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Original Article

The Usefulness of Pre-Radiofrequency Ablation SUV_{max} in ^{18}F-FDG PET/CT to Predict the Risk of a Local Recurrence of Malignant Lung Tumors after Lung Radiofrequency Ablation

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The aim of the present study was to assess the diagnostic usefulness of Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in the prediction of local recurrence of malignant lung tumors by analyzing the pre-radiofrequency ablation (RFA) maximal standardized uptake value (SUV_{max}). We performed a historical cohort study of consecutive malignant lung tumors treated by RFA from January 2007 to May 2008 at Okayama University Hospital. We selected only lung tumors examined by PET/CT within 90 days before RFA and divided them (10 primary and 29 metastatic) into 3 groups according to their tertiles of SUV_{max}. We calculated recurrence odds ratios in the medium group and the high group compared to the low group using multivariate logistic analysis. After we examined the relationship between SUV_{max} and recurrence in a crude model, we adjusted for some factors. Tumors with higher SUV_{max} showed higher recurrence odds ratios (medium group; 1.84, high group; 4.14, respectively). The tumor size also increased the recurrence odds ratio (2.67); we thought this was mainly due to selection bias because we excluded tumors less than 10 mm in diameter. This study demonstrated the pre-RFA SUV_{max} in PET/CT may be a prognostic factor for local recurrence of malignant lung tumors.

Key words: fluorodeoxyglucose (FDG), positron emission tomography (PET), standardized uptake value (SUV), radiofrequency ablation (RFA), lung

Radiofrequency ablation (RFA) is a thermal therapy that results in coagulation tumor necrosis and can be used to treat malignant lung tumors. Preliminary studies of the use of RFA to treat lung tumors have shown promising results for initial local control in carefully selected patient populations [1-6].

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Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is a noninvasive, convenient, and feasible tool that is now integral to the management of various cancers. PET/CT is also a valuable technique for evaluating local control after radiotherapy or prognostic long-term outcome after surgery, chemotherapy or radiotherapy for several cancers [7-13]. This use is sometimes even more important than its ability to be used as an anatomic imaging modality to detect distant metastases and identify remote recurrent disease

[14].

The standardized uptake value (SUV) of FDG is the ratio of activity in tissue per unit volume to the activity in the injected dose per patient body weight, and it is widely used because of its simplicity. The SUV_{max} is the maximal value of the SUV in a tumor section.

It has been reported that the increased expression of glucose transporters in malignant cells may be associated with a higher metabolism and increased rates of glucose utilization in non-small cell lung cancer [15]; therefore, tumor proliferation, progression and metastasis are associated with the SUV [16, 17]. This indicates that the SUV_{max} might reflect the malignant potential in lung tumors.

The aim of this study was to assess the diagnostic utility of PET/CT for the prediction of local tumor recurrence by analyzing the pre-RFA SUV_{max} in primary lung cancers or metastatic malignant lung tumors.

Materials and Methods

The institutional review board of Okayama University Hospital approved the study and informed consent was obtained from all patients before they underwent lung RFA.

The method used for patient selection is shown in Fig. 1. This study included 251 consecutive lung tumors that were treated by lung RFA with multi-

