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Necrosis on pre-radiotherapy ^{18}F-FDG PET/CT is a predictor for complete metabolic response in patients with non-small cell lung cancer

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Abstract

To investigate necrosis on pre-radiotherapy (RT) ^{18}F-FDG PET/CT ($PET_{NECROSIS}$) as a predictor of complete metabolic response (CMR) in patients with non-small cell lung cancer (NSCLC).

We evaluated patients with inoperable stage I–III NSCLC who underwent pre- and post-radiotherapy ^{18}F-FDG PET/CT. The relationship between CMR and $PET_{NECROSIS}$, SUVmax, gross tumor volume calculated with ^{18}F-FDG PET/CT (GTV_{PET-CT}), tumor size, histology, metabolic tumor volume (MTV), and RT dose was assessed using logistic regression analysis. 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 fluorodeoxyglucose (FDG) uptake on PET images. If the SUVmax was lower than the blood pool SUVmax and showed significantly lower attenuation (10–30 Hounsfield units [HU]) from the surrounding tissue on non-intravenous contrast-enhanced low-dose correlative CT, we defined it as necrotic ($PET_{NECROSIS}$).

Fifty-three patients were included in this study. The mean age was 68.1 ± 9.8 years. Twenty-one patients had adenocarcinoma, and 32 had squamous cell carcinoma. All parameters were independent of histologic status. Multivariate logistic regression analysis showed that SUVmax ≤11.6 vs >11.6, ($P = .003$; OR, 7.670, 95CI%: 2.013–29.231) and $PET_{NECROSIS}$ absence/presence were independent predictors for CMR ($P = .028$, OR: 6.704, 95CI% 1.214–30.394).

The necrosis on ^{18}F FDG PET/CT and SUVmax > 11.6 could be an imaging marker for the complete metabolic response after definitive chemoradiotherapy or definitive RT alone in patients with NSCLC.

Abbreviations: ($PET_{NECROSIS}$) = Necrosis on pre-radiotherapy RT ^{18}F-FDG PET/CT, ^{18}F-FDG PET/CT) = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, 3DCRT = three-dimensional conformal radiotherapy, AJCC = American Joint Committee on Cancer staging system, AUC = area under the curve, CI = confidence interval, CMR = complete metabolic response, CRT = chemoradiotherapy, CTV = clinical target volume, FDG = fluorodeoxyglucose, GTV = gross tumor volume, GTV_{PET-CT} = gross tumor volume calculated with ^{18}F-FDG PET/CT, HU = Hounsfield units, IM = inner margin, ITV = internal target volume, MoTV = morphological tumor volume, MTV = metabolic tumor volume, NSCLC = non-small cell lung cancer, OR = odds ratio, PTV = planning target volume, ROC = receiver operating characteristic, ROI = region of interest, RT = radiotherapy, SCC = squamous cell carcinoma, SUV = standardized uptake value.

Keywords: fluorodeoxyglucose, necrosis, non-small cell lung cancer, positron emission tomography, radiotherapy, response

1. Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide and poses a significant public health issue.[1] Although concomitant chemoradiotherapy (CRT) improves local control and long-term survival, local control failure is still observed in most patients.[2] Residual malignancy after treatment is associated with poor survival.[3]^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) offers crucial prognostic information in patients treated with CRT, in addition to its use in staging in patients with NSCLC.[4–7] High FDG

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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uptake before treatment is associated with poor local control.[8] Hypoxia is a predictor of RT and chemotherapy responses. Low oxygen levels are known to reduce the distribution of chemotherapy, and hypoxic tissues are more resistant to radiotherapy (RT).[9–11] Some authors argue that hypoxic regions within the tumor should be identified and that the RT dose administered to these regions should be escalated.[12] Due to chronic ischemic damage, rapid tumor growth leads to necrosis in solid tumors. Necrosis is the irreversible final result of hypoxia, and the degree of intra-tumoral hypoxia reflects the extent of necrosis.[13–15] Microscopic necrosis in surgical materials is associated with poor prognosis in various types of cancer.[16,17] However, patients with lung cancer are often diagnosed at an inoperable stage. Detection of necrosis on pre-RT ^{18}F FDG PET/CT may predict treatment response in these patients.

Our study aimed to investigate whether necrosis, as identified on pre-RT ^{18}F-FDG PET/CT, was a complete metabolic response (CMR) predictor in patients with NSCLC.

2. Patients and methods

2.1. Ethical approval

The Clinical Research Ethics Committee of our institute reviewed and approved this retrospective study (2019/54). As this was a retrospective study, it was exempt from the need for informed consent by the institutional review board. All procedures performed in the studies involving human participants were performed in accordance with the Declaration of Helsinki.

