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Original Article

The Maximum Standardized Uptake Value Is More Reliable Than Size Measurement in Early Follow-up to Evaluate Potential Pulmonary Malignancies Following Radiofrequency Ablation

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We retrospectively evaluated the accumulation of fluorodeoxy glucose (FDG) in pulmonary malignancies without local recurrence during 2-year follow-up on positron emission tomography (PET)/computed tomography (CT) after radiofrequency ablation (RFA). Thirty tumors in 25 patients were studied (10 non-small cell lung cancers; 20 pulmonary metastatic tumors). PET/CT was performed before RFA, 3 months after RFA, and 6 months after RFA. We assessed the FDG accumulation with the maximum standardized uptake value (SUVmax) compared with the diameters of the lesions. The SUVmax had a decreasing tendency in the first 6 months and, at 6 months post-ablation, FDG accumulation was less affected by inflammatory changes than at 3 months post-RFA. The diameter of the ablated lesion exceeded that of the initial tumor at 3 months post-RFA and shrank to pre-ablation dimensions by 6 months post-RFA. SUVmax was more reliable than the size measurements by CT in the first 6 months after RFA, and PET/CT at 6 months post-RFA may be more appropriate for the assessment of FDG accumulation than that at 3 months post-RFA.

Key words: fluorodeoxy glucose (FDG), positron emission tomography (PET), standardized uptake value (SUV), radiofrequency ablation (RFA), non-small cell lung cancer (NSCLC)

Radiofrequency ablation (RFA) has gained increasing acceptance as an intervention technique for the local control of non-small cell lung cancers (NSCLC) and pulmonary metastatic tumors [1–3], and the evaluation of ablated tumors has become more important in the follow-up period. However, the morphologic modality of computed tomography (CT) and magnetic resonance imaging (MRI) has not been sufficient for surveillance of post-RFA lung tumors because of peritumoral inflammation and bleeding, especially in the early period after RFA [4–6]. Fluorine-18-fluorodeoxyglucose positron emission tomography (F-18 FDG-PET) is now a standard nuclear imaging modality for staging and for follow-up after radiotherapy and chemotherapy in patients with pulmonary malignancy [7–11]. Several investigators have shown that F-18 FDG PET/CT is helpful in the evaluation of the therapeutic response after RFA for

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lung tumors and have discussed the timing of PET/CT after pulmonary RFA in retrospective studies [5, 12, 13]. In one preliminary study, F-18 FDG-PET at 2 months after RFA predicted regrowth [5]. However, another report has determined that the diagnostic accuracy of PET/CT in the first 3 months after RFA was not sufficient, suggesting that the appropriate follow-up initiation time point was at least 3 months after RFA [12]. We evaluated F-18 FDG accumulation at pre-RFA, 3 months post-RFA, and 6 months post-RFA with semiquantitative analyses of the maximum standardized uptake value (SUVmax) and the retention index (RI) of SUVmax (RI-SUVmax) and compared these evaluations with evaluation of the lesion size. The aims of this retrospective study were to investigate whether size measurement by CT or SUVmax measurement by F-18 FDG PET/CT is more reliable in the early (first 6 months) follow-up after RFA and to determine which time point is more appropriate, 3 months or 6 months post-RFA.

Materials and Methods

Patient population. This is a retrospective review of the prospective electronic database of the radiology department of a single center (Okayama University Hospital). Patients who underwent LeVeen needle pulmonary RFA between January 2007 and June 2008 (196 tumors in 112 patients; 36 NSCLC, 160 pulmonary metastatic tumors). Only patients who underwent both CT with intravenous administration of contrast medium and F-18 FDG PET/CT studies at pre-RFA and 3 months and 6 months post-RFA were included. Patients were excluded if they had local recurrence or had received adjuvant chemotherapy during the 2 years following RFA. There were 30 tumors that met these conditions, 10 NSCLC and 20 pulmonary metastatic tumors, in 16 men and 9 women aged 64.89 ± 13.79 years (mean $\pm$ SD), range, 51 to 94 years.

This retrospective study was approved by the ethical committee of Okayama University Graduate School of Medicine, which waived informed consent from the patients.

Approval from the institutional review board and informed consent from the patients had previously been obtained to perform RFA.

