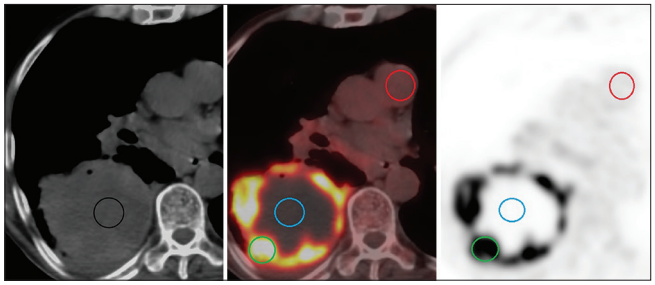

Figure 2: A 64-year-old male with right lung SCC. On PET and fusion images, a wide hypometabolic region at the center of the tumor [SUV_{max}: 1.02, blue region of interest (ROI)], high FDG uptake at the periphery of the tumor (SUV_{max}: 21.01, green ROI), and the FDG activity in the arcus aorta (SUV_{max}: 1.57, red ROI) are shown. On non-intravenous contrast-enhanced low-dose correlative CT, the low-attenuation area (average 19 HU, black ROI) corresponds to the hypometabolic area on PET images. We define this area as $PET_{NECROSIS}$

RESULTS

Images of 77 patients were evaluated. We observed $PET_{NECROSIS}$ in 27 patients. Sixteen patients treated with standard CRT regimen with stage IIIB NSCLC (15 males, 1 female; 6 had adenocarcinoma, 10 had SCC; mean age 71.81 ± 4.95) were included in the PFS analysis. All variables were independent of histopathological subtype. Patients and tumor characteristics are given in Tables 1 and 2.

By using the ROC curve, we determined the threshold values for ^{18}F FDG PET/CT parameters according to optimal sensitivity-specificity values. We divided the patients into two groups according to the threshold values and included them in the univariate logistic regression analysis. SUVmax ≤13 versus >13 (sensitivity 83%, spesifitivity 100%, $P = 0.018$, AUC: 0.906, 95% CI: 0.757–1.000), tumor size ≤42 mm versus >42 mm (sensitivity 72.%, spesifitivity 80%, $P = 0.017$, AUC: 0.882, 95% CI: 0.715–1.000) were determined.

In univariate Cox proportional hazard regression analysis SUVmax ≤13 versus >13 ($P = 0.028$, HR: 10.689, 95% CI: 1.293–88.356), tumor size ≤ 42 mm versus >42 mm ($P = 0.013$, HR: 7.751, 95% CI: 1.527–39.345), and $PET_{NECROSIS}$ presence/absence ($P = 0.008$, HR: 8.844, 95% CI: 1.779–43.959) were statistically significant predictors for PFS.

Multivariate Cox proportional hazard regression analysis showed that tumor size ≤42 mm versus >42 mm ($P = 0.044$, HR: 6.103, 95% CI: 1.053–35.358) and $PET_{NECROSIS}$ presence/absence ($P = 0.027$, HR: 6.719, 95% CI: 1.245–36.264) were statistically significant independent predictors for PFS. SUVmax ≤13 versus >13 was not found as an

Table 1: Patient characteristics

Characteristic	*N* (%)
Sex	
Female	1 (6.3)
Male	15 (93.8)
Histology	
Adenocarcinoma	6 (37.5)
Squamous cell carcinoma	10 (62.5)
Necrosis identified on FDG PET/CT	
Presence	7 (43.8)
Absence	9 (56.3)

independent predictor for PFS (P = 0.234, HR: 4.270, 95% CI: 0.391–46.594) [Table 3].

Patients with tumor size ≤42 mm and $PET_{NECROSİS}$ absence were associated with higher 1-year PFS rates than the patients with tumor size >42 mm and $PET_{NECROSİS}$ presence (86% vs. 63.5%, P = 0.005 and 87.5% vs. 29%, P = 0.001, respectively) [Figure 3].