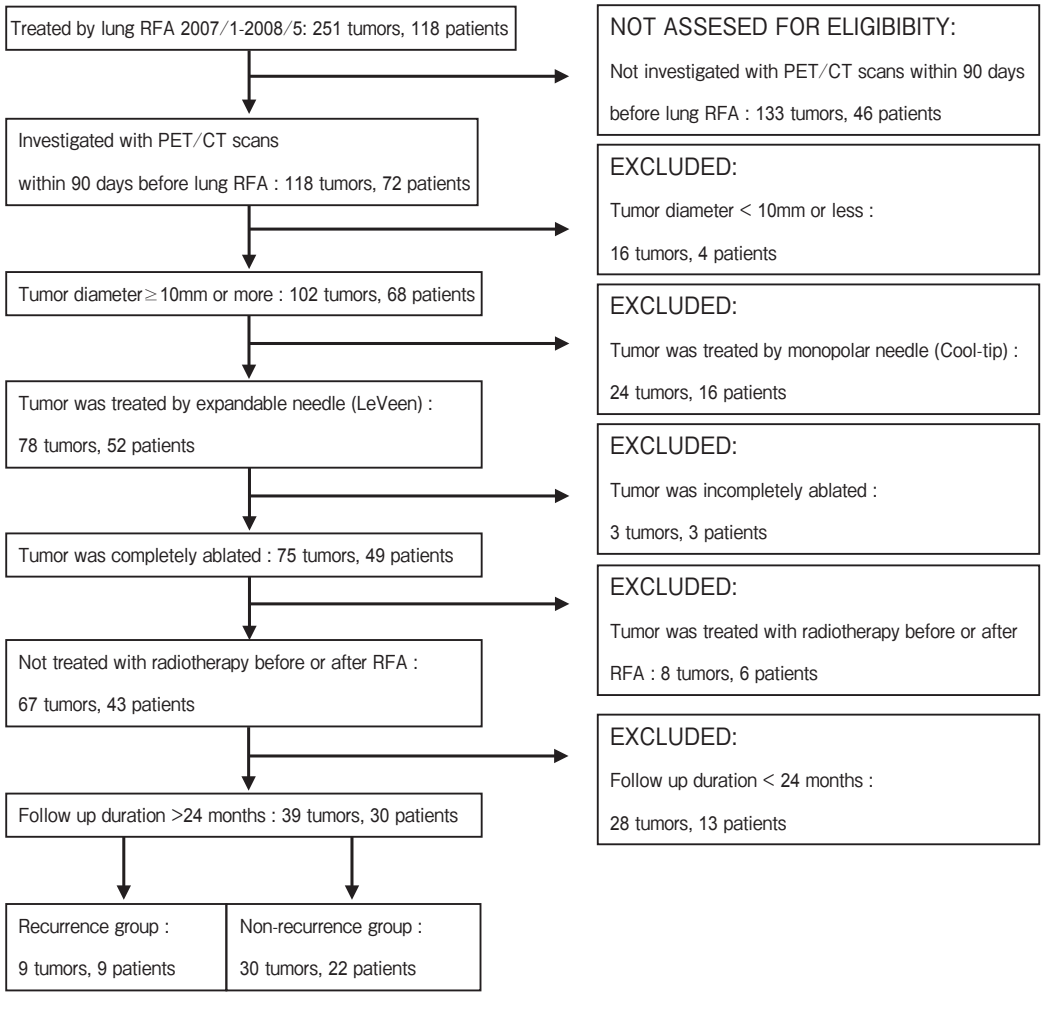

Fig. 1 A flowchart depicting the patient selection. ※Sometimes there were multiple nodules in the same patient.

tined expandable electrodes from January 2007 to May 2008 at Okayama University Hospital. We then selected only tumors that were investigated using PET/CT scans within 90 days before lung RFA. Whole-body pre-RFA PET/CT was performed as a routine examination for most of these patients. We excluded tumors less than 10 mm in diameter (their maximum diameters were measured on pulmonary window setting CT images). We also excluded tumors ablated with a single internally cooled electrode (Cool-tip; Covidien, Mansfield, MA, USA), ablated incompletely, or treated with radiotherapy before or after RFA. Some patients underwent systemic chemotherapy before lung RFA (14 patients, 20/39 tumors) or after lung RFA (11 patients, 15/39 tumors). We did not exclude these tumors treated by chemotherapy before and after RFA. No concurrent chemotherapy was administered within the treatment period of the lung RFA. For the recurrent group, we stopped following up patients when tumor recurrence was found. For the non-recurrent group, we excluded tumors for which the follow-up duration was less than 24 months; in order to distinguish non-recurrent tumors from recurrent tumors. The mean follow-up duration was 29.5 ± 4.1 mo (range, 24.1–36.7 mo) in the nonrecurrence group. Finally, the selected tumors consisted of 10 primary lung cancers and 29 metastatic malignant lung tumors (mean size, 16.4 mm). The patients consisted of 17 males and 12 females (mean age, 68.0 years).

