Necrosis, as Identified 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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Research Article

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Abstract

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

Methods: We studied 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 to 30 Hounsfield Units (HU)] from the surrounding tissue on non-intravenous contrast-enhanced low dose correlative CT, we defined it as necrotic ($PET_{NECROSİS}$).

Results: Fifty-three patients were included in the study. The mean age was 68.1±9.8 years. Twenty-one patients had adenocarcinoma, 32 had squamous cell carcinoma. All parameters were independent of histologic status. Multivariate logistic regression analysis showed that, SUVmax ≤11.6vs>11.6 (p=0.003, OR:7.670, 95CI%:2.013-29.231) and $PET_{NECROSİS}$ absence/presence were independent predictors for CMR (p=0.028, OR:6.704, 95CI%1.214-30.394).

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

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). The presence of residual malignancy after treatment is associated with worse 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 patients with NSCLC (4–6). High FDG uptake before treatment is associated with poor local control (7). Hypoxia is a predictor for RT and chemotherapy response. Low oxygen levels are known to reduce the distribution of chemotherapy, and hypoxic tissues are more resistant to radiotherapy (RT) (8, 9). Some authors argue that hypoxic regions within the tumor should be identified and that the RT dose given to these regions should be escalated (10). Rapid tumor growth is considered to lead to necrosis in solid tumors due to chronic ischemic damage. Necrosis is the irreversible, final result of hypoxia and the degree of intra-tumoral hypoxia reflects the extent of necrosis (11, 12). It has been shown in various types of cancer that microscopic necrosis in surgical material is associated with poor prognosis (13, 14). However, patients with lung

cancer are often diagnosed at the 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 if necrosis, as identified on pre-RT ^{18}F-FDG PET/CT, was a predictor for complete metabolic response (CMR) in patients with NSCLC.

Patients And Methods:

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 by the institutional review board from the need for informed consent. All procedures performed in studies involving human participants were by the Helsinki declaration.

Patient Selection: Patients diagnosed as NSCLC histopathologically, had inoperable stage I-III disease, 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, 24 patients had stage III disease, according to the seventh edition of the American Joint Committee on Cancer staging system (AJCC 7th edition) (15).

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 applied to 64% of patients, and three-dimensional (3D) conformal radiotherapy (3DCRT, n=19) was applied to 36% of patients. Patients were simulated with their arms elevated using a T-bar. Radiotherapy planning computed tomography was performed in spontaneous breathing without the use of 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). To cover microscopic extension and create clinical target volume (CTV), delineation was performed by adding 8 mm to the GTV in patients with adenocarcinoma and 6 mm to the GTV in patients with SCC. Internal target volume (ITV) was created by adding an inner margin (IM) to CTV. In the absence of 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) (16). A total median of 64.8 (range, 60-70) Gy with 1.8 Gy per fraction was given to patients. All the patients received four weekly doses of carboplatin and paclitaxel concurrently with radiotherapy.

^{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

Image Analysis: All analyses were conducted through consensus by a nuclear medicine specialist (O.K.) with nine years experience and by a radiation oncology specialist (G.E.) with nine 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-CT}), metabolic tumor volume calculated according to the threshold values of 50% of tumor SUVmax (MTV) (17) and the tumor size were measured.

Treatment Response Assessment: In the post-RT ^{18}F-FDG PET/CT, tumor SUVmax < aorta SUVmax was considered complete metabolic response (CMR) (3, 18-20) (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 time interval between the radiotherapy and post-RT ^{18}F-FDG PET/CT is median 93 days (82-133 days).

Necrosis on ^{18}F FDG PET/CT Evaluation: The area showing visually very low/or 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 was significantly lower attenuation from the surrounding tissue in non-intravenous contrast-enhanced low-dose correlative CT, we evaluated it as necrotic ($PET_{NECROSIS}$). On non-intravenous contrast-enhanced low-dose correlative CT, low attenuation areas were identified with Hounsfield units (HUs) between 10-30 units (21-23). 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 Fig 3. In addition, we calculated the percentage of necrosis by proportioning the volume of the necrotic component to the tumor volume (24). Lung cavities are gas-filled space, seen as a lucency or low-attenuation area, within pulmonary consolidation, a mass, or a nodule (25) distinguished from $PET_{NECROSIS}$.