DISCUSSION

This study investigated whether necrosis on staging ^{18}F-FDG PET/CT predicted worse PFS in patients with stage IIIB NSCLC. This method has not been investigated previously in this group of patients. We determined the criteria for $PET_{NECROSIS}$ to have lower FDG uptake in the tumor than blood pool activity and have prominent lower attenuation from the surrounding tissue (attenuation 10-30 HU) non-intravenous contrast-enhanced low-dose correlative CT. Although this method has not been studied in NSCLC patients, similar approaches have been used in different cancers. In a study of patients with diffuse large B-cell lymphoma (DLBCL), the periphery of the tumor was hypermetabolic; however, the center was hypometabolic and had attenuation (10-30 HU) in non-intravenous contrast-enhanced CT and had no increase in HU on intravenous contrast-enhanced CT was described as necrosis. They concluded that ^{18}F FDG PET/CT could accurately detect the presence or absence of necrosis in patients with DLBCL.[14] In a study of patients with sarcoma, the relationship between necrosis and survival was investigated. The hypometabolic area in the center of the tumor, which had a hypermetabolic area in the periphery, was evaluated as necrosis if it corresponded to low attenuation on CT. A threshold value for SUV was not determined; they only defined it as hypometabolic visually. In 39 of the 42 patients (92.9%), the presence of necrosis on ^{18}F FDG PET/CT was confirmed histopathologically. The MRI results were also highly consistent. Finally, they stated that necrosis observed in ^{18}F FDG PET/CT was a reliable marker and a predictive value on patient outcomes.[13]

In a study of patients with DLBCL, necrosis was defined as areas with no FDG uptake within FDG avid lymphomatous lesions. No specific visual scale was used. Necrosis on ^{18}F FDG PET/CT was a predictor of worse survival.[15] Adams *et al*.[18]

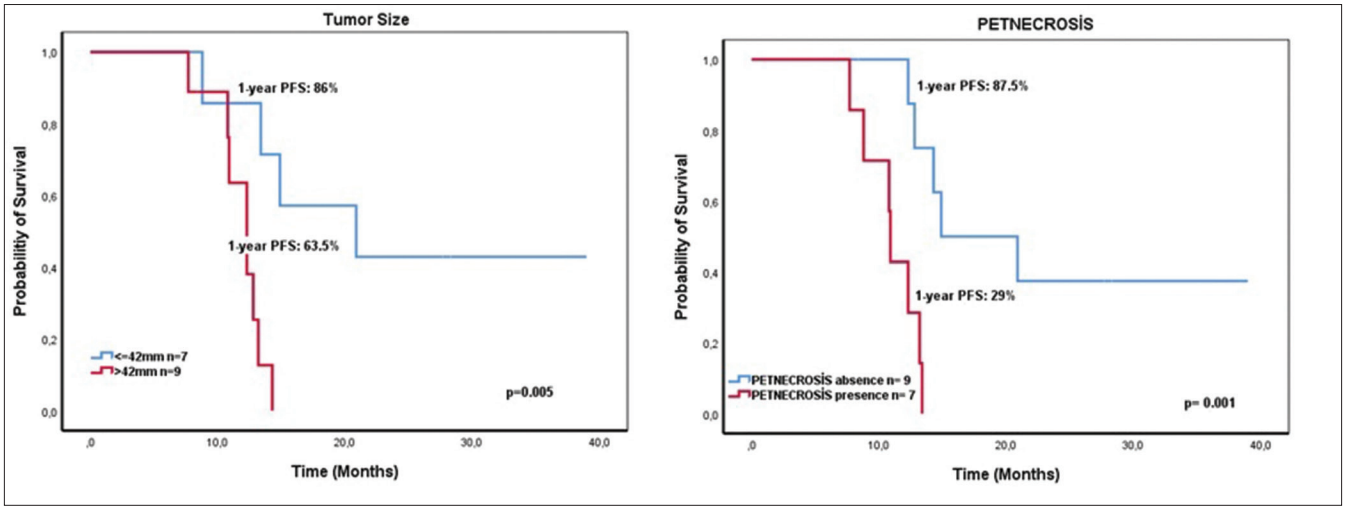

Figure 3: Kaplan–Meier curves of independent prognostic predictors for progression-free survival

