Pre-Radiotherapy ^{18}F FDG PET/CT Predicts High-Risk Subvolumes for Residual Disease in Patients with Non-Small Cell Lung Cancer

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ABSTRACT

The appearance of residual disease in ^{18}F-FDG-PET/CT after radiotherapy (RT) in non-small cell lung cancer (NSCLC) is associated with worse survival. The aim of this study was to demonstrate the corresponding subvolume of tumours in pre-RT ^{18}F-FDG-PET/CT (PET1) in patients in whom residual tumour was seen in post-RT ^{18}F-FDG-PET/CT (PET2) after definitive RT/chemoradiotherapy (CRT). Patients with inoperable stage I-III NSCLC and who received chemoradiotherapy and/or radiotherapy alone and had residual tumour in PET2 were included. After matching the SUV threshold (70%, 80%, and 90%) delineated image seen in PET2 with PET1, we manually increased the tumour threshold of volume of interest (VOI) in PET1. We found which SUV threshold (70%, 80%, 90%) delineated VOI in PET2 corresponded to which tumour subvolume in PET1. Thirty patients were included in the analysis. The median subvolume threshold corresponding to a SUV threshold of 70% VOI in PET2 was 50% (range, 40-65%). The mean SUV subvolume threshold in PET1 corresponding to an 80% SUV threshold VOI in PET2 was 56.3±7.5% (range, 40-70%). The mean SUV subvolume threshold in PET1 corresponding to a 90% threshold VOI in PET2 was 64.5 ± 7.5% (range, 50-80%). Pre-RT ^{18}F-FDG-PET/CT can predict high-risk subvolumes for residual disease after radiotherapy. Threshold values of SUVmax 50%, 56.3%, and 64.5% corresponded to high risk areas for residual disease in pre-RT 18F FDG PET/CT.

Keywords: 18F FDG PET/CT, Lung cancer, Radiotherapy, Residual malignancy

INTRODUCTION

The established treatment method in patients with locally advanced stage non-small cell lung cancer (NSCLC) with no planned surgery and planned curative treatment is simultaneous chemoradiotherapy (CRT) and the local-regional recurrence rate is approximately 50%.[1] ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) provides important prognostic information in patients with NSCLC treated with chemoradiotherapy.[2-4] The observation of residual disease in ^{18}F-FDG-PET/CT after radiotherapy is associated with worse survival.[5] The survival of patients with NSCLC with metabolic complete response (MCR) has been shown to be better than in patients without MCR.[6-8] For this reason, it is important to identify patients at high risk of local failure because additional treatment may be of potential benefit for these patients.

Most local failure occurs within the RT target volume, suggesting insufficient RT dose.[9-11] Radiation pneumonia is a dose-limiting adverse effect of dose escalation. While keeping dose escalation, the target volume should be as small as possible in order to keep RT-related toxicity at a minimal level.[12]

For this purpose, it is important to determine the radio-resistant tumour subvolumes. In several studies, tumour subvolumes with a high 18F-FDG uptake on ^{18}F-FDG-PET/CT before RT have been shown to have a high risk of recurrence after RT.[5,13-15] The aim of this study was to demonstrate the corresponding tumour subvolume in pre-RT ^{18}F-FDG-PET/CT (PET1) in patients in whom a residual tumour was seen in post-RT ^{18}F-FDG-PET/CT (PET2) after definitive RT/chemoradiotherapy (CRT). Thus, subvolumes that have a high potential to remain after treatment can be predicted before treatment.

PATIENTS and METHODS

Patient Selection

We evaluated patients with lung cancer who were treated in our hospital between January 2016 and January 2019. Patients who were histopathologically diagnosed as having inoperable stage I-III NSCLC, without distant metastasis, who received CRT or RT, and who had residual tumour in PET2 were included in the study. All patients had PET1 and PET2 imaging.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (ref. no.40465587-050, 2019/54) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As this was a retrospective study where the data was de-identified, it was exempt by the institutional review board from the need for informed consent.

Exclusion criteria: Patients with small cell lung cancer (SCLC) were excluded. Patients who received additional therapy between RT and PET2 were excluded from the study. Patients in whom complete overlapping could not be performed due to the development of significant anatomic changes in the tumour/lung after treatment were excluded from the study. Optimal overlapping could not be performed in tumours including large necrosis and/or cavitation areas in PET1 because significant anatomic changes develop in these tumours after treatment and these cases were excluded from the study. Patients who had interrupted and incomplete treatment were excluded.

