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Fluorine-18-fluorodeoxyglucose positron emission tomography for assessment of patients with unresectable recurrent or metastatic lung cancers after CT-guided radiofrequency ablation: Preliminary results

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Objectives: We compared the diagnostic value of fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) with that of computed tomography (CT) following radiofrequency ablation (RFA) of inoperable recurrent or metastatic cancers in the lung. ***Methods:*** Twelve patients (9 males and 3 females; 5 had recurrent lung cancer and the other 7 had metastatic nodules from a variety of primary cancers) were treated by RFA for 17 pulmonary nodules. FDG-PET was performed before and 2 months after RFA, and the mean standardized uptake value (SUV) was calculated. The response evaluation was based on the percent reduction relative to the baseline and the absolute values of SUV on FDG-PET performed at 2 months after RFA. We compared the response evaluations made based on findings of FDG-PET and CT at 2 and ≥6 months (mean 10.2) after RFA. ***Results:*** The percent reduction in uptake at 2 months was significantly lower in nodules considered progressive (69.6 ± 18.6%) than nonprogressive disease (38.7 ± 12.5%; $p < 0.01$) based on CT findings at ≥6 months after RFA. The absolute SUV at 2 months was significantly higher in nodules considered progressive (2.61 ± 0.75) than nonprogressive disease (1.05 ± 0.67; $p < 0.01$) based on CT findings at ≥6 months post-RFA. ***Conclusion:*** Although our pilot study comprised few cases of various histopathological types of cancers in the lung, the results suggest that FDG-PET could predict regrowth on subsequent follow-up CT. Regrowth could be diagnosed earlier by FDG-PET than by CT, and nodules with residual uptake and with <60% reduction of uptake relative to baseline on FDG-PET at 2 months after ablation might require additional therapy.

Key words: lung cancer, radiofrequency ablation, FDG-PET

INTRODUCTION

Radiofrequency ablation (RFA) is used to induce thermocoagulation necrosis in the treatment of lesions. RFA is minimally invasive and valuable for the percutaneous treatment, primarily of liver tumors, but recently it has also been used for the treatment of renal, musculoskeletal, adrenal, breast, and bone tumors.[1–7] In 2000, Dupuy et al. reported the first clinical application of RFA in three patients with lung tumors without encountering serious complications.[8] RFA has been indicated as a new treatment for patients with inoperable lung cancers or inability to tolerate chemotherapy. Several reports have described the clinical benefits from RFA for lung tumors and the lack of serious complications.[8–19] However, the early response after RFA is often difficult to evaluate using computed tomography (CT) images, because of postablation inflammatory change or bleeding. It is known that CT taken in the early period after RFA is of limited value

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in evaluating changes in the size of tumors.[9–12] To our knowledge, only a few reports have investigate these responses after RFA.

Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a complementary modality using nuclear imaging for the diagnosis of cancers. Several studies have found FDG-PET to be useful for staging evaluation of patients with lung cancer, early diagnosis of metastatic disease and recurrence, and monitoring the therapeutic response to treatment.[20–22] To our knowledge, only a few studies have assessed post-RFA lung tumor by FDG-PET, although FDG-PET seems to be ideally suited for early follow-up of patients after RFA.[13,14] In this study, we investigated the usefulness of FDG-PET following RFA in patients with inoperable cancer in the lung.

MATERIALS AND METHODS

Patient selection

Between January 2001 and October 2004, we retrospectively studied FDG-PET imaging in 12 patients (9 males and 3 females) with a mean age of 71.3 years (range; 40 to 87) with 17 lung nodules treated by RFA. Tumor size ranged from 10 to 41 mm in diameter, with a mean of 20.6. Five patients had recurrent non-small-cell lung cancers and seven had metastatic lung tumors (including two from the rectum, two from the thyroid, one from the esophagus, one from the kidney, and one from the larynx). All patients were considered to have unresectable tumors or to be unable to tolerate chemotherapy because of poor ventilatory function or additional metastases. Table 1 lists the patient characteristics and tumor size on CT. The institutional review board at our hospital had reviewed and approved CT-guided RFA therapy for lung tumors, as this was considered an alternative treatment. Written informed consent was obtained from all patients before they entered this study.