2.2. Patient selection

Patients diagnosed with NSCLC histopathologically who had inoperable stage I-III, underwent ^{18}F FDG PET/CT before and after CRT or definitive RT alone, and were admitted to our center between August 2015 and July 2019 were included in this retrospective study. Ten patients had stage I, 19 patients had stage II, and 24 patients had stage III disease, according to the American Joint Committee on Cancer staging system (AJCC 7th edition).[18]

2.3. Radiotherapy technique and chemotherapy regimens

All operations were performed using a Varian Trilogy IX linear accelerator (Varian Medical Systems). Intensity-modulated radiotherapy (IMRT, n = 34) was administered to 64% of patients, and three-dimensional (3D) conformal radiotherapy (3DCRT, n = 19) was administered to 36% of the patients. The patients were simulated with their arms elevated using a T-bar. Radiotherapy planning computed tomography was performed during spontaneous breathing without using the breath-holding technique. Primary tumor and lymph nodes with short axes >1 cm on 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 margin (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 target volume (PTV).[19] A total median of 64.8 (range, 60–70) Gy with 1.8 Gy per fraction was given to patients. All patients received four weekly doses of carboplatin and paclitaxel concurrently with radiotherapy.

2.4. ^{18}F-FDG PET image acquisition and reconstruction

A PET/CT scanner (Biograph mCT; Siemens Healthcare, Erlangen, Germany) was used. After at least 6 hours 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. 64.7 ± 6.98 minutes in pre-RT and 65.4 ± 8.57 minutes in post-RT after FDG injection, imaging was performed in the supine position with arms up. PET imaging was adjusted to 2 minutes per bed position. Low-dose CT parameters: voltage, 120 kV; CARE Dose 4D mA tube current; and slice thickness, 5.00 mm.

2.5. Image analysis

All analyses were conducted through consensus by a nuclear medicine specialist (O.K.) with 9 years experience and by a radiation oncology specialist (G.E.) with 9 years experience (GE). The maximum standardized uptake value normalized to body mass (SUVmax), gross tumor volume calculated with data gathered from ^{18}F-FDG PET/CT ($GTV_{PET\text{-}CT}$), metabolic tumor volume calculated according to the threshold values of 50% of tumor SUVmax (MTV)[20] and the tumor size were measured.

2.6. Treatment response assessment

In the post-RT ^{18}F-FDG PET/CT, tumor SUVmax < aorta SUVmax was considered a complete metabolic response (CMR)[3,15,21–23] (Figs. 1 and 2). There was a mean of 17.09 ± 7.52 days between pre-RT ^{18}F-FDG PET/CT and RT starting time. The median time interval between radiotherapy and post-RT ^{18}F-FDG PET/CT was 93 days (82–133 days).

2.7. Necrosis on ^{18}F FDG PET/CT evaluation

The area showing visually very low/ no FDG uptake on PET and PET/CT fusion images was confirmed on the non-attenuation correction (NAC) PET images. We drew a region of interest (ROI) in this area. If the SUVmax was less than the blood pool SUVmax and this hypometabolic area showed significantly lower attenuation from the surrounding tissue in non-intravenous contrast-enhanced low-dose correlative CT, we evaluated it as necrotic ($PET_{NECROSIS}$). In non-intravenous contrast-enhanced low-dose correlative CT, low-attenuation areas were identified with Hounsfield units (HUs) between 10 and 30 units have been previously defined as tumor necrosis.[24–26] We evaluated low attenuation areas between 10 and 30 HU as necrotic on non-intravenous contrast-enhanced low-dose correlative CT. Size-adjustable oval-shaped ROIs were also used. We drew the ROI with the maximum size from which we would obtain a value of SUVmax lower than the aorta (Fig. 3). In addition, we calculated the percentage of necrosis by proportioning the volume of the necrotic component to the tumor volume.[27] Lung cavities are gas-filled spaces, seen as lucency or low-attenuation areas, within pulmonary consolidation, a mass, or a nodule[28] distinguished from $PET_{NECROSIS}$.