Evaluation of residual disease: Residual disease was accepted as when the SUVmax obtained from the volume of interest (VOI) drawn on the point demonstrating the most intense FDG uptake in PET2 was higher than the SUVmax of the aorta blood pool [SUV> SUV blood pool].[14,16]

^{18}F-FDG-PET procedures: 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 a FDG injection at an approximate dose of 3.7 MBq/kg. After a median 61 minutes (min-max 52-81 minutes), imaging was performed in the supine position with their 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.

PET/CT parameters: The longest dimension (Tsize) of the tumour in PET1 was measured. SUVmax was measured in PET1 and PET2. In addition, gross tumour volume (GTV-PET) was measured using the CT component of the ^{18}F-FDG-PET/CT in PET1 and PET2. SUV threshold (70%, 80%, and 90%) delineated VOI was used to measure the metabolic tumour volume (MTV) in PET2.

Image analyses: Siemens Healthineers Syngo, via a VB30 workstation, MM Oncology, post-processing Unit was used for the analyses. All analyses were performed together by a radiation oncologist (G.E.) with 10 years' experience and a nuclear medicine specialist (O.K.) with 9 years' experience.

PET1 and PET2 Overlapping: PET, PET/CT fusion, and CT images of PET1 and PET2 were opened on the same screen as the bottom row and top row. In PET2, we drew a SUV threshold (70%, 80%, and 90%) VOI of the tumour in PET and PET/CT fusion image. We checked the boundaries of VOI in transaxial-sagittal and coronal plane images, and made manual corrections according to their relationship with adjacent organs. In PET1, we drew a VOI according to the SUV threshold (0%) and again checked the boundaries of VOI in transaxial-sagittal and coronal correction. Then we

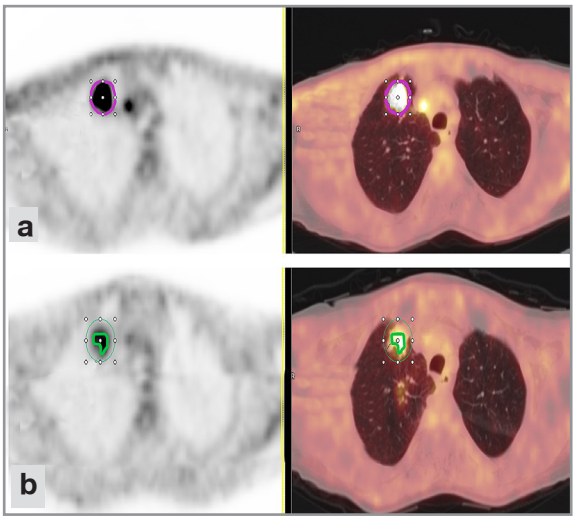

Figure 1. A 64-year-old male with right lung adenocarcinoma. **a)** Pre-treatment (PET1) PET and PET/CT fusion image. We drew the volume of interest (VOI) of the tumour such that the SUV threshold was "0". **b)** After treatment (PET2), PET and PET/CT image. We drew a VOI according to the SUV threshold of 70%. We automatically registered these images and manual corrections were made in case there was no complete overlapping. Then, we started to increase the PET1 VOI threshold.

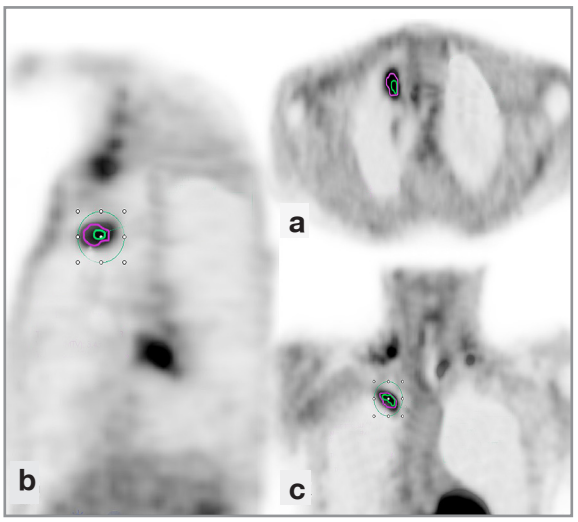

Figure 2. A 64-year-old male with right lung adenocarcinoma (The same patient with Figure 1) **a)** PET-registered transaxial image; while PET2 threshold was 70% (green), PET1 VOI (magenta) threshold can be maximum 40%. We cannot increase the PET1 threshold even more in order not to have PET2 VOI exceeding the PET1 VOI. While the PET1 threshold is 40% in the overlapped sagittal **b)** and coronal **c)** images, the VOIs do not exceed each other. If we increase the PET1 threshold further, we can see that it can exceed PET2 VOI, especially in the coronal image **(c)** (PET1 and PET2 VOIs have overlapping edges).

took the transaxial PET image of PET2 and registered it on the PET1 transaxial PET image. We also registered the CT image in the same way. If the overlapping of the PET and CT transaxial-sagittal and coronal images was incomplete, we made manual interventions and made corrections according to the large vessels, large bronchus, and bones.