RFA technique

CT-guided percutaneous RFA was performed under local anesthesia. All patients underwent unenhanced CT (X-Vigor; Toshiba, Tokyo, Japan; slice thickness, 2 mm; pitch; 1). An umbrella-shaped 15-gauge LeVeen Needle Electrode (Radio Therapeutics, Sunnyvale, CA) with an array diameter of 3.0 cm and a shaft length of 15 cm was connected to a 100-watt generator (RF 2000; Radio Therapeutics). Arterial blood pressure, respiration, pulse, and electrocardiogram were monitored throughout the ablation procedure. A grounding pad was placed on the thigh. After subcutaneous local anesthesia with 1% procaine (Omnicain; Daiichi Pharmaceutical, Tokyo), a LeVeen Needle Electrode was introduced into the lesion. For the first ablation, the generator power was set initially at 20 watts and increased by 5 to 10 watts per minute until maximum impedance was reached. Subsequently, RFA was repeated at the same position until maximum impedance was obtained. To complete tumor ablation, several ablations were performed in different portions of the tumor. The mean time for an ablation session was 56.3 min (range; 12.0 to 110.0).

FDG-PET

FDG was synthesized using the NKK-Oxford superconducting cyclotron and the NKK synthesis system. A

Table 1 Patients' characteristics; lesion size on CT before, at 2 and ≥6 months post-RFA; tumor SUV on FDG-PET, and percent reduction rate in SUV

Pt. No.	Age/ Sex	Primary lesion	Tumor size before RFA (mm)	Lesion size 2 mo after RFA (mm)	2 mo after Judgment RECIST*	Lesion size 6 or more mo after RFA (mm)	Last follow CT (months)	Outcome Judgment RECIST*	Tumor SUV before RFA	Lesion SUV 2 mo after RFA	Percent reduction in SUV
1a	40/F	Rectal ca.	10 × 10	14 × 11	SD	Scar	10	CR	2.4	0.7	−70.8
1b	40/F	Rectal ca.	20 × 20	30 × 23	PD	Scar	10	CR	3.6	2.4	−33.3
2	68/F	Thyroid ca.	18 × 16	18 × 18	SD	Scar	20	CR	3.1	1	−67.8
3	68/F	Renal cell ca.	26 × 18	23 × 20	SD	25 × 18	6	SD	4.2	1.2	−71.4
4	87/M	Rectal ca.	20 × 20	31 × 21	PD	25 × 25	9	SD	3.8	0.8	−78.9
5	70/M	Non-small cell lung ca.	20 × 17	20 × 15	SD	20 × 15	16	SD	4.4	0.2	−95.5
6	70/M	Thyroid ca.	41 × 31	42 × 30	SD	50 × 28	9	PD	3.7	2.4	−35.1
7	72/M	Laryngeal cancer	18 × 18	18 × 12	SD	30 × 28	14	PD	4.3	1.8	−58.1
8a	71/M	Esophageal cancer	20 × 18	25 × 20	SD	30 × 25	6	PD	3.9	2.5	−35.9
8b	71/M	Esophageal cancer	30 × 20	32 × 20	SD	65 × 30	6	PD	7	4.5	−35.7
8c	71/M	Esophageal cancer	20 × 17	20 × 20	SD	37 × 37	6	PD	4.5	3.2	−28.9
9a	78/M	Non-small cell lung ca.	16 × 14	30 × 20	PD	25 × 25	10	PD	4.6	2.2	−52.2
9b	78/M	Non-small cell lung ca.	28 × 15	22 × 19	SD	40 × 30	11	PD	3	1.7	−43.3
10a	82/M	Non-small cell lung ca.	17 × 15	20 × 18	SD	28 × 15	8	PD	4.8	2	−58.1
10b	82/M	Non-small cell lung ca.	10 × 10	10 × 10	SD	20 × 12	12	PD	3.4	2.8	−17.6
11	77/M	Non-small cell lung ca.	18 × 18	25 × 17	PD	30 × 30	12	PD	4.6	3	−34.8
12	72/M	Non-small cell lung ca.	18 × 18	25 × 17	PD	38 × 35	8	PD	3.5	2.6	−25.7

Note-*RECIST = Response Evaluation Criteria in Solid Tumors, CR = complete response, PR = partial response, SD = stable disease, PD = progress disease

HEADTOME IV SET-1400W-10 (Shimadzu, Kyoto, Japan), which has effective spatial resolution of 4.5 mm in full width at half maximum, and four detector rings providing seven contiguous slices at 13-mm intervals, was used for PET imaging. Transmission scans were performed for 10 min with a $^{68}Ge/^{68}Ga$ line source for attenuation correction. After fasting for at least 4 hours, patients received an intravenous injection of FDG (4 MBq/kg; range; 176 to 320 MBq). In all patients, the serum glucose level was less than 120 mg/d*l*. Emission scans were performed at 60 min after the intravenous injection. Reconstruction was performed using a filtered-back projection method.