Statistical Analysis: 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 in non-parametric. Discontinuous variables were shown as frequency. The treatment-related changes of numerical parameters were evaluated with 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 and threshold values providing the optimal sensitivity and specificity were determined, and those with a $p < 0.05$ were included in the univariate analysis. Parameters with p values <0.2 were detected in the univariate analysis included in multivariate logistic regression analyses. For multivariate analyses, the full model included the variables that detected $p<0.2$ in univariate analysis, and the final model was constructed using the backward stepwise procedure (backward elimination method). The statistical significance value was accepted as 0.05. The software package SPSS v. 25 (Chicago, USA) was used for statistical analysis.

Results:

Fifty-three patients with NSCLC were included in the study; 50 were male, and three were female. The mean age was 68.1±9.8 years. Seven patients underwent only RT [four patients were not a candidate for chemotherapy due to comorbid diseases, concomitant chemotherapy was not given to 2 patients due to chemotherapy toxicity, one patient refused chemotherapy treatment) furthermore, 46 patients received CRT. Patient characteristics are given in table 1. Twenty-one patients were adenocarcinoma, and 32 were squamous cell carcinoma (SCC). All parameters were independent of histopathological subtype. Tumor characteristics were given in table 2. Pre and post-RT SUV, GTV_{PET-CT}, and MTV values were given 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 ($p = 0.019$, $Z = -2.342$), GTV_{PET-CT} ($p = 0.007$, $Z = -2.674$), MTV ($p = 0.048$, $Z= -1.974$), tumor size ($p = 0.011$, $Z = -2.531$) values were statistically significantly higher than 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 all 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 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 $PET_{NECROSIS}$ presence/absence ($p= 0.009$, OR: 1.036, 95CI%: 1.009-1.064). Using the ROC curve, we divided patients into two groups according to tumor size (<44.5mm vs ≥44.5mm, sensitivity: 80%, specificity: 60.9%, AUC = 0.755, 95CI% 0.614-0.897, $p = 0.004$). Presence of $PET_{NECROSIS}$ was statistically significantly different between the groups with tumor size <44.5mm and ≥44.5mm [$p = 0.012$, 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, $p = 0.002$). Presence of $PET_{NECROSIS}$ was statistically different between the groups with GTV_{PET-CT} <47.5 **mL** vs ≥47.5 **mL** ($p = 0.002$, OR: 9.818, 95CI%: 2.311-41.706).

By using ROC curve, we determined 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. GTV_{PET-CT} ≤ 28.25 **mL** vs >28.25 **mL** (Sensitivity, 76.7%, spesifitivity 60.1%, AUC=0.716, $p= 0.007$, 95CI%: 0.575-0.857), tumor size ≤43mm vs >43mm (Sens:70%, spes:60.1%, AUC=0.704, $p=0.011$, 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%, $p= 0.019$, AUC=0.689, 95CI%: 0.542-0.837) were determined.

In univariate logistic regression analysis; SUVmax ≤11.6vs>11.6 (p=0.003, OR:6.161, 95CI%:1.846-20.557), tumor size ≤43mm vs >43mm (p=0.027, OR:3.630, 95CI%:1.155-11.406), GTV_{PET-CT} ≤ 28.25 **mL** vs >28.25 **mL** (p=0.007, OR:5.111, 95CI%:1.554-16.807) and $PET_{NECROSİS}$ (p=0.039, OR:4.444, 95CI%:1.078-18.321) were statisticaly significant predictors for CMR. MTV ≤ 22.85 **mL** vs >22.85 **mL** (p=0.135, OR:2.333, 95CI%:0.768-7.089), radiation dose (p=0.263, OR:1.108, 95CI%: 0.926-1.326) and histology (p=0.285, 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=0.003, OR:7.670, 95CI%:2.013-29.231) and $PET_{NECROSİS}$ (p=0.028, OR:6.704, 95CI%1.214-30.394) were independent predictors for CMR. Table 5.

Discussion

This study examined if 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 found independent predictor of CMR. We could not find a study searching for a relation between necrosis on ^{18}F-FDG PET/CT and CMR in patients with NSCLC. We determined 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 in different cancers to predict survival. 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 have between 10 and 30HU in non-intravenous contrast-enhanced low-dose CT and no increase in attenuation (maximum 5HU) on intravenous contrast-enhanced full-dose CT. Necrosis on PET/CT was found a predictor of worse survival (22). Rakheja et al. investigated the relationship between necrosis and survival in sarcoma patients. 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 visual hypometabolic. They evaluated whether the hypometabolic area in the tumor had a corresponded 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. MRI results were also found to be highly concordant. Finally, they stated that metabolically diagnosed necrosis in FDG PET /CT was a reliable marker and predictive value on patient outcomes (24). In a study of Moo-Kon 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 10-30HU in non-intravenous contrast-enhanced low-dose CT as necrosis. They concluded that necrosis might reflect an advanced disease status and worse prognosis, and PET/CT could accurately detect the presence or absence of necrosis in patients with DLBCL (23). In a study of patients with DLBCL, necrosis has been defined as areas with no FDG uptake within the nodal or extranodal FDG avid lymphomatous lesions. No specific visual scale was used. Necrosis on PET was found a predictor of worse survival (26). In a study of patients with NSCLC, it was stated that the relative ratio of 18F-FDG PET/CT in the tumor