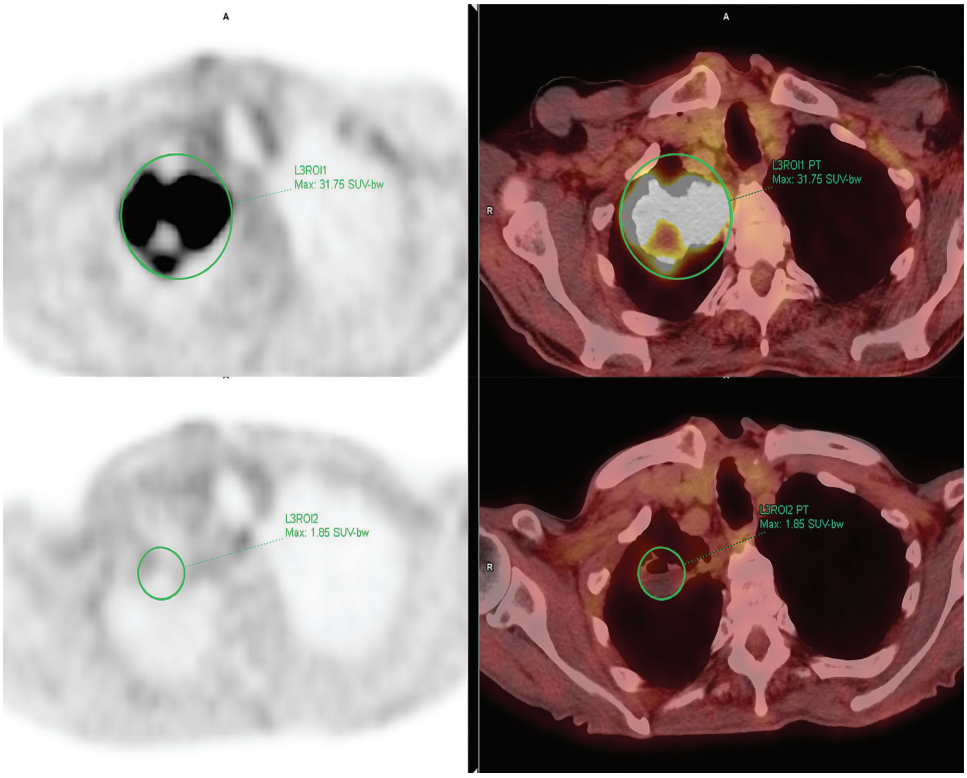

Figure 1. A 78-year-old male, squamous cell carcinoma, images before treatment are in the top row. PET/CT scan performed three months after radiotherapy is in the bottom row. The tumor SUVmax declines from 31.75 to 1.85; SUVmax measured from the aorta is 2.2. This is considered a complete metabolic response.

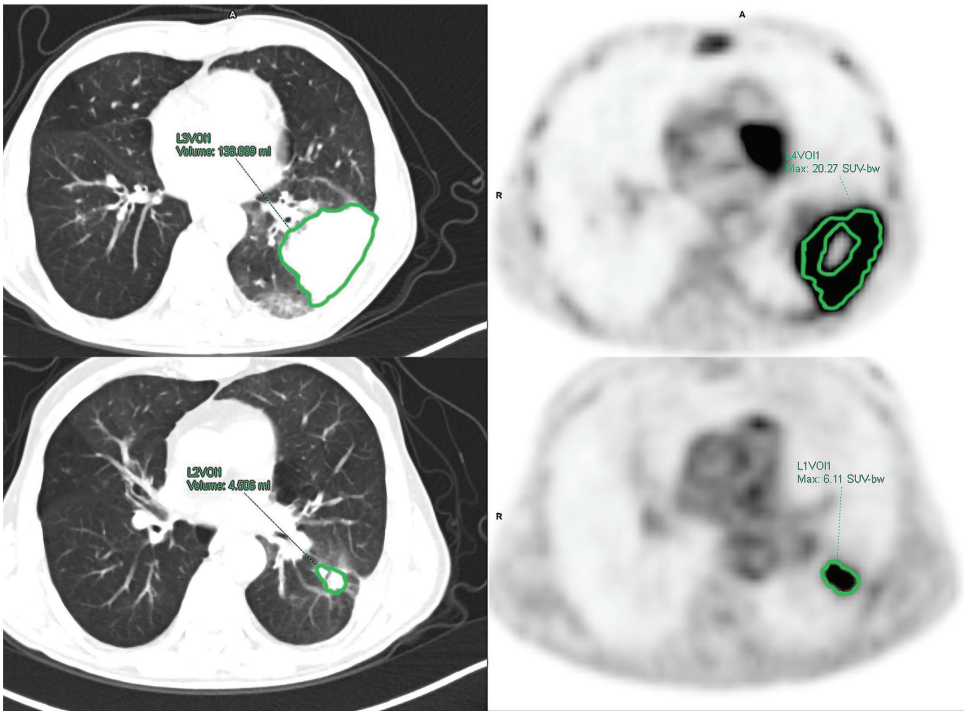

Figure 2. A 66-year-old male, adenocarcinoma, CT, and PET images before treatment are in the top row. Images performed three months after radiotherapy is in the bottom row. Necrotic tumor, SUVmax declines from 20.27 to 6.11, $GTV_{PET\text{-}CT}$ declines from 138.7 to 4.5 mL. This is considered a residual tumor.