FDG-PET analysis

We visually and semiquantitatively analyzed FDG-PET images. Regions of interest (ROI) in the lesions, which represented the area in the lesion showing the highest FDG accumulation, were delineated using the CT outlines of the nodule. The mean standardized uptake value (SUV) was calculated for each nodule using the following formula: mean SUV = mean tissue concentration (MBq/g)/ injected activity (MBq) per body weight (g). In all 12 patients, FDG-PET was performed before RFA and repeated 2 months after RFA. The mean time interval between the pretreatment FDG-PET and RFA was 9.3 ± 9.4 days. PET images of all patients were reviewed by two experienced radiologists.

CT imaging

All patients underwent unenhanced CT scans. Follow-up CT scans were performed to measure the tumor size at 2 months and again at over 6 months (mean, 10.2) after the procedure. CT was performed using lung window settings (window width, 1800 to 2000 HU; window level, −500 to −600 HU). The diameter of an ablated lesion including surrounding parenchyma was measured at these lung window settings.

CT imaging analysis

The response to RFA was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[23] 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 by CT, and "stable disease" (SD) as a decrease of no more than 30% or an increase of no more than 20% in tumor diameter. In our study, tumors showing CR, PR, or SD on CT images obtained 6 or more months after RFA were considered to be nonprogressive disease (non-PD), while those showing PD represented progressive disease. CT images of all patients were reviewed by the other two experienced radiologists.

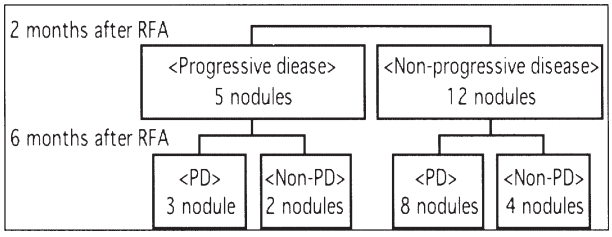

Fig. 1 Of 17 nodules evaluated by CT at 2 months and again at ≥6 months post-RFA, 12 were categorized at 2 months as nonprogressive disease, while 5 represented progressive disease. Among the 12, 4 were categorized as nonprogressive disease and 8 as progressive disease at ≥6 months post-RFA. Among the 5 nodules considered progressive disease at 2 months, 2 were nonprogressive disease and 3 were progressive disease at ≥6 months post-RFA.

Investigation and statistical analysis

The relationship between responses evaluated by CT at 2 months after RFA and those evaluated 6 or more months after RFA was examined. The response evaluated by visual analysis of FDG-PET performed before RFA and those 2 months after RFA was investigated. Baseline PET images and those obtained 2 months after RFA were scored as either negative or positive for uptake. The response evaluated by CT at 6 months was based on the RECIST criteria. The percent reduction in SUV relative to baseline FDG-PET performed 2 months after RFA was compared between CT-defined progressive and nonprogressive disease groups using unpaired Student's *t*-test. P values less than 0.05 were considered statistically significant. The response evaluated by CT findings at 6 or more months based on RECIST criteria and the absolute SUV values by PET at 2 months were compared between progressive and nonprogressive disease groups using unpaired Student's *t*-test. P values less than 0.05 were considered statistically significant.

RESULTS

Table 1 shows patient characteristics, tumor sizes at 2 months and ≥6 months after RFA, clinical outcome based on RECIST, tumor SUV by FDG-PET performed before and 2 months after RFA, percent reduction in SUV, and responses evaluated based on findings at 2 months after RFA and those obtained ≥6 months after RFA.

Responses based on CT findings at 2 and ≥6 months post-RFA

Twelve nodules were categorized as non-PD based on CT findings at 2 months after RFA; the other 5 were considered PD. Among the 12 non-PD nodules at 2 months, 8 became PD according to CT at ≥6 months post-RFA. On the other hand, the 5 nodules that were categorized as PD by CT at 2 months post-RFA included 2 later defined as

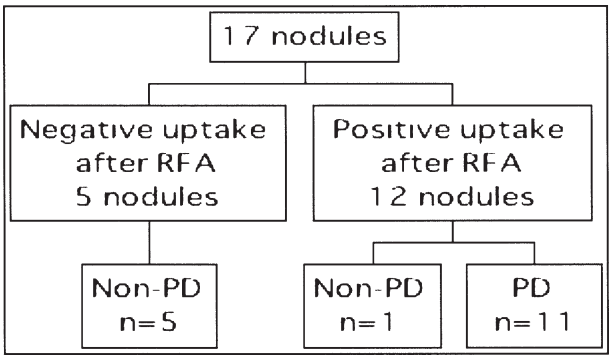

Fig. 2 Seventeen nodules showed abnormal FDG uptake at baseline study before RFA. Five nodules showed no FDG uptake at 2 months after RFA, and were considered nonprogressive on CT at ≥6 months post-RFA. Twelve nodules showed positive uptake at 2 months after RFA, and 11 nodules considered progressive, while 1 of these 12 nodules showed complete response by CT at ≥6 months post-RFA.

non-PD based on CT at ≥6 months post-RFA. The sensitivity, specificity, and accuracy of CT performed 2 months after RFA in predicting results of CT at ≥6 months post-RFA were 27.2%, 66.7%, and 41.1%, respectively. Thus, the response evaluated by CT at 2 months after RFA did not correspond to the response by CT at ≥6 months post-RFA, and the first of these was considered poorly suited for therapeutic evaluation (Fig. 1).