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 have measured MTV with a threshold of 42% of the SUVmax, and they have calculated 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 ($R = -0.570$, $p = 0.042$). They concluded that metabolically inactive regions were presumably indirectly reflecting the extent of the necrosis and apoptotic events in the global tumor volume (27).

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 relative 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 showing heterogeneous FDG uptake, which areas with SUVmax of 15, 10, 5, 4 should be considered hypometabolic? 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 determine 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 (18). 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 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 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 10-30 units. We determined thresholds for metabolic activity and attenuation in non-intravenous contrast-enhanced low-dose CT, which makes our study differs from the others.

It has been shown in many cancers that the detection of necrosis in pathologic materials of tumors is associated with poor prognosis (11, 13, 14, 28). Because microscopic necrosis is a poor prognostic factor for the disease, we were not surprised by the result that the presence of necrosis on the ^{18}F FDG PET/CT scan was found as 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 being able to determine tumor necrosis before treatment could help in the management and risk evaluation.

We calculated the percentage of necrosis in 14 patients. We divided the patients into two groups, with a percentage of necrosis ≤30% and> 30%. No statistically significant difference was found for predicting CMR. Rakheja et al. grouped patients according to the rate of necrosis ≤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 groups consisted of 8 vs. six patients (24). 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 <44.5mm vs. ≥44.5mm (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 (13). Kahle et al. found a correlation between bulky tumor and necrosis on ^{18}F FDG PET/CT (26). Soussan et al. showed that large-volume tumors on pre-treatment CT contained more necrotic components in histological analysis (29).

We found that SUVmax ≤11.6 vs.>11.6 (OR:7.670) was an independent predictor for CMR. In the literature, SUVmax was shown in many studies as a predictor for treatment response, local control, and survival (3,18-22,30); our findings were consistent with these studies (3, 31-35).

In the patient group with post-RT residual disease, GTV_{PET-CT}, MTV, tumor size values were statistically significantly higher than the values in the patient group without the post-RT residual disease. RT doses were not a predictor for MCR in our study. Aerts et al. stated that the total radiation dose was not related to MCR in patients with stage 1-3 NSCLC and that pre-RT GTV was higher in patients with residual tumors after treatment (3). Ohri N. et al. reported that MTV was a predictor for local control, that local control was >90% in patients with MTV <10-20 cc, and that RT dose was not associated with local control in 89 patients NSCLC (36).

Our study had some limitations; it was retrospective and single-center. The number of male and female patients was disproportionate; this was attributed to the study's single-center design and the low cigarette smoking rate among women. The frequency of lung cancer is thus very low in women compared to the men in this region of the country. All of the patients could not receive chemoradiotherapy, and seven patients could receive RT alone. Because of the study's retrospective nature, histopathological analysis of necrotic tumor sites at ^{18}F FDG PET/CT was unavailable.

In conclusion**,** SUVmax ≤11.6vs>11.6, tumor size ≤43mm vs.>43mm, GTV_{PET-CT} ≤ 28.25 mL vs.>28.25 mL, and necrosis on pre-radiotherapy ^{18}F-FDG PET/CT were predictors for CMR after CRT or RT alone. The $PET_{NECROSİS}$ and SUVmax>11.6 could be used as an imaging marker for complete metabolic response in patients with NSCLC.

Declarations

Conflict of Interest: The authors declare that they have no conflict of interest.

Acknowledgment, no potential conflicts of interest were disclosed.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics (2019) CA: Cancer J Clin 2019; 69:7–34

2. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P et al (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28:2181–2190
3. Aerts HJ, van Baardwijk AA, Petit SF, Offermann C, van Loon J, Houben R et al (2009) Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy 18Fluorodeoxyglucose-PET-CT scan. Radiother Oncol 91:386–392
4. Ohri N, Duan F, Machtay M, Gorelick JJ, Snyder BS, Alavi A et al. Pre-treatment FDG-PET metrics in stage III non–small cell lung cancer: ACRIN 6668/RTOG 0235. JNCI: J Natl Cancer Inst 2015; 107
5. Clarke K, Taremi M, Dahele M, Freeman M, Fung S, Franks K et al (2012) Stereotactic body radiotherapy (SBRT) for non-small cell lung cancer (NSCLC): is FDG-PET a predictor of outcome? Radiother Oncol 104:62–66
6. Lovinfosse P, Janvary ZL, Coucke P, Jodogne S, Bernard C, Hatt M et al (2016) FDG PET/CT texture analysis for predicting the outcome of lung cancer treated by stereotactic body radiation therapy. Eur J Nucl Med Mol Imaging 43:1453–1460
7. Hamamoto Y, Sugawara Y, Inoue T, Kataoka M, Ochi T, Takahashi T et al (2011) Relationship between pre-treatment FDG uptake and local control after stereotactic body radiotherapy in stage I non-small-cell lung cancer: the preliminary results. Jpn J Cancer Res 41:543–547
8. Brown JM, Wilson WR (2004) Exploiting tumour hypoxia in cancer treatment. Nat Rev Cancer 4(6):437
9. Hall EJ, Giaccia AJ (2006) Radiobiology for the Radiologist. Lippincott Williams & Wilkins
10. Servagi-Vernat S, Differding S, Sterpin E, Hanin F-X, Labar D, Bol A et al (2015) Hypoxia-guided adaptive radiation dose escalation in head and neck carcinoma: a planning study. Acta Oncol 54:1008–1016
11. Swinson DE, Jones JL, Richardson D, Cox G, Edwards JG, O'Byrne KJ (2002) Tumour necrosis is an independent prognostic marker in non-small cell lung cancer: correlation with biological variables. Lung cancer 37:235–240
12. Langner C, Hutterer G, Chromecki T, Leibl S, Rehak P, Zigeuner R (2006) Tumor necrosis as prognostic indicator in transitional cell carcinoma of the upper urinary tract. J Urol 176:910–914
13. Hiraoka N, Ino Y, Sekine S, Tsuda H, Shimada K, Kosuge T et al (2010) Tumour necrosis is a postoperative prognostic marker for pancreatic cancer patients with a high interobserver reproducibility in histological evaluation. Br J Cancer 103:1057
14. Pollheimer MJ, Kornprat P, Lindtner RA, Harbaum L, Schlemmer A, Rehak P et al (2010) Tumor necrosis is a new promising prognostic factor in colorectal cancer. Hum Pathol 41:1749–1757
15. Edge SB, Compton CC (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17:1471–1474
16. Giraud P, Antoine M, Larrouy A, Milleron B, Callard P, De Rycke Y et al (2000) Evaluation of microscopic tumor extension in non–small-cell lung cancer for three-dimensional conformal radiotherapy planning. Int J Radiat Oncol Biol Phys 48:1015–1024

17. Frings V, van Velden FH, Velasquez LM, Hayes W, van de Ven PM, Hoekstra OS et al (2014) Repeatability of metabolically active tumor volume measurements with FDG PET/CT in advanced gastrointestinal malignancies: a multicenter study. Radiology 273:539–548
18. Ding Q, Cheng X, Yang L, Zhang Q, Chen J, Li T et al (2014) PET/CT evaluation of response to chemotherapy in non-small cell lung cancer: PET response criteria in solid tumors (PERCIST) versus response evaluation criteria in solid tumors (RECIST). J Thorac Dis 6:677
19. Mac Manus MP, Hicks RJ, Matthews JP, Wirth A, Rischin D, Ball DL (2005) Metabolic (FDG–PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. Lung cancer 49:95–108
20. Aerts HJ, Bussink J, Oyen WJ, van Elmpt W, Folgering AM, Emans D et al (2012) Identification of residual metabolic-active areas within NSCLC tumours using a pre-radiotherapy FDG-PET-CT scan: a prospective validation. Lung cancer 75:73–76
21. Hopper K, Diehl L, Cole B, Lynch J, Meilstrup J, McCauslin M (1990) The significance of necrotic mediastinal lymph nodes on CT in patients with newly diagnosed Hodgkin disease. AJR Am J Roentgenol 155:267–270
22. Adams HJ, De Klerk JM, Fijnheer R, Dubois SV, Nievelstein RA, Kwee TC (2015) Prognostic value of tumor necrosis at CT in diffuse large B-cell lymphoma. Eur J Radiol 84:372–377
23. Song M-K, Chung J-S, Shin D-Y, Lim S-N, Lee G-w, Choi J-C et al (2017) Tumor necrosis could reflect advanced disease status in patients with diffuse large B cell lymphoma treated with R-CHOP therapy. Ann Hematol 96:17–23
24. Rakheja R, Makis W, Tulbah R, Skamene S, Holcroft C, Nahal A et al (2013) Necrosis on FDG PET/CT correlates with prognosis and mortality in sarcomas. AJR Am J Roentgenol 201:170–177
25. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246:697–722
26. Kahle XU, Hovingh M, Noordzij W, Seitz A, Diepstra A, Visser L et al (2019) Tumour necrosis as assessed with 18 F-FDG PET is a potential prognostic marker in diffuse large B cell lymphoma independent of MYC rearrangements. Eur Radiol 29:6018–6028
27. Jreige M, Letovanec I, Chaba K, Renaud S, Rusakiewicz S, Cristina V et al (2019) 18 F-FDG PET metabolic-to-morphological volume ratio predicts PD-L1 tumour expression and response to PD-1 blockade in non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 46:1859–1868
28. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H (2002) An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 168:2395–2400
29. Soussan M, Cyrta J, Pouliquen C, Chouahnia K, Orlhac F, Martinod E et al (2014) Fluorine 18 fluorodeoxyglucose PET/CT volume-based indices in locally advanced non–small cell lung cancer: prediction of residual viable tumor after induction chemotherapy. Radiology 272:875–884
30. Kupik O, Bozkurt M, Asa S, Eren G, Gundogdu H, Arpa M. Do Volume-Based and Metabolic 18F FDG PET/CT Parameters Identify Groups at Risk for Poor Prognosis in Patients with Newly Diagnosed