Those tumors comprised 5 tumor types: primary lung cancer ($n = 10$), pulmonary metastases from lung cancer ($n = 3$), colorectal cancer ($n = 19$), hepatocellular carcinoma ($n = 5$), and leiomyosarcoma ($n = 2$). The characteristics of the patients are summarized in Table 1.

PET/CT was performed a mean of 19.3 ± 21.7 d (range 1–83 d) before lung RFA, using a PET/CT scanner (Biograph LSO/Sensation 16, Siemens, Munich, Germany). After fasting for at least 5 h, patients were injected with 3.7 MBq (megabecquerel) of ^{18}F-FDG *per kg* (kilogram) of body weight, and images were acquired 1.5 h later. On arrival at our hospital, their serum glucose was checked before ^{18}F-FDG injection, and was less than 200 mg/dl in all patients. Emission scanning was performed from the skull base to the proximal thigh, and afterward, the CT scanned voxel value was used for attenuation correction. Images were reconstructed using an iterative reconstruction algorithm (ordered-subset expectation maximization: OSEM). The technical parameters for the 16-detector row helical CT included a section thickness of 3 mm in the soft tissue window and 5 mm in the lung window, a pitch factor of 0.8 (1.5 mm × 16 collimation, mm/rotation = 19.2) and a gantry rotation speed of 0.5 s (Care dose 4D, 50 mAs).

Table 1 Characteristics of the patients

Gender (the number of patients)	
Male : Female	17 : 12
Age	
Mean:	68.0
Median:	69.0
Range:	51–87
Histology (the number of tumors)	
Primary Lung Neoplasm (10)	
Squamous	1
Adenocarcinoma	5
NSCLC[1], not specified	4
Recurrent Lung Neoplasm (3)	
Squamous	1
Adenocarcinoma	2
Metastatic (26)	
Colorectal cancer	19
Hepatocellular carcinoma	5
Leiomyosarcoma	2
Chemotherapy	
Yes	15
No	14

[1]NSCLC, Non-small cell lung cancer.

For the regions of interest (ROI), the images were transferred to the workstation (Fujin-Raijin, AZE Inc., Tokyo, Japan), and FDG-PET scans were analyzed by 2 experienced nuclear physicians who were blinded to the histopathological findings and clinical follow-up data. To evaluate the ^{18}F-FDG uptake, they drew ROI for tumors and measured the SUV_{max} in each ROI using the Fujin-Raijin software program.

During the follow-up, CT or PET/CT was performed approximately 1, 3, 6, 9, 12 and then every 6 months after lung RFA. Local control was evaluated with CT. We compared the tumor size and the geometry of the ablation zone with the previous CT images. Local tumor progression was considered to have occurred when the ablation zone was circumferentially enlarged compared to the previous CT images. The appearance of an irregular, scattered, nodular, or eccentric focus in the ablation zone on contrast-

enhanced CT was also considered to indicate local progression [4, 18].

We calculated the SUV_{max} and tumor size for each tumor. To assess to what extent the other most often-quoted prognostic factors have an effect on tumor recurrence, we added 6 other major tumor characteristics which might have affected the tumor recurrence, including: age, sex (male or female), chemotherapy (yes or no), primary or metastatic disease, the interval between PET/CT and RFA execution, and proximity (yes or no; whether or not a tumor was in contact with a large blood vessel or bronchus; if those tumors were contiguous with a vessel of diameter $\geq$ 3 mm or a bronchus with an inner diameter $\geq$ 2 mm, we considered the tumor to have proximity) to the statistical analyses.

Statistical analysis. We divided the tumors into 3 groups according to the tertile of the SUV_{max} value, a low group ($SUV_{max} \leq 2.54$), medium group ($2.54 < SUV_{max} \leq 4.61$) and a high group ($SUV_{max} \geq 4.61$) and performed a descriptive statistical analysis of the tumor characteristics. We calculated the odds ratios and their 95% confidence intervals for recurrence in the tumor group with high SUV_{max} values compared to the tumor group with low SUV_{max} values using multivariate logistic regression analysis. After we examined the relationship between SUV_{max} and recurrence in a crude model, we adjusted for sex and age (model 1), proximity (model 2), and, finally, tumor size (model 3). We also calculated the Spearman's correlation coefficient between the tumor size and SUV_{max}.