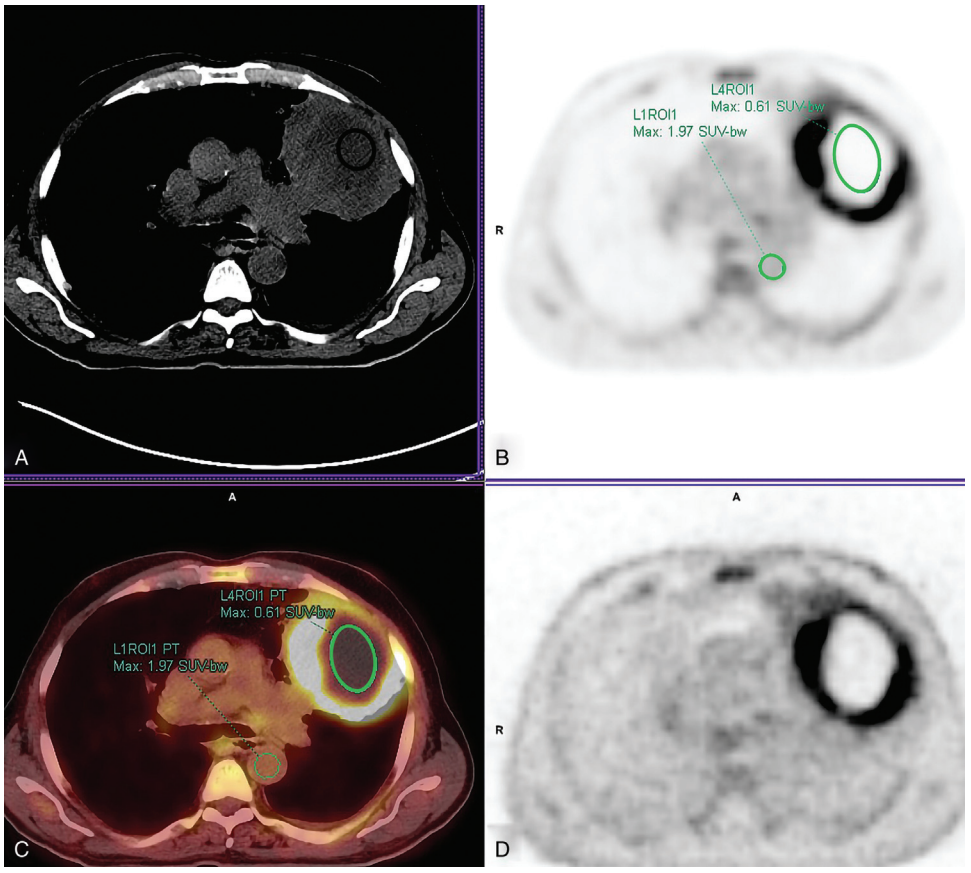

Figure 3. A 64-year-old male, adenocarcinoma. The area showing low FDG uptake in PET (B) and PET/CT fusion (C) images is verified in the non-attenuation correction (NAC) image (D). A region of interest (ROI) is drawn in the necrotic area, and the SUVmax value is compared with the SUVmax value of the aorta. SUVmax < aorta SUVmax (necrotic area SUVmax: 0.61, aorta SUVmax: 1.97) and the necrotic area is low attenuated in non-intravenous contrast-enhanced low-dose correlative CT (average Hounsfield's unit is 17, black ROI) (A). It is considered necrosis ($PET_{NECROSIS}$).

Table 1

Patient characteristics.

Characteristics	N (%)
Sex	
Female	3 (6%)
Male	50 (94%)
Histology	
Adenocarcinoma	21 (39.6%)
SCC	32 (60.4%)
RT dose (Gy)	
70	9 (17%)
64.8	28 (52.8%)
60	16 (30.2%)
Residual malignancy	30 (56.6%)
Adenocarcinoma	10
SCC	20
Treatment	
Radiotherapy only	7 (13%)
Chemoradiotherapy	46 (87%)
PETNECROSİS	15 (28.3)
Adenocarcinoma	4
Squamous cell carcinoma	11

2.8. Statistical analysis

The primary endpoint of our study was to find the predictive parameters for the complete metabolic response after definitive chemoradiotherapy/definitive radiotherapy. We evaluated SUV-max, tumor size, $GTV_{PET\text{-}CT}$, MTV, $PET_{NECROSIS}$, radiation dose, and histology. Continuous demographic data were analyzed according to normality tests. Parametric data were reported as mean ± standard deviation and non-parametric data as median (min-max). Differences between groups were analyzed using Student's *t* test in parametric and Mann–Whitney *U* tests for non-parametric tests. Discontinuous variables were shown as frequencies. The treatment-related changes in the numerical parameters were evaluated using the paired-samples t-test or the Wilcoxon signed-rank test. Receiver operating characteristic (ROC) statistics of ^{18}F FDG PET/CT parameters were estimated, threshold values providing the optimal sensitivity and specificity (SUVmax ≤ 11.6–>11.6, tumor size ≤43 mm–>43 mm, $GTV_{PET\text{-}CT}$≤28.25 mL–>28.25 mL, MTV ≤ 22.85–> 22.85 mL) were determined and those with a $P < .05$ were included in the univariate analysis. In addition, $PET_{NECROSIS}$, radiation dose, histological subtype were included in the univariate analysis as nominal parameters. For multivariate analyses, the full model included the variables that detected $P < .2$ in univariate analysis, and the final model was constructed using the backward stepwise procedure (backward elimination

Table 2

Characteristics of tumor according to histologic subtypes.