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31. Dong M, Liu J, Sun X, Xing L (2017) Prognostic significance of SUV max on pre-treatment 18F-FDG PET/CT in early-stage non-small cell lung cancer treated with stereotactic body radiotherapy: A meta-analysis. J Med Imaging Radiat Oncol 61:652–659
32. Lee J, Lee M, Koom WS, Kim HJ, Kim WC (2018) Metabolic positron emission tomography parameters predict failure patterns in early non-small-cell lung cancer treated with stereotactic body radiation therapy: a single-institution experience. Jpn J Clin Oncol 48:920–926
33. Park J, Choi Y, Ahn KJ, Park SK, Cho H, Lee JY (2019) Maximum standardized uptake value at pre-treatment PET in estimating lung cancer progression after stereotactic body radiotherapy. Radiat Oncol J 37:30
34. Takeda A, Yokosuka N, Ohashi T, Kunieda E, Fujii H, Aoki Y et al (2011) The maximum standardized uptake value (SUVmax) on FDG-PET is a strong predictor of local recurrence for localized non-small-cell lung cancer after stereotactic body radiotherapy (SBRT). Radiother Oncol 101:291–297
35. Horne ZD, Clump DA, Vargo JA, Shah S, Beriwal S, Burton SA et al (2014) Pre-treatment SUV max predicts progression-free survival in early-stage non-small cell lung cancer treated with stereotactic body radiation therapy. Radiat Oncol 9:1–6
36. Ohri N, Bodner WR, Halmos B, Cheng H, Perez-Soler R, Keller SM et al (2017) 18F-fluorodeoxyglucose/positron emission tomography predicts patterns of failure after definitive chemoradiation therapy for locally advanced non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 97:372–380

Tables

Table 1
Patient characteristics

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

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	0.417 (t=-0.811)
End of RT - PET/CT time (days)	93 (82–133)	92 (87–132)	93 (75–133)	0.110 (Z=-1.629)
Tumor size (mm)	45 (12–109)	47 (12–84)	44 (20–109)	0.383 ((Z=-0.873)
SUVmax	13.6 (4.9–38.2)	12.5 (4.9–38.2)	14.05 (6.8–37.8)	0.856 (Z=-0.182)
MTV (mL)	14.8 (1-206)	14.8 (1–84)	15.65 (2-206)	0.263 (Z=-1.119)
GTV_{PET-CT} (mL)	38.9 (2-413)	28.5 (2-250)	42.5 (5-413)	0.309 (Z=-1.091)

(*) no statistically significant difference in variables between adenocarcinoma and squamous cell carcinoma.

Abbreviations: GTV_{PET-CT}, gross tumor volume measured on PET/CT; RT, radiotherapy; MTV, metabolic tumor volume calculated for 50 % of SUVmax.

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)	< 0.0001/ -5.803
MTV (mL)	14.8 (1-206)	2.8 (0-190)	< 0.0001/ -5.812
GTV_{PET-CT} (mL)	38.9 (2-413)	3.1 (0-224)	< 0.0001/ -3.789

(*) The values decreased statistically significantly, depending on the treatment.

Abbreviations: GTV_{PET-CT}, gross tumor volume measured on PET/CT, metabolic tumor volume calculated for 50 % of SUVmax.