Analysis: A VOI was drawn in PET2 in order that the tumour SUV threshold would be 70% and this image registered with PET1. Then, we started manually increasing the threshold of the VOI drawn on the tumour in PET1. We increased the threshold of VOI in PET1 until VOI edges intersected in at least one of the transaxial-sagittal and coronal plane images. When VOIs intersect on any plane, we stopped increasing the threshold of PET1 VOI. Hence, the corresponding threshold of VOI drawn in PET2 for SUV threshold 70% in PET1 was defined. In other words, we obtained the minimum subvolume in PET1 to cover the VOI drawn according to a SUV threshold of 70% in PET2 (Figures 1 and 2). We performed the same procedure with PET2 images with SUV thresholds of 80% and 90%, respectively.

Radiotherapy procedures and dose planning: All operations were performed using a Varian Trilogy IX linear accelerator (Varian Medical Systems). Intensity-modulated radiotherapy (IMRT, n= 18) was applied to 60% of patients and three-dimensional (3D) conformal radiotherapy (3DCRT, n= 12) was applied to 40% 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). In order 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. Considering the tumor movement, internal target volume (ITV) was created by adding internal margin (IM) to CTV. In the absence of a four-dimensional (4D-CT), we determined a 1 cm value of IM in all directions to encompass a full breathing cycle. Five millimeters was added to the ITV considering set-up errors to create a planning

Table 1. Patient characteristics

Parameters	n	(%)
Sex		
Male	29	(97)
Female	1	(3)
Histologic subtype		
Adenocarcinoma	11	(37)
Squamous cell carcinoma	19	(63)
Treatment		
Chemoradiotherapy	22	(73)
Only radiotherapy	8	(27)
Radiotherapy		
3DCRT	12	(40)
IMRT	18	(60)

Abbreviations: *3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy*

Table 2. Tumour characteristics

Parameters	Mean± SD/median (min-max)
Time between pre-RT PET/CT and RT start date (days)	14.73±6:35
Radiotherapy dose (Gy)	64 (60-72)
Pre-RT GTV-PET (cm^3)	51 (5-237)
Pre-RT SUVmax	18.5 (6.4-38.2)
Time between the end of RT and post-RT PET/CT (days)	96.5 (65-148)
Post-RT SUVmax	5.45 (2-13.4)
Post-RT GTV-PET (cm^3)	5.5 (1-30)

Abbreviations: *Pre-RT, before radiotherapy; GTV-PET, tumour volume calculated using CT component of the PET/CT image; Post-RT, after radiotherapy; SD, standard deviation*

target volume (PTV).[17] A median total of 64 Gy (60-72 Gy) RT was performed in patients with a median 2 Gy per fraction. Time between the end of RT and post-RT 18F FDGPET/CT was 96.5 days (65-148 days).

Statistical Analyses

Methods of descriptive statistics were used. The distribution of numerical parameters was determined using the Shapiro-Wilk normality test. Mean±standard deviation (SD) was used for parametric normally distributed parameters, and median [min-max] for non-normally distributed parameters. The mean-median threshold values of the subvolume in preRT corresponding to the SUV threshold VOI of the residual tumour in post-RT 18F FDG PET/CT was demonstrated using boxplot graphics. The distribution of patients according to SUV thresholds is demonstrated with a pie chart. The Statistical Package for the Social Sciences version 22 (SPSS, Inc., Chicago, IL) was used for all analyses.

RESULTS

Patient Characteristics:

The images of 38 patients who had PET1 and PET2 imaging and who had inoperable stage I-III NSCLC with residual tumour on PET2 were examined. Eight patients were excluded because the PET1 and PET2 images could not be registered due to the development of significant anatomic changes after treatment. We included 30 patients in the analysis (29 males, 1 female, mean age 67.9±10.99 year). Twenty-two patients received CRT, eight patients who could not receive CT, received RT alone. Patient and tumour characteristics are given in Tables 1 and 2.