We considered a p-value < 0.05 (two-sided test) to be a statistically significant difference. All statistical analyses were performed by using the SPSS 17.0 for Windows software package (SPSS, Inc., Chicago, IL, USA).

Results

During the follow-up period, tumor recurrences were observed in 9 of 39 tumors (23.1%). Three recurrences occurred within the first 6 months, another 5 within the next 6 months, and 1 at 31 months after lung RFA.

Among the 3 tumor groups established according to the SUV_{max} values, only the tumor size was significantly different (Table 2).

Table 2 Comparison of descriptive statistics

Tumor characteristics		Low	Medium	High	*P*-value
		$SUV_{max} \leq 2.54$ (n = 13)	$2.54 < SUV_{max} \leq 4.61$ (n = 13)	$SUV_{max} > 4.61$ (n = 13)	
Chemotherapy	Yes	9	9	10	0.88
	No	4	4	3	
Tumor size (mm)	Mean ± SD	13.9 ± 6.1	16.9 ± 5.5	18.5 ± 7.7	0.049*
Primary or metastatic	Primary	4	3	3	0.88
	Metastatic	9	10	10	
PET/CT-RFA interval (days)	Mean ± SD	29.8 ± 29.4	16.8 ± 15.7	11.3 ± 13.5	0.41
Proximity	Yes	1	2	3	0.56
	No	12	11	10	
Recurrence	Yes	1	3	5	0.18
	No	12	10	8	

PET/CT, positron emission tomography/computed tomography; RFA, radiofrequency ablation; SD, standard deviation; SUV_{max}, maximal standardized uptake value.

P-values were calculated using the upper-sided Kruskal-Wallis test and $p < .05$ was considered to represent statistical significance, as indicated by*.

Adjusting for sex, age, proximity, and tumor size, we found that higher SUV_{max} was associated with higher odds ratios for recurrence (medium group: 1.84; high group: 4.14) compared with the low group (Table 3, model 3). Other factors that increased the odds ratios for recurrence were gender (being male; odds ratios=4.38) and tumor size (odds ratio = 2.67), although their 95% confidence intervals were quite wide. Regarding age and proximity, however, we found no clear association with the odds ratios for recurrence (odds ratios = 1.06, 0.84, respectively).

The Spearman's correlation coefficient between the tumor size and SUV_{max} was 0.456 ($p = 0.004$), indicating that the tumor size and SUV_{max} were in moderate correlation. Fig. 2A and 2B show a recurrence case, whereas Fig. 3A and 3B show a non-recurrence case.

Discussion

In many institutes, ^{18}F-FDG PET/CT has been used to assess the presence of whole body metastases before and after lung RFA. Although the SUV_{max} has been suggested to be helpful in predicting the risk of local recurrence after radiotherapy in lung cancer and other several cancers [7, 8], it has not been fully verified whether the pre-RFA SUV_{max} is capable of predicting the risk of local recurrence after lung RFA. This historical cohort study examined whether the pre-RFA SUV_{max} can be useful to predict the risk of local recurrence after lung RFA. We demonstrated that, in addition to its original diagnostic purpose, ^{18}F-FDG PET/CT could also provide a prognostic factor for local tumor recurrence after lung RFA.

Table 3 Odds ratios and 95% confidence intervals for recurrence

		Crude model		Model 1		Model 2		Model 3	
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
SUV_{max}	Low	1.00		1.00		1.00		1.00	
	Medium	3.60	(0.32–40.23)	2.22	(0.18–28.18)	2.25	(0.17–29.41)	1.84	(0.13–25.41)
	High	7.50	(0.73–76.77)	5.26	(0.45–62.12)	5.33	(0.43–65.62)	4.14	(0.31–54.44)
Sex	Male			4.35	(0.36–52.69)	4.33	(0.36–52.69)	4.38	(0.38–50.58)
Age	(1 year)			1.06	(0.94–1.21)	1.07	(0.94–1.21)	1.06	(0.94–1.20)
Proximity						0.94	(0.11–8.17)	0.84	(0.09–7.77)
Tumor size ≥15 mm								2.67	(0.39–18.54)

CI, confidence interval; OR, odds ratio; SUV_{max}, maximal standardized uptake value.