Variable	Whole Patients (n = 53) median (Min-max)/mean ± SD	Adeocarcinoma (n = 21) median (Min-max)/Mean ± SD	Squamous cell carcinoma (n = 32) median (Min-max)/Mean ± SD	P^{*} (t/Z)
Pre-RT PET/CT – RT start time (days)	17.09 ± 7.52	15.05 ± 6.19	18.44 ± 8.100	.417 (t = −0.811)
End of RT – PET/CT time (days)	93 (82–133)	92 (87–132)	93 (75–133)	.110 (Z = −1.629)
Tumor size (mm)	45 (12–109)	47 (12–84)	44 (20–109)	.383 (Z = −0.873)
SUVmax	13.6 (4.9–38.2)	12.5 (4.9–38.2)	14.05 (6.8–37.8)	.856 (Z = −0.182)
MTV (mL)	14.8 (1–206)	14.8 (1–84)	15.65 (2–206)	.263 (Z = −1.119)
GTV_{PET-CT} (mL)	38.9 (2–413)	28.5 (2–250)	42.5 (5–413)	.309 (Z = −1.091)

GTV_{PET-CT} = gross tumor volume measured on PET/CT, MTV = metabolic tumor volume calculated for 50% SUVmax, RT = radiotherapy

* There was no statistically significant difference in variables between adenocarcinoma and squamous cell carcinoma.

method). The statistical significance was set at 0.05. SPSS v. 25 (Chicago, IL) was used for statistical analysis. We did a post hoc power analysis with G Power version 3.1.9.4. (Germany). The power of our study was 0.8510949.

3. Results

Fifty-three patients with NSCLC were included in the study; 50 were men, and three were female. The mean age was 68.1 ± 9.8 (Median age: 69, 48–92). Seven patients underwent only RT (4 patients were not candidates for chemotherapy due to comorbid diseases, concomitant chemotherapy was not administered to 2 patients due to chemotherapy toxicity, one patient refused chemotherapy treatment), and 46 patients received CRT. Patient characteristics are shown in Table 1. Twenty-one patients had adenocarcinoma, and 32 had squamous cell carcinoma (SCC). All parameters were independent of histopathological subtype. The tumor characteristics are given in Table 2. Pre- and post-RT SUV, GTV_{PET-CT}, and MTV values are shown in Table 3.

We analyzed whether there was any difference between pre-treatment SUVmax, GTV_{PET-CT}, MTV, and tumor size values between patient groups with and without post-RT residual disease. In the patient group with post-RT residual disease, pre-RT SUVmax (P = .019, Z = −2.342), GTV_{PET-CT} (P = .007, Z = 2.674), MTV (P = .048, Z = −1.974), and tumor size (P = .011, Z = −2.531) values were significantly higher than those in the patient group without post-RT residual disease (Table 4).

Fifteen patients had $PET_{NECROSIS}$ (4 adenocarcinomas, 11 SCC). We calculated the percentage of necrosis in 14 patients (27.36 ± 8.94%, range: 13–43). Of the six patients with a necrosis percentage, ≥ 30% had residual disease on post-RT ^{18}F FDG PET/CT, 5 of 8 patients with necrosis < 30% had a residual disease, and 3 had no residual disease on post-RT ^{18}F FDG PET/CT.

Increased tumor size was associated with the presence of $PET_{NECROSIS}$. There was a statistically significant relationship between tumor size and the presence or absence of $PET_{NECROSIS}$ (P = .009; OR: 1.036, 95CI%: 1.009–1.064). Using the ROC curve, we divided patients into two groups according to tumor size (<44.5 mm vs ≥44.5 mm, sensitivity: 80%, specificity: 60.9%, AUC = 0.755, 95CI% 0.614–0.897, P = .004). The presence of $PET_{NECROSIS}$ was statistically significantly different between the groups with tumor size <44.5 and ≥44.5 mm (P = .012, odds ratio [OR]: 6.133, 95CI%: 1.479–25.440). Using the ROC curve, we divided patients into two groups based on the GTV_{PET-CT} (<47.5 mL vs ≥47.5 mL, sensitivity: 80%, specificity: 77.1%, AUC = 0.775, 95CI%: 0.635–0.916, P = .002). Presence of $PET_{NECROSIS}$ was statistically different between the groups with GTV_{PET-CT} <47.5 mL vs ≥47.5 mL (P = .002, OR: 9.818, 95CI%: 2.311–41.706).