Subvolumes in Pre-RT Corresponding to Post-RT Tumour:

The median SUV threshold of the tumour subvolumes in PET1 corresponding to the VOI we created according to a SUV 70% tumour threshold in PET2 was 50% (min-max: 40-65%) (95% CI: 49.2-55.1%). The mean SUV threshold of the tumour subvolumes in PET1 corresponding to the VOI of SUV 80% tumour threshold in PET2 was 56.3±7.5% (min-max: 40-70%) (95% CI: 53.5-59.1%). The mean SUV threshold of the tumour subvolumes in PET1 corresponding to the VOI of SUV 90% tumour threshold in PET2 was 64.5±7.5%d (min-max: 50-80%) (95% CI: 61.7-67.3%) (Figures 3 and 4).

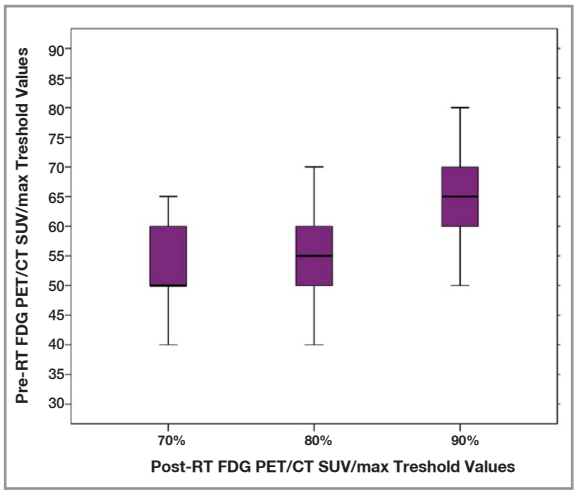

Figure 3. Boxplot graph showing the SUV threshold distributions of the subvolume that the VOIs we created based on tumour SUV thresholds of 70%, 80%, and 90% on PET2 correspond to PET1.

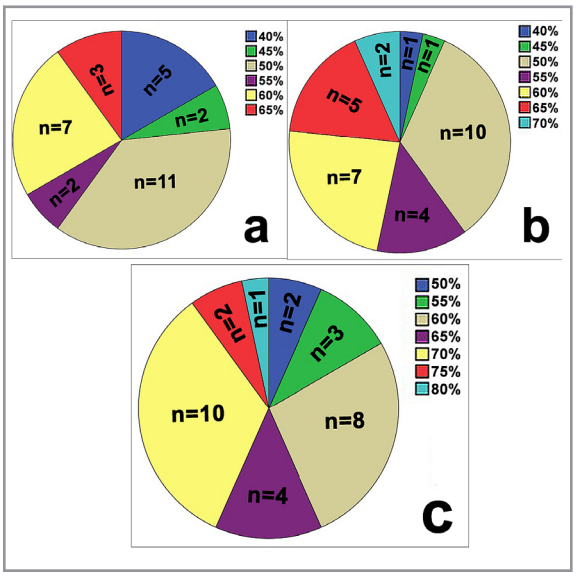

Figure 4 a-c. Pie chart showing the number of patients and SUVmax thresholds in PET1 corresponding the VOIs we created according to the tumour SUV thresholds of 70%, 80%, and 90% in PET2.

Metabolic Tumour Volumes Calculated for Three Different Thresholds in Residual Tumours:

MTV decreased as the SUV threshold of VOI was increased in PET2. For a 70% threshold, median 1.52 mL (range, 0.45-6.2 mL) (95% CI: 1.3-2.2). For an 80% threshold: median 0.625 mL (range, 0.15-2.6 mL) (95% CI: 0.6285-1.1015). For a 90% threshold: median 0.25 mL [range, 0.05-0.80 mL) (95% CI: 0.21-0.37)

Follow-up After Post-RT 18F FDG PET/CT:

Of the 30 patients we included in the study, 14 had only 1 post-RT ^{18}F-FDG-PET/CT scan. Sixteen patients had at least 2 Post-RT 2 ^{18}F-FDG-PET/CT scans [There were 5 patients with post-RT 2 ^{18}F-FDG-PET/CT scans, 7 patients with 3 post-RT ^{18}F-FDG-PET/CT scans and 4 patients with 4 post-RT ^{18}F-FDG-PET/CT scans]. The median time from post-RT 1st ^{18}F-FDG-PET/CT to the last ^{18}F-FDG-PET/CT of these 16 patients was 8.5 months (minimum: 4- maximum 30 months). In follow-up ^{18}F-FDG-PET/CT images; the residual tumor progressed in 11 patients, the residual tumor regressed in 3 patients, and the residual tumor remained stable in 2 patients.