RFA technique. The RFA procedure was always performed percutaneously under CT fluoroscopy (Asteion; Toshiba, Tokyo, Japan). The electrodes used included a multitined expandable electrode with a 2-cm ($n = 10$), 3-cm ($n = 14$), 3.5-cm ($n = 4$), and 4-cm ($n = 2$) diameter array (LeVeen; Boston Scientific, Natick, MA, USA). The electrode was introduced into the tumor and was connected to an RF generator (RF2000 or 3000 generator, Boston Scientific, for multitined expandable electrodes). The numbers of ablations performed per lesion were 4.20 ± 1.55 for NSCLC and 3.95 ± 1.15 for metastatic tumors; the difference between them was not statistically significant ($p = 0.5916$). The ablation durations were 30.61 ± 10.93 min for NSCLC and 24.48 ± 13.29 min for metastatic tumors; again, no significant difference was identified between them ($p = 0.2184$).

Post-RFA monitoring. Post-RFA monitoring was performed by chest CT with intravenous contrast (Iopamidol, Iopamiron300; Bayer HealthCare) and PET/CT examinations on the same day, on both the first (median 95 days) and second monitoring visits (median 187 days). When evaluated for the presence of local tumor recurrence after RFA by 2-year clinical follow-up including contrast-enhanced CT, all patients included in the present study were without local recurrence. The effectiveness of RFA was assessed on the basis of the CT images as follows: when the entire ablation zone was not contrast-enhanced or when the ablation zone had contrast enhancement, but it was peripheral, concentric, symmetric, and uniform, with smooth inner margins, the tumor was considered to be completely treated, whereas an irregular, scattered, nodular, or eccentric enhancement in the ablation zone or circumferential tumor enlargement with contrast enhancement was considered to indicate local tumor progression. These radiological assessments were carried out by the consensus of 2 radiologists unaware of the clinical results.

F-18 FDG PET/CT. PET image acquisition started 90 min after injection of FDG with the patient in a relaxed supine position using an integrated PET/CT scanner (Biograph LS/Sensation16, Siemens, Munchen, Germany) at Okayama Diagnostic Imaging Center. Patients had been instructed to fast for at least 5 h, after which blood glucose levels were determined to ensure a level of < 140 mg/dL. Patients then received an intravenous injection of 3.7 MBq/kg (1.0×10^{-4} Ci/kg) body weight FDG. The patients were

asked to remain resting on a reclining chair to minimize FDG consumption by the muscles just before scans. First, a total-body low-dose CT scan for calculation of attenuation correction was performed, using a standardized protocol involving 140 kV, 12 to 14 mAs, a tube-rotation time of 0.5 s per rotation, a pitch of 0.8, a section thickness of 3 mm, and scan field from head up to the mid-thigh level (consisting of 7–8 bed positions with 2.4 min per table position). The PET images were reconstructed with an ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm. Integrated, coregistered PET/CT images were obtained using a workstation (PET Viewer, AZE), which enabled image fusion and analysis.

Image data analysis. Two nuclear physicians unaware of the chest CT results interpreted all F-18 FDG PET/CT findings by consensus. For semiquantitative analyses of FDG uptakes, the SUV was adopted. SUVs were calculated using lean body mass as follows: SUV = radioactivity in regions of interest (ROI) (Bq/mL) × lean body mass (kg)/injected radioactivity (Bq). Circular ROIs were drawn to encompass the entire tumor using the PET/CT image. To minimize partial-volume effects, the SUVmax values within ROIs were used. The SUVmax was obtained before RFA (SUV1), 3 months after RFA (SUV2), and 6 months after RFA (SUV3) for all pulmonary tumors, NSCLC and pulmonary metastatic tumors. Furthermore, we calculated RI-SUVmax from the SUVmax (3 or 6 months post-RFA) according to the following formula: RI-SUVmax (%) = (SUVmax [3 or 6 months post-RFA] − baseline SUVmax [pre-RFA]) × 100/baseline SUVmax (pre-RFA).

On chest CT images, the long-axis diameters of 26 target lesions (lesions ≥ 10 mm) were calculated. At 3 and 6 months after RFA, the response to ablation was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria [14]. According to RECIST, "complete response" (CR) is defined as tumor disappearance or scarring, "partial response" (PR) as a decrease of more than 30% in maximum tumor diameter, "progressive disease" (PD) as more than a 20% increase in maximum tumor diameter and 5-mm absolute increase, and "stable disease" (SD) as a decrease of no more than 30% or an increase of no more than 20% in tumor diameter.