Table 2: Tumor characteristics according to histopathological subtype

Variable	All Patients (n = 16)	Adenocarcinoma (n = 6)	Squamous cell Carcinoma (n = 10)	P* (t/Z)
SUVmax	14.850 ± 5.86	13.350 4.99	15.750 6.40	0.447 (t=0.783)
Tumor size (mm)	41.94 ± 17.75	33.17 ± 15.64	47.2 ± 17.52	0.130 (t = -1.610)
Age (year)	71.81 ± 4.95	72.17 6.047	71.60 4.52	0.883 (t=0.214)
Progression-free survival (months)	13 (7.7-39)	17.9 (10.9-39)	12.3 (7.7-28.3)	0.051 (Z = -1.954)

(*) No, statistical significance was found between adenocarcinoma and squamous cell carcinoma

Table 3: The summary of univariate and multivariate analysis

Variable	Univariate analysis			Multivariate analysis		
	P	HR	95%CI	P	HR	95% CI
SUVmax≤13 vs. > 13	0.028	10.689	1.293-88.356	0.234	4.270	0.391-46.594
Tumor size<=42 mm vs. >42 mm	0.013	7.751	1.527-39.345	0.044	6.103	1.053-35.358
$PET_{NECROSİS}$ presence/absence	0.008	8.844	1.779-43.959	0.027	6.719	1.245-36.264

Abbreviations: HR; hazard ratio, CI; confidence interval

investigated the relationship between necrosis on ^{18}F FDG PET/CT and survival in patients with DLBCL. They determined the necrotic area as the areas with low attenuation between 10 and 30 HU in non-intravenous contrast-enhanced low-dose CT and the areas which did not have increased contrast in intravenous contrast-enhanced full-dose CT (maximum 5HU). Necrosis on PET/CT as a predictor of worse survival. In a study conducted with NSCLC patients, it was stated that the proportion of the areas showing FDG uptake at the periphery of the tumor in ^{18}F FDG PET/CT and the areas not showing FDG uptake in the center might indicate the extent of necrosis (either biopsy or surgical resection-obtained tumor tissue. The absence or presence and the percentage of necrosis were recorded). They calculated the metabolic/morphological volumes of the tumor. They measured metabolic tumor volume (MTV) with the threshold of 42% of SUVmax and calculated morphological tumor volume (MoTV) according to lesion definition on CT images. They calculated the ratio of metabolically active volume to global lesion volume (MMVR) by dividing MTV by MoTV, and the ratio was expressed as a percentage. They found that MMVR was inversely proportional to the extent of tumor necrosis ($r = -0.570, P = 0.042$). They concluded that metabolically inactive regions might indirectly reflect the degree of necrosis and apoptotic events in the global tumor volume.[21]

In the studies mentioned above, the areas showing central hypometabolism in FDG avid tumors were defined as necrotic and supported by some CT findings. Hypometabolism is a relative definition. Relative hypometabolic areas will be monitored in a tumor showing heterogeneous FDG uptake. Which hypometabolic areas should we evaluate for necrosis? For instance, in a lung tumor which heterogeneous FDG uptake with a SUVmax of 25, an area with a SUVmax of 10 is hypometabolic. At the same time, an area with a SUVmax of 5 is also hypometabolic. Which one should we accept as necrosis? We thought it would be more accurate to determine the upper limit of SUVmax for hypometabolism, which was defined as one of the parameters used to assess necrosis.