DISCUSSION

It is important to detect high-risk subvolumes in RT prior to treatment in order to perform dose escalation in areas in which residual tumours will possibly remain after CRT/RT in NSCLC. In this present study, residual tumour was demonstrated to correspond to areas with high FDG uptake before treatment.

We registered residual tumour in PET2 with the tumour in PET1 and studied which threshold subvolume corresponded to the residual tumour. We did not include the entire volume showing FDG uptake of VOI in the residual tumour. We drew three VOIs according to the three different threshold values of the SUVmax of the residual tumour (70%, 80%, and 90%). Susharina et al.[15] suggested drawing a SUVmax threshold of 80% VOI to distinguish the residual tumour from adjacent tissues. In addition, Aerts et al.[5] showed that 70% and 80% threshold volumes in residual tumour matched highly with pre-RT gross tumour volume (94% and 96.5%, respectively), and when the threshold was taken as 90%, it coincided with 100% GTV. They also showed that 70-90% threshold subvolumes of residual tumour SUVmax corresponded to the pre-RT SUVmax 50% threshold subvolume. The

threshold was determined in this study according to these values, which were mostly studied in similar trials. Each was studied separately.

When we took the SUVmax threshold as 70% and 80% in PET2, we obtained similar results in the corresponding subvolume threshold values in PET1 (min-max: 40-65% and 40-70%, respectively). When we took the SUVmax threshold as 90%, the volume was found to be decreased significantly; however, the corresponding threshold value in PET1 was increased (mean 64.5±7.5%, min-max: 50-80%). In fact, the values we found for all three thresholds were consistent with the literature data. We found the median pre-RT threshold as 50% even though we took the post-RT threshold as 70%; this value was even increased for thresholds of 80% and 90%. Namely, the residual tumour observed in post-RT ^{18}F-FDG-PET/CT remains at least at the SUV threshold 50% subvolume in pre-RT 18F FDG PET/CT. We recommend that ≥SUVmax 50% threshold subvolume should be performed if dose escalation is planned. Calais et al.[18] recommended a 70% pre-RT tumour SUVmax threshold for dose escalation. Aerts et al.[14] stated that the residual tumour corresponded to a 50% SUVmax threshold subvolume in pre-RT ^{18}F-FDG-PET/CT. Abramyuk et al. found the highest overlap fraction of the residual tumour with pre-RT tumor GTV as 50% SUVmax threshold.[13] Susharina et al. suggested a ≥50% SUV threshold for dose escalation.[15] The findings of this study are consistent with the results of the few studies mentioned above.

In other studies, overlap fraction (OF) was calculated using software after the images were registered.[13-15] No software calculations for OF values were used in this present study. After registering the PET1 and PET2 images, we manually increased the PET1 threshold value and tried to achieve the minimum volume so as not to cut the PET2 VOI. We had to confirm that no intersection occurred in any of the contours in all three plane images. However, in tumours with heterogeneous FDG uptake, which were usually bulky tumours, the FDG distribution in VOI was heterogeneous even when the threshold was 70% and 80% in PET2, and we had difficulty in overlapping them with PET1 images. Accordingly, we had to remove some patients from the analysis. In fact, when we increased the threshold to 90% in PET2, the heterogeneity of FDG uptake was decreased because the volume was significantly decreased and it was easier to overlap them.

There are some limitations of this study; our main limitation is that the study is retrospective and single-centered. All patients could not receive CRT, and eight patients received RT alone. No histopathologic confirmation of residual disease was performed. Significant anatomic changes were noted after treatment in large tumours and in those with necrosis/cavitation and therefore the overlapping procedure was challenging in those cases. A great majority of patients with these characteristics could not be included in the analysis; therefore, the method used in this study is not easily applicable in patients with large tumours and tumours with cavitation/necrosis. The number of male and female patients was disproportionate. This was attributed to the single-centre design of the study and the low rate of cigarette smoking among women in this region. The frequency of lung cancer is thus very low in women compared with men in this region.

Conclusion

Pre-RT ^{18}F-FDG-PET/CT can predict high-risk subvolumes for residual disease. Residual disease observed after RT corresponds to subvolumes with high FDG uptake prior to treatment. SUV thresholds of 70%, 80%, and 90% in post-RT tumours correspond to pre-RT SUV threshold values of 50%, 56.3%, and 64.5%, respectively.

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