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)	0.019/ -2.342
Pre-treatment MTV (mL)	13 (2-256)	30 (4-201)	0.048/ -1.974
Pre-treatment GTV_{PET-CT} (cm^3)	24 (2-413)	60.5 (6-371)	0.007/ -2.674
Pre-treatment tumor size (mm)	38 (12–107)	53 (21–109)	0.011/-2.531
(P)* The median values in the group with residual disease on post-RT PET/CT were statistically significantly higher than in the patient group with complete metabolic response			
Abbreviations: GTV_{PET-CT}, gross tumor volume measured on PET/CT; MTV, metabolic tumor volume calculated for 50 % of SUVmax;			

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 *	0.003	6.161	1.846–20.557	**0.003**	**7.670**	**2.013–29.231**
Tumor size ≤ 43mm - >43mm*	0.027	3.630	1.155–11.406	0.687	1.575	0.173–14.327
GTV_{PET-CT}≤28.25mL-> 28.25mL *	0.007	5.111	1.554–16.807	0.388	3.084	0.239–39.756
MTV ≤ 22.85 - > 22.85mL *	0.135	2.333	0.768–7.089	0.416	0.324	0.021–4.899
$PET_{NECROSIS}$ *	0.039	4.444	1.078–18.321	**0.028**	**6.074**	**1.214–30.394**
Radiation Dose (Gy)	0.263	1.108	0.926–1.326	-	-	-
Histology	0.285	1.833	0.601–5.597	-	-	-
(*) Indicates parameters included in multivariate analysis.						
Abbreviations: GTV_{PET-CT}, gross tumor volume measured on PET/CT; RT, radiotherapy; MTV, metabolic tumor volume calculated for 50 % of SUVmax; $PET_{NECROSIS}$, necrosis observed on PET/CT; OR, Odds ratio; CI confidence interval						