Statistical analysis. Wilcoxon signed-rank U test or Student's *t* test was used to determine the significance of differences in SUVmax and RI-SUVmax among all of the study groups. Student's *t* test or the Mann-Whitney U test was used to determine the significance of differences between CT-defined PD and SD groups in SUVmax at 3 and 6 months after RFA and the percentage changes in CT measurements at 3 and 6 months after RFA relative to the size before RFA. All statistical analysis was performed using the Statview 5.0 (SAS institute Inc., Berkeley, CA, USA). Probability values < 0.05 were taken to indicate significant differences.

Results

Characteristics of Patients and Pulmonary tumors. The study included 9 patients (5 men and 4 women, mean age 71.44 ± 7.72 years) with 10 solitary NSCLCs and 16 patients (8 men and 8 women, mean age 67.06 ± 9.82 years) with 20 pulmonary metastatic tumors. Histopathologically, there were 8 adenocarcinomas and 2 squamous cell carcinomas in the patients with NSCLC. The pulmonary metastatic tumors included 13 from colorectal cancer, 2 from hepatocellular carcinoma, 2 from renal cell carcinoma, 2 from esophageal cancer, and 1 from oropharyngeal cancer (Table 1). Eleven nodules were assessed as PD and 15 nodules were assessed as SD at 3 months post-RFA on RECIST. Six nodules were assessed as PD and 20 nodules were assessed as SD at 6 months post-RFA on RECIST.

Maximum standardized uptake values and retention index of SUVmax. Table 2 shows SUVmax values at each time point for all study groups. The mean and median SUVmax values were 4.6 and 3.98 (range 1.18 to 11.2) for SUV1, 4.29 and 3.9 (range 1.1 to 10.6) for SUV2, and 2.95 and 1.9 (range 0.83 to 8.09) for SUV3 in all pulmonary tumors (Fig. 1). The mean and median SUVmax values were 4.4 and 4.32 (range 1.18 to 10.3) for SUV1, 4.34 and 3.8 (range 1.39 to 8.03) for SUV2, and 2.87 and 2.5 (range 0.9 to 6.32) for SUV3 in NSCLC. The mean and median SUVmax values were 4.70 and 3.65 (range 1.25 to 11.2) for SUV1, 4.21 and 3.9 (range 1.1 to 10.6) for SUV2, and 2.99 and 1.9 (range 0.83 to 8.09) for SUV3 in the pulmonary metastatic tumors.

The SUV1 was significantly higher than SUV3 in

Table 1 Characteristics of solitary non-small cell lung cancer (NSCLC) and pulmonary metastatic tumor

NSCLC		
10 nodules in 9 patients (5 men and 4 women; age, 71.44 ± 7.72 years; range 54–78 years)		
	No of lesions	Size (mm)
Adenocarcinoma	8	15.4
Squamous cell carcinoma	2	7.5
Clinical Stage		
IA (T1N0M0)	7	14.0
IB (T2N0M0)	3	11.6
Size of nodules: 20.90 ± 11.87 mm (mean ± SD), range 6.0–42.0 mm		
Pulmonary metastatic tumors		
20 nodules in 16 patients (8 men and 8 women; age, 67.06 ± 9.82 years; range 51–94 years)		
	No of lesions	Size (mm)
Colorectal cancer	13	9.0
Hepatocellular carcinoma	2	11.5
Renal cell carcinoma	2	17.0
Esophageal cancer	2	9.5
Oropharyngeal cancer	1	20.0
Size of nodules: 11.15 ± 4.44 mm (mean ± SD), range 5.0–30.0 mm		

SD, standard deviation.

Table 2 Results of SUVmax and tumor size at each time point in each groups

	pre-RFA	3 mo after RFA	6 mo after RFA
All pulmonary tumors (n = 30)	4.60 ± 2.65*	4.29 ± 2.54†	2.95 ± 2.07
Non-small cell lung cancers (n = 10)	4.40 ± 2.56	4.34 ± 2.20	2.87 ± 1.68
Metastatic pulmonary tumors (n = 20)	4.70 ± 2.75*	4.21 ± 2.78†	2.99 ± 2.28
Tumors size of all pulmonary tumors (mm)	11.5 ± 1.62‡	19.0 ± 2.70	15.5 ± 1.73