Using the ROC curve, we determined the threshold values for ^{18}F FDG PET/CT parameters according to the optimal sensitivity-specificity values. We divided the patients into two groups according to threshold values and included them in the univariate logistic regression analysis. GTV_{PET-CT} ≤ 28.25 mL vs >28.25 mL (sensitivity, 76.7%, specificity 60.1%, AUC = 0.716, P = .007, 95CI%: 0.575–0.857), tumor size ≤43 mm vs >43 mm (Sens:70%, spes:60.1%, AUC = 0.704, P = .011, 95CI%: 0.562–0.847), MTV ≤ 22.85 mL vs >22.85 mL (Sens:60%, spes:60.1%, AUC = 0.659, p = 0.048, 95CI% = 0.512–0.807), SUVmax ≤11.6 vs>11.6 (Sens: 76.7%, spes: 65.2%, P = .019, AUC = 0.689, 95CI%: 0.542–0.837) were determined.

In univariate logistic regression analysis; SUVmax ≤11.6 vs >11.6 (P = .003, OR:6.161, 95CI%:1.846–20.557), tumor size ≤43 mm vs >43 mm (P = .027, OR: 3.630, 95CI%:1.155–11.406), GTV_{PET-CT} ≤ 28.25 mL vs >28.25 mL (P = .007, OR:5.111, 95CI%:1.554–16.807) and $PET_{NECROSIS}$ (P = .039, OR:4.444, 95CI%:1.078–18.321) were statistically significant predictors for CMR. MTV ≤ 22.85 mL vs >22.85 mL (P = .135, OR:2.333, 95CI%:0.768–7.089), radiation dose (P = .263, OR:1.108, 95CI%: 0.926–1.326) and histology (P = .285, OR:1.833, 95CI%:0.601–5.597) were not statistically significant predictors of CMR.

Multivariate logistic regression analysis demonstrated that SUVmax ≤11.6 vs >11.6 (P = .003, OR:7.670, 95CI%:2.013–29.231) and $PET_{NECROSIS}$ (P = .028, OR:6.704, 95CI%1.214–30.394) were independent predictors for CMR (Table 5).

4. Discussion

This study examined whether necrosis on pre-RT ^{18}F-FDG PET/CT predicted CMR in patients with NSCLC. Necrosis on pre-RT ^{18}F-FDG PET/CT was an independent predictor of CMR. We could not find a study searching for a relationship between necrosis on ^{18}F-FDG PET/CT and CMR in patients with NSCLC. We determined the criteria for $PET_{NECROSIS}$ to have lower FDG uptake in the tumor than blood pool activity and lower attenuation from the surrounding tissue (Attenuation 10–30 HU) in non-intravenous contrast-enhanced low-dose correlative CT. Although this method has not been studied in NSCLC patients, similar methods have been used to predict survival in different cancers. Adams et al investigated the relationship between survival and necrosis on PET in patients with diffuse large B-cell lymphoma (DLBCL). They determined the criteria of necrosis to be between 10 and 30 HU on non-intravenous contrast-

Table 3

Pre-radiotherapy and post-radiotherapy values of tumor SUVmax, MTV and GTV_{PET-CT}.

Variable	Pre-radiotherapy median (min-max)	Post-radiotherapy median (min-max)	P^*/Z
SUVmax	13.6 (4.9–38)	4.2 (0–24–3)	<.0001/–5.803
MTV (mL)	14.8 (1–206)	2.8 (0–190)	<.0001/–5.812
GTV_{PET-CT} (mL)	38.9 (2–413)	3.1 (0–224)	<.0001/–3.789

GTV_{PET-CT} = gross tumor volume measured on PET/CT, MTV = metabolic tumor volume calculated for 50% of SUVmax.
* The values decreased significantly depending on the treatment.

Table 4

Median (min-max) pre-RT SUV, GTV_{PET-CT}, tumor size, and MTV values in patient groups with and without residual disease in post-RT FDG PET'CT.

Variable	Patients with complete metabolic response (n = 23)	Patients with residual disease (n = 30)	P^*/Z
Pre-treatment SUVmax	11.2 (4.9–37.8)	18.2 (6.8–38.2)	.019/–2.342
Pre-treatment MTV (mL)	13 (2–256)	30 (4–201)	.048/–1.974
Pre-treatment GTV_{PET-CT} (cm^3)	24 (2–413)	60.5 (6–371)	.007/–2.674
Pre-treatment tumor size (mm)	38 (12–107)	53 (21–109)	.011/–2.531

GTV_{PET-CT} = gross tumor volume measured on PET/CT, MTV = metabolic tumor volume calculated for 50% of SUVmax.
* The median values in the group with residual disease on post-RT PET/CT were significantly higher than those in the patient group with complete metabolic response.