Figures

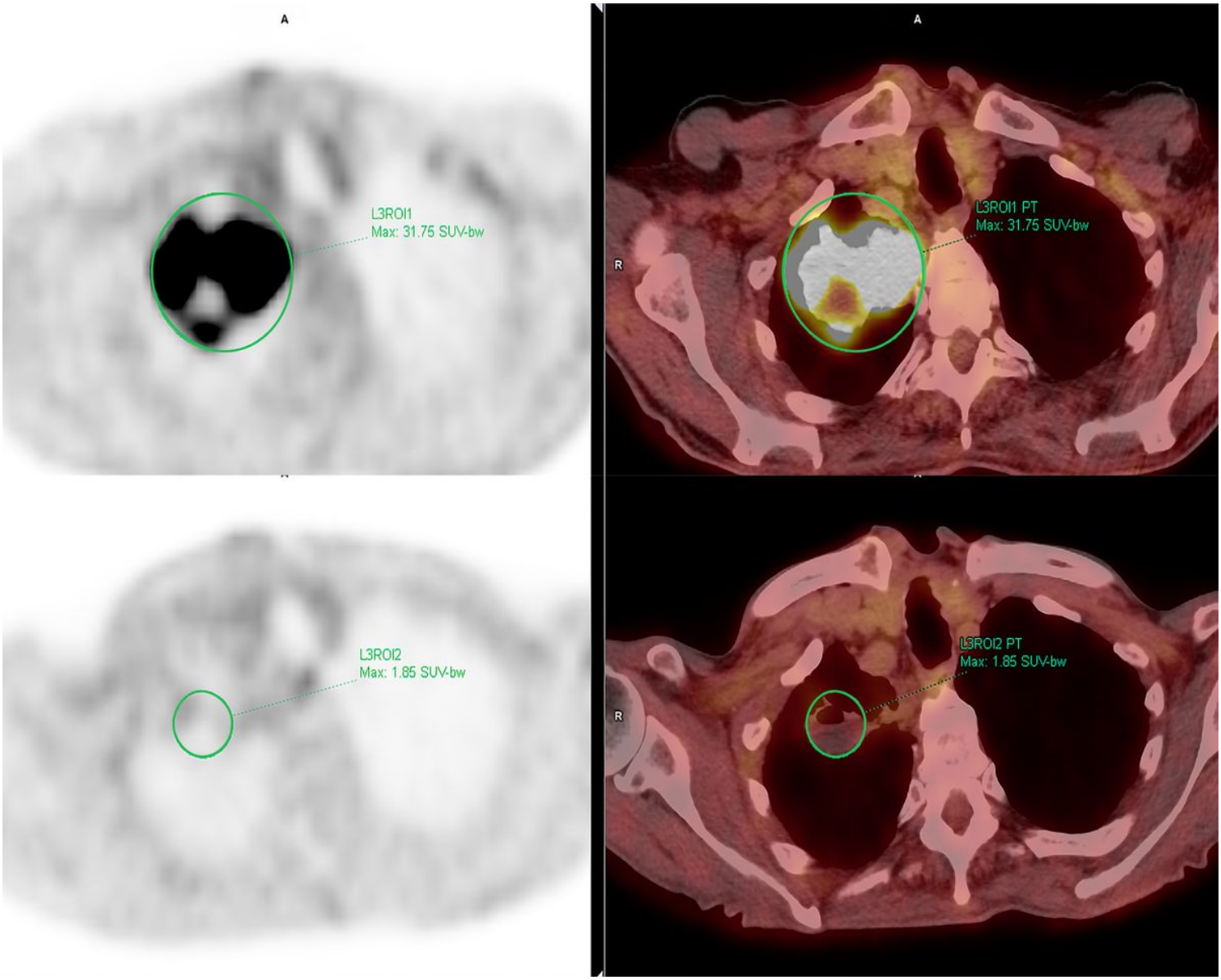

Figure 1

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.

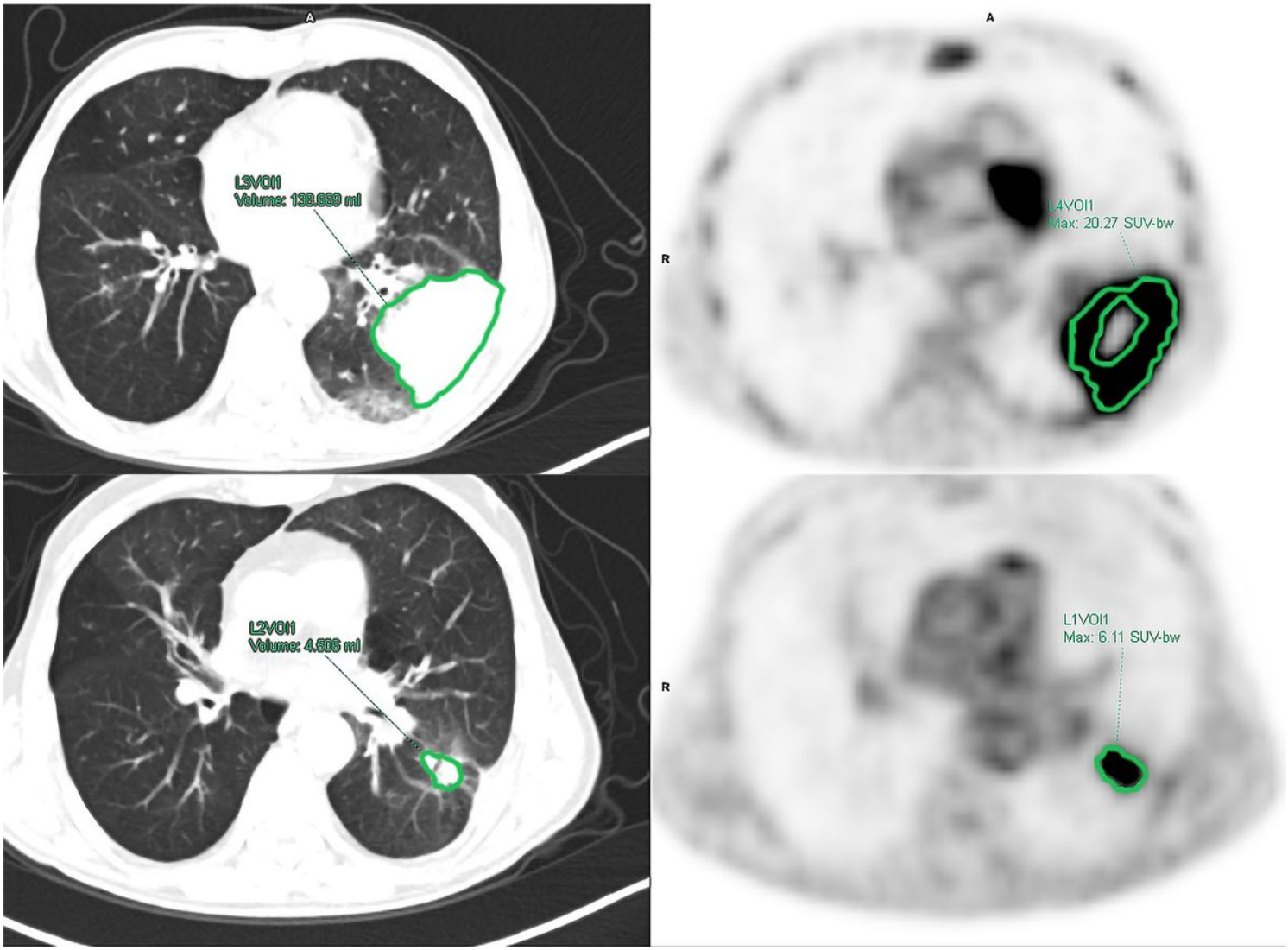

Figure 2

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, GTVPET-CT declines from 138.7 mL to 4.5 mL. This is considered a residual tumor.