SUV, standardized uptake value.
The data represent mean ± standard devision.
*$p<0.05$ versus 6 months after RFA: †$p<0.05$ versus 6 months after RFA; ‡$p<0.05$ versus 3 months after RFA

all pulmonary tumors ($p = 0.0157$) and in the pulmonary metastatic tumors ($p = 0.032$). The SUV2 was significantly higher than SUV3 in all pulmonary tumors ($p = 0.021$) and in the pulmonary metastatic tumors ($p = 0.022$). No significant difference was identified between SUV1 and SUV2 in all pulmonary tumors ($p = 0.5885$) and the pulmonary metastatic tumors ($p = 0.6211$). No significant difference was identified between SUV1 and SUV2 ($p = 0.9587$), between SUV1 and SUV3 ($p = 0.1327$), or between SUV2 and SUV3 ($p = 0.1109$) in NSCLC.

Median RI-SUVmax were −3.4% (range −81.91 to 272.03%) for those at 3 months post-RFA, and −32.9% (range −87.61 to 160.99%) for those at 6 months post-RFA. The RI-SUVmax was significantly lower at 6 months post-RFA than at 3 months post-RFA ($p = 0.0329$).

The SUVmax values at 3 months post-RFA were 4.16 ± 2.28 in the PD group and 4.18 ± 2.85 in the SD group (Table 3). No significant difference was identified in the SUVmax between the PD and SD groups ($p = 0.983$). The SUVmax values at 6 months post-RFA were 3.13 ± 2.16 in the PD group and 2.80 ± 2.12 in the SD group (Table 3). No significant difference was identified in the SUVmax between the PD and SD groups ($p = 0.7396$).

Lesion size over time after pulmonary RFA. The long-axis diameters of all pulmonary tumors

ranged from 5 to 42 mm with a mean of 11.4 and a median of 11.5 mm at pre-RFA. The long-axis lesion diameters were 20.9 ± 11.87 mm in NSCLC and 11.15 ± 4.44 mm in metastatic tumors at pre-RFA. A significant difference was identified in the size of pulmonary tumors at pre-RFA between NSCLC and metastatic tumors ($p = 0.0449$). The long-axis diameter of the pulmonary lesions ranged from 7 to 73 mm with a mean of 24.13 mm and a median of 19 mm at 3 months post-RFA, and from 5 to 52 mm with a mean of 17.96 mm and a median of 15.5 mm at 6 months post-RFA (Fig. 2). A significant difference was found between pre-RFA and 3 months post-RFA in the long-axis diameter of pulmonary lesions ($p = 0.001$). No significant difference in long-axis lesion diameter was identified between pre-RFA and 6 months post-RFA ($p = 0.1376$), or between 3 month- and 6 months post-RFA ($p = 0.0593$). The median values of the percentage changes in CT measurements at 3 months post-RFA were 133.0% (range 21.4 to 275.0%) in the PD group and 13.0% (range 0 to 57.0%) in the SD group

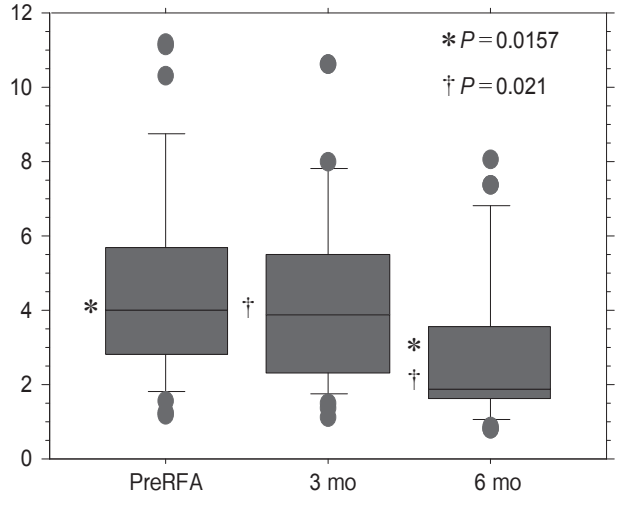

Fig. 1 Change of SUVmax over time after radiofrequency ablation. The graph shows significant differences for the median SUVmax between pre-RFA and 6 months after RFA ($p = 0.0157$), and between 3 month- and 6 month-after RFA ($p = 0.021$) in all tumors. However, no significant differences were identified for the median SUVmax between pre-RFA and 3 month-after RFA in all tumors.