Furthermore, we set the blood pool SUVmax for its upper limit. It is already known that tumor FDG uptake should not be higher than blood pool uptake in PET/CT to define it as a complete metabolic response,[22] that is, if the tumor's SUVmax is higher than the blood pool's SUVmax, the presence of residual/viable tumor can be considered. Therefore, we assume that the SUVmax of the necrotic area should be at least lower than the SUVmax of the blood pool. In non-intravenous contrast-enhanced low-dose correlative CT, low-attenuation areas were defined with HUs between 10 and 30 units. We determined the thresholds for metabolic activity and attenuation in non-intravenous contrast-enhanced low-dose CT, which makes our study different from the others.

In univariate Cox proportional hazard regression analysis, SUVmax $\leq$13 versus >13, tumor size $\leq$42 mm versus >42 mm, and $PET_{NECROSIS}$ absence-presence were associated with PFS. Multivariate Cox regression analysis showed that SUVmax $\leq$13 versus >13 was not an independent predictor of PFS. However, studies claim that SUV is associated with survival.[23-25] Studies also state that SUVmax has no prognostic significance for survival.[26-28] In our study, tumor size >42 mm was an independent predictor for worse survival. In various studies, tumor size is a poor prognostic factor for survival; our findings support the general literature knowledge.[29,30] In the PFS analysis, we did not include MTV and total lesion glycolysis (TLG). The primary purpose of our study was to investigate the prognostic value of necrosis identified on staging ^{18}F FDG PET/CT for survival. Since our examination did not consist of many patients, we had to select a limited number of parameters to create a statistical model. In the analysis, we chose to include tumor size, the main morphological parameter, and SUVmax, the most used PET parameter in clinical practice.

In our study, $PET_{NECROSIS}$ presence was an independent predictor of worse survival. One-year PFS was 87.5% versus 29% of the patients with $PET_{NECROSIS}$ absence and presence, respectively. As the tumor growth continues, hypoxia is inevitable due to the disruption of the blood supply and exceeding local tissue perfusion, creating necrosis areas.[31] The detection of necrosis in the pathological tumor material has been shown as a poor prognostic factor in many types of cancer.[8,10-12] Because microscopic necrosis in pathologic specimens is a poor prognostic factor for disease, we are not surprised that the presence of $PET_{NECROSIS}$ is also a poor prognostic factor. However, most patients with lung cancer receive their diagnosis when their disease is inoperable, so we think it may be essential to know the presence of tumor necrosis, a poor prognostic factor, before treatment in this large group. Studies investigating the relationship between visual necrosis on FDG PET/CT and survival have shown that necrosis is a marker for poor prognosis in patients with various cancer types. Rakheja *et al*.[13] found that the presence of necrosis on PET in soft tissue sarcomas was an independent poor prognostic marker. Moo-Kon Song *et al*.[14] investigated the predictive value of necrosis with ^{18}F FDG PET/CT and conventional CT in patients with DLBCL and found that the presence of necrosis was a poor prognostic factor. Kahle *et al*.[15] investigated the relationship between prognosis and $PET_{NECROSIS}$ in patients with DLBCL and found $PET_{NECROSIS}$ as an independent marker for poor prognosis. Adams *et al*.[18] showed necrosis on PET/CT as a predictor of worse survival.

Our study has limitations. First, our study is a single-center and retrospective. Male dominance in the patient group can be explained by the fact that the female population smoked less in this region and had a relatively low incidence of lung cancer. Because of the study's retrospective nature, histopathological confirmation of necrotic tumor sites was unavailable. We were able to include 16 patients in the PFS analysis. The number of patients may seem small, but we excluded patients with distant metastases, patients who underwent lung surgery, and patients who did not regularly follow. Thus, we chose to

analyze patients at the same stage, who received standard CT/CRT, and were regularly followed up. We are already using this method for the first time in this patient group. Since we know that the number of our patients is relatively small, we recommend working with larger patient groups.

In conclusion, we found that necrosis identified on staging ^{18}F FDG PET/CT was an independent predictor for PFS in patients with stage IIIB NSCLC. $PET_{NECROSIS}$ is helpful to distinguish patients who would suffer worse survival. There is a need for studies with larger groups of patients.

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Conflicts of interest
There are no conflicts of interest.

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