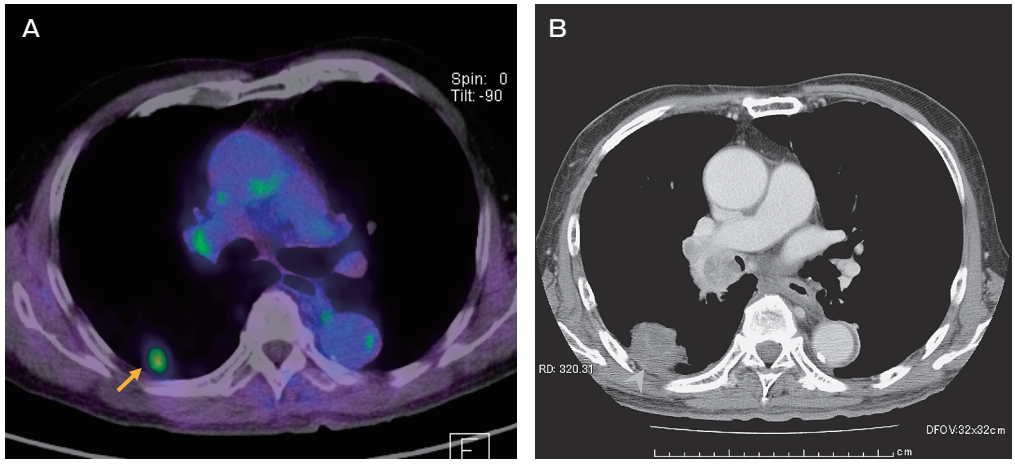

Fig. 2 **A**, Pre-RFA PET/CT of a 77-year-old male with local recurrence. The PET/CT showed primary lung cancer (adenocarcinoma) in the right lower lobe (oblique arrow). This tumor was treated by RFA. The SUV_{max} of the tumor was 3.89; **B**, The follow-up CT examination was performed 9 months after RFA. The contrast-enhanced CT showed local tumor progression. The ablation zone was circumferentially enlarged. Also, an irregular focus appeared in the ablation zone on contrast-enhanced CT (arrow head).

This result was in agreement with a similar study by Singnurkar *et al.* [20]. Our study was performed strictly using only subjects whose tumors were treated with a LeVeen Needle Electrode (Boston Scientific Japan Corp., Tokyo, Japan). We also reviewed the most effective prognostic factors of those currently reported and investigated their prognostic value in predicting local tumor recurrence.

Hiraki T. *et al.* previously reported that the overall local control rates of malignant primary lung cancer and pulmonary metastasis after lung RFA were 97%, 86%, 81%, and 76% at 6, 12, 18, and 24 months, respectively [19]. In other words 24% of malignant lung tumors recur within 2 years after RFA.

Although pre-RFA ^{18}F-FDG uptake in lung tumors might not be a direct indicator of residual micrometastases after RFA, we expected that ^{18}F-FDG uptake might be correlated with the malignant potential of tumor cells. The pre-RFA SUV_{max} in tumors reflects their glucose metabolism, which is facilitated in the most malignant tumors. This parameter may lead to a better understanding of the malignant potential of the tumor, and therefore, can be used to predict the risk of local tumor recurrence after lung RFA. Our results indicate that when the pre-RFA SUV_{max} is high, the risk of recurrence is high.

The other factors associated with higher odds ratios for recurrence were gender (being male; odds ratio = 4.38) and tumor size (odds ratio = 2.67). With regard to the tumor size, we calculated the odds ratio for the recurrence of tumors with a diameter $\geq$ 15 mm compared to tumors with a diameter $<$ 15 mm. Note that, however, there were many tumors from male patients in the recurrence group (8/9) and that there were only 2 tumors of $<$ 15 mm in the recurrence group (2/9) because tumors $<$ 10 mm in diameter were excluded from this study. Thus, the present findings should be carefully interpreted in light of a possible selection bias.