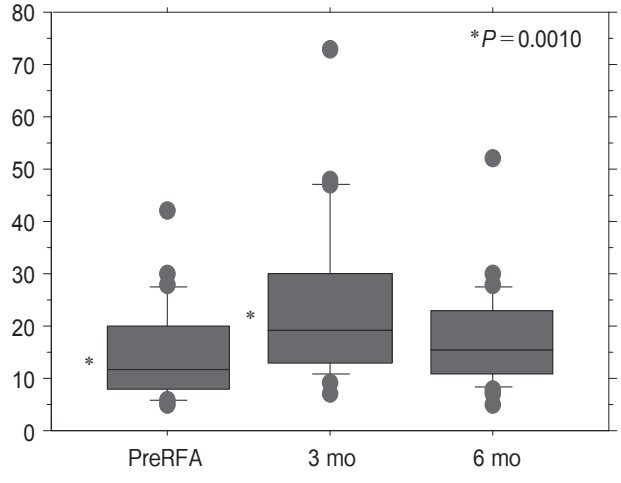

Fig. 2 Change of mean lesion size over time after radiofrequency ablation. The graph demonstrates that the size of pulmonary tumor at 3 month-after ablation was significantly larger than pre-RFA ($p = 0.001$). There were no significant differences in size between pre-RFA and 6 month-after RFA, and the change between 3 month- and 6 month-after RFA was not statistically significant.

Table 3 Summary of data by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

	PD group	SD group
No. of tumors		
3 mo after RFA	11	15
6 mo after RFA	6	20
SUVmax (mean ± SD)		
3 mo after RFA	4.16 ± 2.28	4.18 ± 2.85
6 mo after RFA	3.13 ± 2.16	2.80 ± 2.12
Percent reduction in size (median ± SEM)		
3 mo after RFA	133.0 ± 24.22%*	13.0 ± 3.94%*
6 mo after RFA	138.2 ± 16.20%*	0.0 ± 3.188%*

SUV, standardized uptake value; PD, progressive disease; SD, stable disease.
*$p < 0.05$ versus SUVmax in CT-defined PD and SD groups (Mann-Whiteny U test).

(Table 3). The median values of the percentage changes in CT measurements varied significantly between the PD and SD groups ($p < 0.0001$). The median values of the percentage changes in CT measurements at 6 months after RFA were 138.2% (range 55.6 to 157.1%) in the PD group and 0.0% (range −28.6 to 17.7%) in the SD group (Table 3). The median values of the percentage changes in CT measurements differed significantly between the PD and SD groups ($p = 0.0002$). Fig. 3 shows the CT images of a pulmonary metastatic tumor from rectal carcinoma during the 2-year follow-up after RFA.

Discussion

The present study assessed the accumulation of F-18 FDG in pulmonary lesions with semiquantitative analyses on PET/CT at 3 and 6 months after patients underwent RFA with a LeVeen needle. We found a decreasing tendency of FDG accumulation at the site