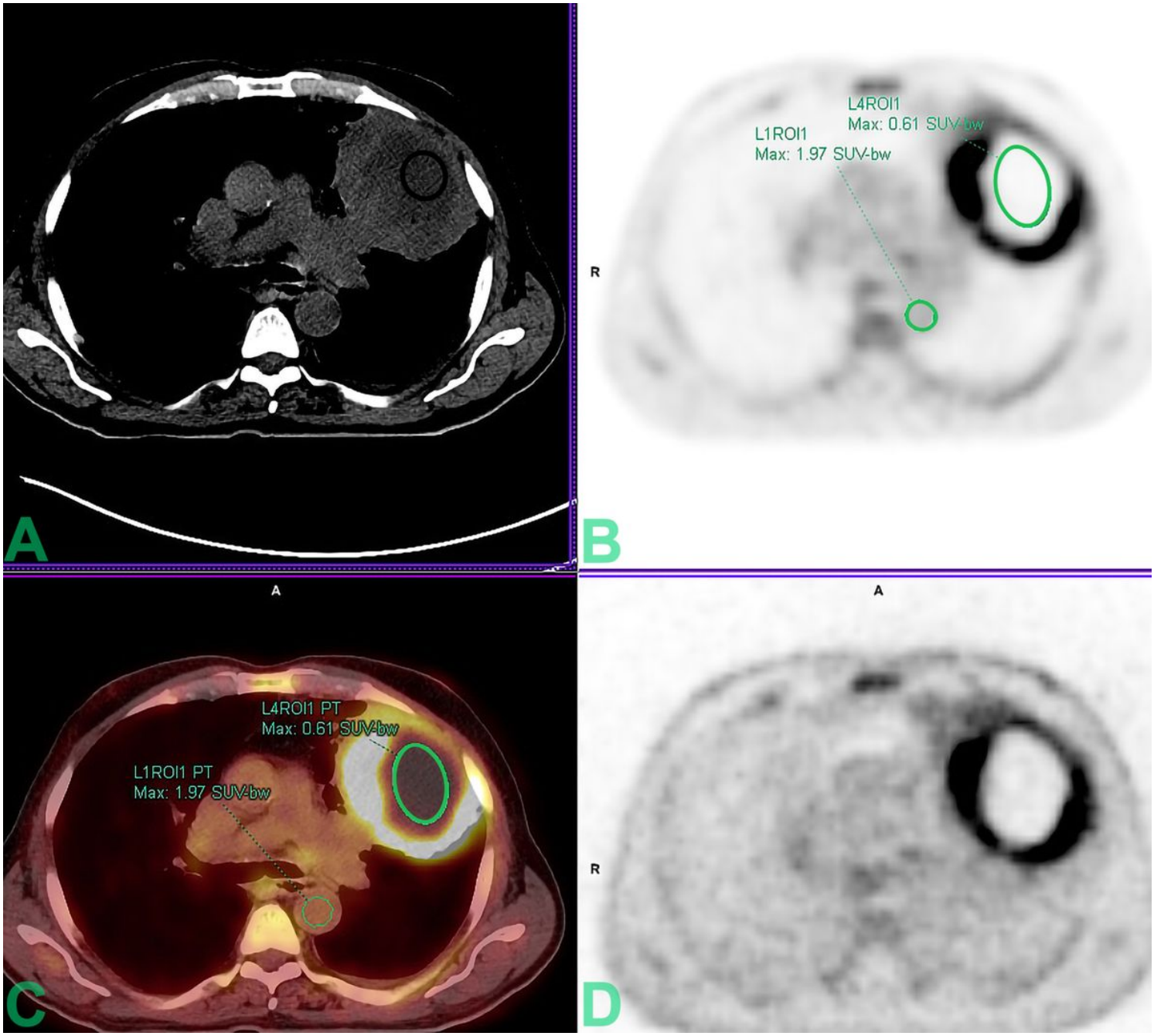

Figure 3

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 (PETNECROSIS).