Various studies have shown that tumor size is a very important factor in predicting the local control of lung tumors after RFA [20–23]. Many studies have also reported that the SUV_{max} values of tumors are associated with their pathological diameter [24–26]. This may indicate that the SUV_{max} and the tumor size measured on CT will be correlated. A Spearman's test of our present data supported this hypothesis, and showed that the tumor size and SUV_{max} had a moderate correlation (correlation coefficient = 0.456, $p = 0.004$).

There were several limitations to this study. First, all of the cases of primary lung cancer were diagnosed on the basis of histological evidence. However, most of the cases of pulmonary metastases were diagnosed only by CT without histological evidence; they had surgically or biopsy-proven primary cancers, and the diagnoses of lung metastasis and local progressions after RFA were only based on radiological images. The second limitation is that the number of cases was

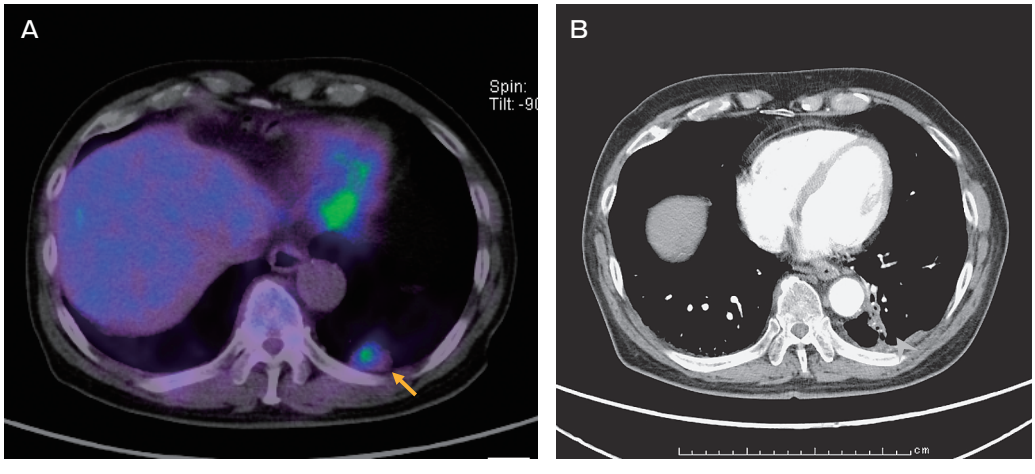

Fig. 3 **A**, Pre-RFA PET/CT of a 67-year-old male without local recurrence. The PET/CT showed a metastatic lesion in the left lung from primary rectal cancer (oblique arrow). The metastatic tumor was treated by RFA. The SUV_{max} in the tumor was 2.36; **B**, The follow-up CT examination was performed 25 months after RFA. The contrast-enhanced CT shows no irregular enhancement (arrow head).

small because we enforced strict selection criteria. We excluded tumors < 10 mm in diameter (their maximum diameters were measured on pulmonary window setting CT images) because we could not reliably measure the SUV_{max} in such small tumors. In addition, although we excluded some tumors that were treated with a mono-polar needle, ablated incompletely, or were also treated with radiotherapy before or after RFA, this selection was necessary to equalize the experimental conditions. If we included tumors that were ablated under different conditions, the biological behavior of these tumors might modify the study results in such a small population. In addition, the effects of radiotherapy would potentially make a significant impact on the local control of lung tumors. The third limitation is that ablation factors, such as the maximum power, the ablation time, and the number of overlapping ablations, were not evaluated in the investigation of risk factors for local tumor progression. Although our ablation algorithm varies according to tumor size (thus according to the array diameter of the electrodes), almost all tumors (38/39) were treated using the same ablation technique. Therefore, the ablation conditions for each tumor were similar. Another possible limitation is that the selected tumors included varied histological types in this study. However, Hiraki T. *et al.* reported that the tumor type *per se* did not significantly influence the local control [19]. We did not adjust any of the study data based on the differences between tumor types.

In conclusion, this study demonstrated that the SUV_{max} determined using PET/CT may be an effective new prognostic factor for tumor recurrence after lung RFA. We believe that ^{18}F-FDG PET can be performed as a pre-RFA risk evaluation for local tumor recurrence after RFA, rather than just for the detection of whole body metastasis.

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