enhanced low-dose CT and no increase in attenuation (maximum 5HU) on intravenous contrast-enhanced full-dose CT. Necrosis on PET/CT as a predictor of poor survival.[25] Rakheja et al investigated the relationship between necrosis and survival in patients with sarcomas. They considered the hypometabolic area in the center of the rim-shaped hypermetabolic area in the tumor as necrosis. A threshold value for SUV was not determined; only they defined it as a visual hypometabolic region. They evaluated whether the hypometabolic area in the tumor had a corresponding low attenuation on CT. The presence of necrosis in 39 of 42 patients (92.9%) with necrosis on ^{18}F FDG PET/CT was confirmed by pathology. The MRI results were also highly concordant. Finally, they stated that metabolically diagnosed necrosis on FDG PET/CT was a reliable marker and predictive value for patient outcomes.[27] In a study by Song et al in patients with DLBCL, they defined a hypometabolic area within the peripheral hypermetabolic area in the tumor and the absence of contrast enhancement in the center of the peripheral enhancing tumor in intravenous contrast-enhanced full-dose CT and the attenuation between 10 and 30 HU in non-intravenous contrast-enhanced low-dose CT as necrosis. They concluded that necrosis might reflect an advanced disease and worse prognosis, and PET/CT could accurately detect the presence or absence of necrosis in patients with DLBCL.[26] In a study of patients with DLBCL, necrosis was defined as areas with no FDG uptake within the nodal or extranodal FDG-avid lymphomatous lesions. No specific visual scales were used in this study. Necrosis on PET was a predictor of poor survival.[29] A study of patients with NSCLC stated that the relative ratio of 18F-FDG PET/CT in tumors showing peripheral FDG uptake and not showing central FDG uptake could show the extent of necrosis. They investigated the ratio of metabolic to morphological tumor volumes; namely, they measured MTV with a threshold of 42% of the SUVmax and calculated the morphological tumor volume (MoTV) based on lesion delineation on CT images. The ratio of metabolically active volume to global lesion volume (MMVR) was calculated by dividing MTV by MoTV and expressed as a percentage. They found that MMVR was inversely correlated with the extent of tumor necrosis ($R = -0.570$, $P = .042$). They concluded that metabolically inactive regions presumably indirectly reflect the extent of necrosis and apoptotic events in the global tumor volume.[30]

In the studies mentioned above, the area of central hypometabolism in FDG-avid tumors was defined as necrotic, and in some studies, it was supported by CT findings. Hypometabolism is a relevant description. A tumor with heterogeneous FDG uptake will have relatively hypometabolic areas; which areas should we consider necrosis? For instance, in a lung tumor with a SUVmax of 35 and heterogeneous FDG uptake, the areas with SUVmax of 15, 10, 5, and 4 should be considered hypometabolic? We thought it would be more accurate to determine the upper limit of the SUVmax for hypometabolism, which was defined as one of the parameters used to determine necrosis. Furthermore, we set the blood pool SUVmax to 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.[21] That is, if the tumor SUVmax is higher than the blood pool SUVmax, the presence of residual/viable tumors can be considered. Therefore, we assume that the SUVmax of the necrotic area should be at least lower than the SUVmax of the blood; any area lower than the blood pool SUVmax should be evaluated as necrosis; however, in non-intravenous contrast-enhanced low-dose CT, it should

Table 5

Summary of univariate and multivariate logistic regression analyses to predict complete metabolic response.

Variables	Univariate analyses			Multivariate analyses		
	P	OR	95% CI	*P*	OR	95% CI
SUVmax ≤11.6–>11.6*	.003	6.161	1.846–20.557	.003	7.670	2.013–29.231
Tumor size ≤43 mm–>43 mm*	.027	3.630	1.155–11.406	.687	1.575	0.173–14.327
GTV_{PET-CT}≤28.25 mL–> 28.25 mL*	.007	5.111	1.554–16.807	.388	3.084	0.239–39.756
MTV ≤22.85–> 22.85 mL*	.135	2.333	0.768–7.089	.416	0.324	0.021–4.899
$PET_{NECROSIS}$*	.039	4.444	1.078–18.321	**.028**	**6.074**	**1.214–30.394**
Radiation dose (Gy)	.263	1.108	0.926–1.326	–	–	–
Histology	.285	1.833	0.601–5.597	–	–	–

CI = confidence interval, GTV_{PET-CT} = gross tumor volume measured on PET/CT, MTV = metabolic tumor volume calculated for 50% of SUVmax, OR = odds ratio, $PET_{NECROSIS}$ = necrosis observed on PET/CT, RT = radiotherapy.
* Indicates parameters included in multivariate analysis.

correspond to low attenuation relative to the surrounding tissue. In non-intravenous contrast-enhanced low-dose correlative CT, low-attenuation areas were identified with Hounsfield units (HUs) between 10 and 30 units have been previously defined as tumor necrosis.[24–26] We determined thresholds for metabolic activity and attenuation in non-intravenous contrast-enhanced low-dose CT, which makes our study differs from the others.