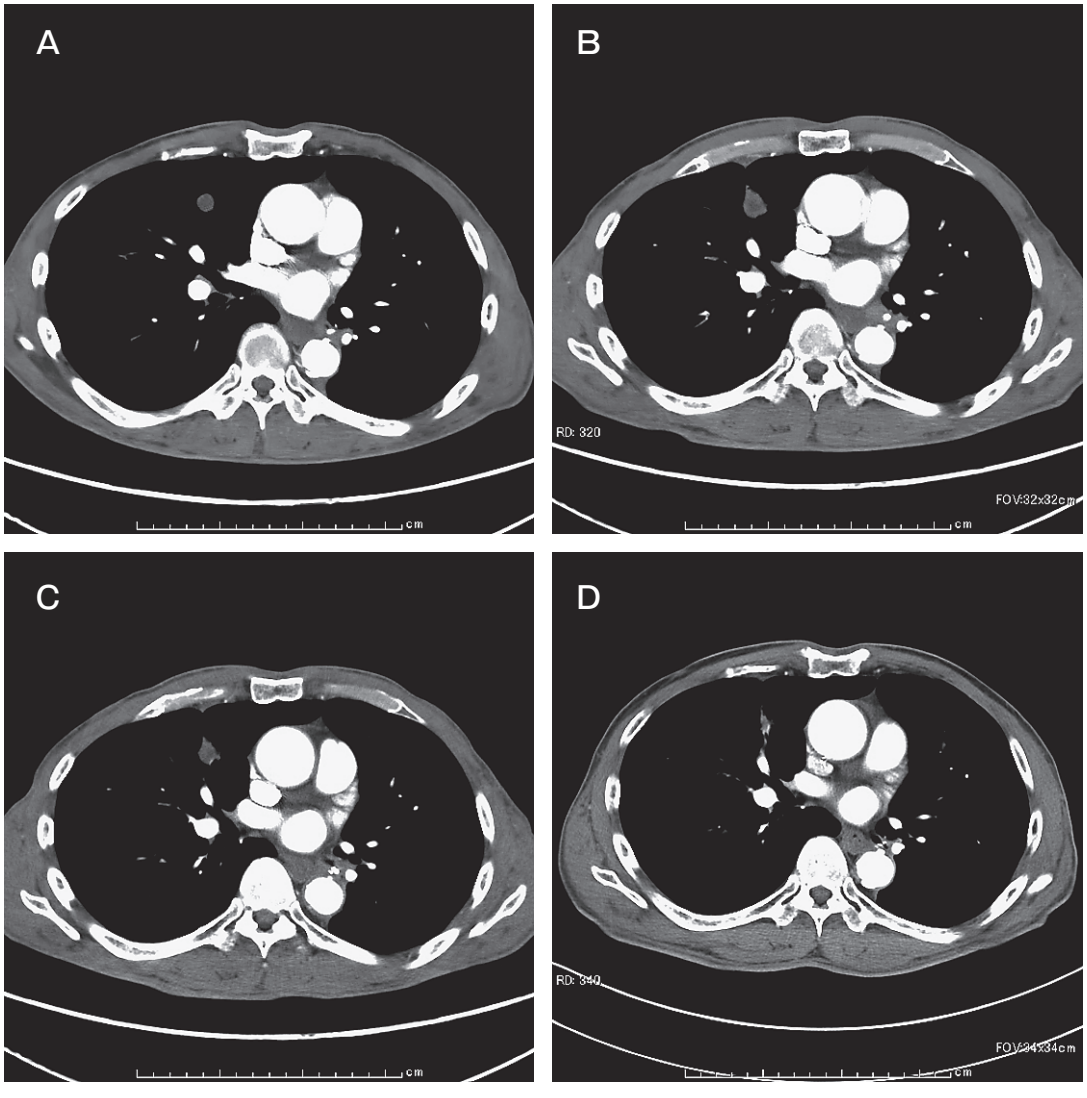

Fig. 3 CT images after pulmonary RFA in patients with metastatic tumor from rectal carcinoma. **A**, Pre-RFA CT of 62-year-old male with pulmonary metastatic tumor in the right upper lobe; **B**, **C**, **D** The follow-up CT examination showed the dimension of tumor had enlarged at 3 months after RFA(B). The dimension of tumor had gradually shrunk during the first 24 months after RFA. At 6 month- and 24 month-after ablation, there was the vessels enhancement at the peripheral of the ablated lesion; however CT showed no irregular enhancement within the ablated lesions (C, D). There was no tumor enlargement with contrast enhancement at each time points.

of pulmonary lesions in first 6 months. FDG accumulation was less affected by inflammatory changes at 6 months than at 3 months after RFA. We also analyzed the size change of the ablated lesion on CT and found that the diameter of the ablated lesion exceeded that of the initial tumor at the first 3 months and then shrank to pre-ablation dimensions, also indicating that PET/CT study at 6 months post-RFA may be more appropriate for the assessment of FDG accumulation in pulmonary lesions than PET/CT study at 3 months post-RFA.

In the present study, we demonstrated that there is a decreasing tendency of FDG accumulation in pulmonary tumors within the first 6 months after RFA and that median SUVmax at pre-RFA was significantly higher than that at 6 months post-RFA in pulmonary tumors without tumor regrowth. There was no significant difference between the median SUVmax at pre-RFA and that at 3 months post-RFA. Moreover, we demonstrated that the RI-SUVmax at 6 months post-ablation was significantly lower than at 3 months post-ablation. Higaki *et al.* reported that the diagnostic accuracy of PET/CT within 3 months after RFA was not sufficient, owing to the marked inflammatory change following ablation [12]. These findings suggest that 6 months after LeVeen needle pulmonary RFA is a more appropriate follow-up initiation time point compared with 3 months post-ablation.