Not every FDG uptake we observed in treatment response evaluation PET/CT reflects residual disease. Monitoring of FDG uptake due to inflammation after RT is a situation that can be encountered in daily practice. Therefore, it is recommended that PET/CT be applied at least three months after RT.[31] In our study, the median time between the end of RT and PET/CT was 93 days (minimum 82, maximum 133). Another condition that can cause false positives is radiation pneumonitis. In this case, patients may have clinical symptoms, and medical treatment support may be required. FDG uptake can continue for up to 15 months. A biopsy may be required for the differential diagnosis of residual-recurrent tumor/inflammation.[32] None of the patients in our study group had FDG PET/CT findings compatible with radiation pneumonitis. Some situations can cause false negatives. Hyperglycemia is one of them. In order to prevent this situation, we ensured that the blood glucose level of the patients was <200 mg/dL. Another factor is the partial volume effect.[33]

It has been shown in many cancers that the detection of necrosis in pathologic materials of tumors is associated with poor prognosis.[13,16,17,34] Because microscopic necrosis is a poor prognostic factor for the disease, we were not surprised that the presence of necrosis on the ^{18}F FDG PET/CT scan was a predictor of residual malignancy after RT. However, most patients with lung cancer are diagnosed at an inoperable stage; thus, we designed this study considering that determining tumor necrosis before treatment could help manage and evaluate risk.

We calculated the percentage of necrosis in the 14 patients. We divided the patients into two groups, with percentages of necrosis ≤30% and >30%. No statistically significant difference was found in predicting the CMR. Rakheja et al grouped patients according to necrosis rate ≤30%> and ≤50%>. They found a worse prognosis in the patient groups with a higher percentage of necrosis. One of the reasons our results were statistically insignificant might be the low number of patients examined in the necrosis percentage. In their analysis, while there were 47 vs 19 patients in the groups, our group consisted of 8 vs 6 patients.[27]

The presence of necrosis was associated with increased tumor size/volume. There was a statistically significant difference in the presence of necrosis between the groups with tumor size <44.5 mm vs ≥44.5 mm (OR: 6.133) and GTV_{PET-CT} < 47.5 mL vs ≥47.5 mL (OR: 9.818). Hiraoka et al showed a relationship between tumor size and necrosis in patients with pancreatic cancer.[16] Kahle et al found a correlation between bulky tumors and necrosis on ^{18}F FDG PET/CT.[29] Soussan et al showed that large-volume tumors on pre-treatment CT contained more necrotic components in histological analysis.[35] Our findings are compatible with the literature regarding tumor size and necrosis relationship.

We found that SUVmax ≤11.6 vs >11.6 (OR:7.670) was an independent predictor for CMR. In the literature, SUVmax has been shown in many studies as a predictor for treatment response, local control, and survival.[3,21–25,36] Our findings were consistent with those of previous studies.[3,37–41]

In the patient group with post-RT residual disease, GTV_{PET-CT}, MTV, and tumor size values were significantly higher than those in the patient group without the post-RT residual disease. RT doses were not predictors of MCR in our study. Aerts et al stated that the total radiation dose was not related to MCR in patients with stage 1 to 3 NSCLC and that pre-RT GTV was higher in patients with residual tumors after treatment.[3] Ohri et al reported that MTV was a predictor for local control, that local control was >90% in patients with MTV <10 to 20 cc, and that RT dose was not associated with local control in 89 patients with NSCLC.[42]

Our study has limitations; our main limitation is that our study is retrospective and single-center. The fact that our number of patients is not higher may be a limitation that affects our results. Only definitive RT in 7 of our patients (13%) affected treatment homogenization. The number of male and female patients was disproportionate. Only 3 of our patients in our study group were women. When designing the study, we collected the files of patients who received definitive chemo-radiotherapy or only RT during a specific period. As a result of the analysis, we realized that we only had three female patients. In order to avoid bias, we did not exclude these patients from the study. The incidence of lung cancer in female patients is relatively low in our country. In 2013 data, only 9.6% of lung cancer patients were women.[43] In our study, the rate of female patients was 5.6%. The disproportion in the number of male and female patients may be due to the single-center nature of our study. The prognostic value of gender was investigated.[44] However, we could not analyze the prognostic value of the gender factor due to the disproportion between the numbers of male and female patients. Another limitation can be seen as the necrosis that we described in PET/CT is not confirmed histopathologically. We could not confirm necrosis histopathologically because we retrospectively studied inoperable patients. Histopathological confirmation of necrosis requires a study of the total surgical specimen, which would have been possible in operable patients. In addition, even if it were a prospective study, it would not be easy to confirm necrosis histopathologically. Because, even if the area defined as necrotic on PET/CT is present in the surgical specimen, it may be challenging to confirm that it corresponds to the necrotic area.

In conclusion, SUVmax ≤ 11.6 vs >11.6, tumor size ≤43 mm vs >43 mm, GTV_{PET-CT} ≤ 28.25 mL vs >28.25 mL, and necrosis on pre-radiotherapy ^{18}F-FDG PET/CT were predictors of CMR after definitive CRT or RT alone. $PET_{NECROSIS}$ and SUVmax > 11.6 could be used as imaging markers for complete metabolic response in patients with NSCLC. Our findings need to be supported by prospective design studies involving more patients.

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Author contributions

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