Okuma *et al.* reported that tumor regrowth, as demonstrated by CT at 6 or more months after LeVeen needle pulmonary RFA, could be predicted earlier with SUVmean and RI-SUVmean on FDG-PET at 2 months after ablation compared with CT evaluation [5]. The discrepancy of these findings with our results may be attributed to differences in study design. There were differences in choice between SUVmax and SUVmean for semiquantitative analysis of FDG uptakes. In the studies for FDG uptake with SUV analyses, SUVmax is generally used rather than SUVmean because it is suggested that SUVmax is less dependent on the placement and drawing of the ROIs [15]. Moreover, SUVmean is proposed to be less variable because its reproducibility is worse than that of SUVmax and SUVmean is subject to operator bias [16].

In the present study, the SUV1 and the SUV2 were significantly higher than SUV3 in metastatic tumors. However, no significant difference was identified among time points in NSCLC. The mean size of the pulmonary lesion at pre-RFA was significantly larger in NSCLC than in metastatic tumors. No significant differences were identified between NSCLC and metastatic tumors in the numbers of ablations and ablation time; however, the mean number of ablations was larger and the ablation duration longer in NSCLC than in metastatic tumors. We hypothesized that, in the present study, RFA procedures for the NSCLC would need more ablations and longer ablation times due to the larger size of NSCLC than metastatic tumors. These factors would prolong the inflammatory changes following ablation and increase the FDG uptake in pulmonary lesions of NSCLC. The number of lesions in NSCLC was smaller, and that might have had the potential to erase the differences in SUVmax among the different time points.

Another finding of this study was that the size of pulmonary tumors at 3 months after ablation was significantly larger than that at pre-RFA, and that the mean and median sizes of pulmonary tumors at 6 months post-ablation were smaller than those at 3 months but still larger than those before RFA. Moreover, we did not identify any significant difference between the CT-defined PD and SD groups in the SUVmax at either 3 and 6 months post-RFA. Okuma *et al.* reported that LeVeen needle-ablated lesions appeared larger on CT performed immediately after ablation because of the surrounding parenchymal edema, inflammation, and hemorrhage caused by RFA thermal damage [5]. Steinke *et al.* demonstrated that lesions ablated with multitined expandable electrodes are typically expected to be bigger at 1 week after RFA than at baseline, and then to slowly decrease in size. At 3 months after RFA, the lesions may still be larger than at baseline, and at 6 months after RFA, they may be the same size or smaller than before RFA [17]. These findings suggest that size comparison of pulmonary tumors after RFA with multitined expandable electrodes is not useful for prediction of local recurrences in the early 6 months, and that the SUVmax values have the potential to more precisely reflect the condition in the ablated region compared with size comparisons, even at 3 months post-RFA.

Our study has several limitations. First, the sample sizes were relatively small for the primary lung cancers and the pulmonary metastatic tumors. Second, our study design was retrospective. Third,

there was no histopathological confirmation after RFA. Finally, the present study consists of pulmonary lesions without local recurrence, as confirmed by 2-year clinical follow-up. Therefore, there is no comparison with the FDG uptake by recurrent lesions after RFA. A larger number of patients in a prospective study using histological examinations after RFA, with comparison of FDG uptake between the pulmonary tumors with and without recurrence, would be useful for further investigation of the appropriate timing of F-18 PET/CT in post-RFA pulmonary tumors.

Despite these limitations, our results suggest the possibility of providing a more appropriate evaluation of FDG accumulation in pulmonary lesions after RFA by using F-18 FDG PET/CT at 6 months rather than 3 months post-RFA. Size comparison of the pulmonary lesions did not prove useful for evaluation of local recurrences within 6 months of RFA.

In conclusion, we analyzed semiquantitatively the accumulation in lung tumors on PET/CT before RFA, at 3 months after RFA, and at 6 months after RFA compared with the size ofthe pulmonary lesions at the same time point. The size comparison of pulmonary tumorsafter RFA was not useful for prediction of local recurrences in the first 6 months afterablation, and the accumulation at 3 months after RFA was greater than at 6 months. PET/CT at 6 months could provide a more appropriate evaluation of the FDG accumulation in pulmonary lesions than that at 3 months.

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