Visual analysis of FDG-PET before and 2 months post-RFA

Seventeen nodules showed abnormal FDG uptake at baseline study. Of 12 nodules showing uptake at 2 months after RFA, 11 were considered to show PD and 1 nodule considered to show non-PD on CT at ≥6 months post-RFA (Fig. 2). The sensitivity, specificity, and accuracy of FDG-PET performed at 2 months after RFA in predicting results of CT at ≥6 months post-RFA were 100%, 83.3%, and 94.1% respectively.

Reduction in SUV according to FDG-PET at 2 months post-RFA and response based on CT findings at ≥6 months post-RFA

There was a significant difference in mean SUV between non-PD (69.6 ± 18.6%) and PD (38.7 ± 12.5%; $p < 0.01$, Student's *t*-test). The response based on CT findings at ≥6 months post-RFA tended to correspond to the percent reduction in SUV at 2 months (Fig. 3).

Absolute mean SUV by FDG-PET at 2 months after RFA and response evaluation based on CT at ≥6 months post-RFA

Figure 4 shows the distribution of mean absolute SUVs obtained by PET at 2 months in groups considered non-PD and PD based on CT findings at ≥6 months post-RFA according to RECIST criteria. The mean absolute SUV on

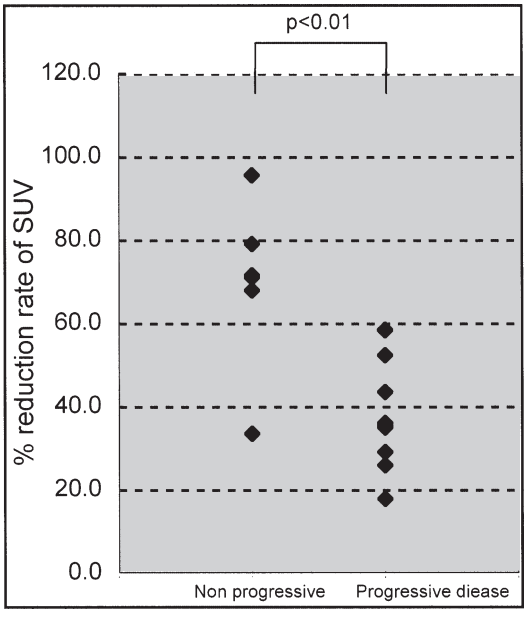

Fig. 3 Percent reduction in SUV for nodules categorized as nonprogressive vs. progressive disease at ≥6 months post-RFA. The percent reduction in SUV at 2 months was significant compared with at ≥6 months post-RFA. Data are mean ± SD.

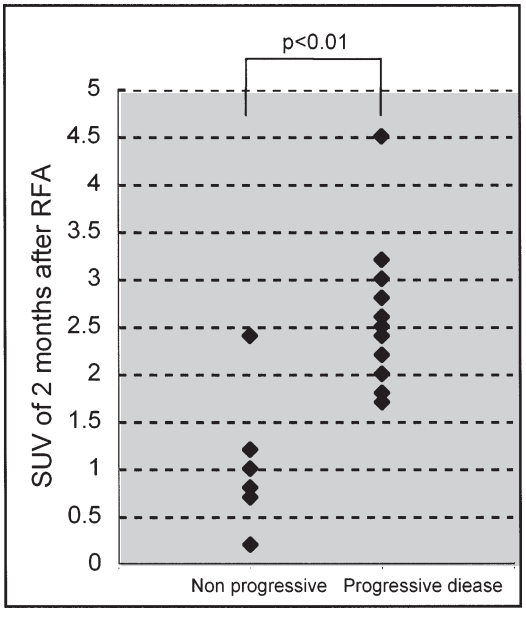

Fig. 4 Absolute SUV by FDG-PET at 2 months after RFA in nonprogressive disease vs. progressive disease according to CT performed at ≥6 months post-RFA. Absolute SUV was significantly higher in nodules categorized as PD in non-PD nodules ($p < 0.01$).

PET at 2 months (2.61 ± 0.75) was significantly higher in nodules categorized as PD based on CT at ≥6 months post-RFA than in non-PD nodules (1.05 ± 0.67; $p < 0.01$, Student's *t*-test) (Fig. 4).

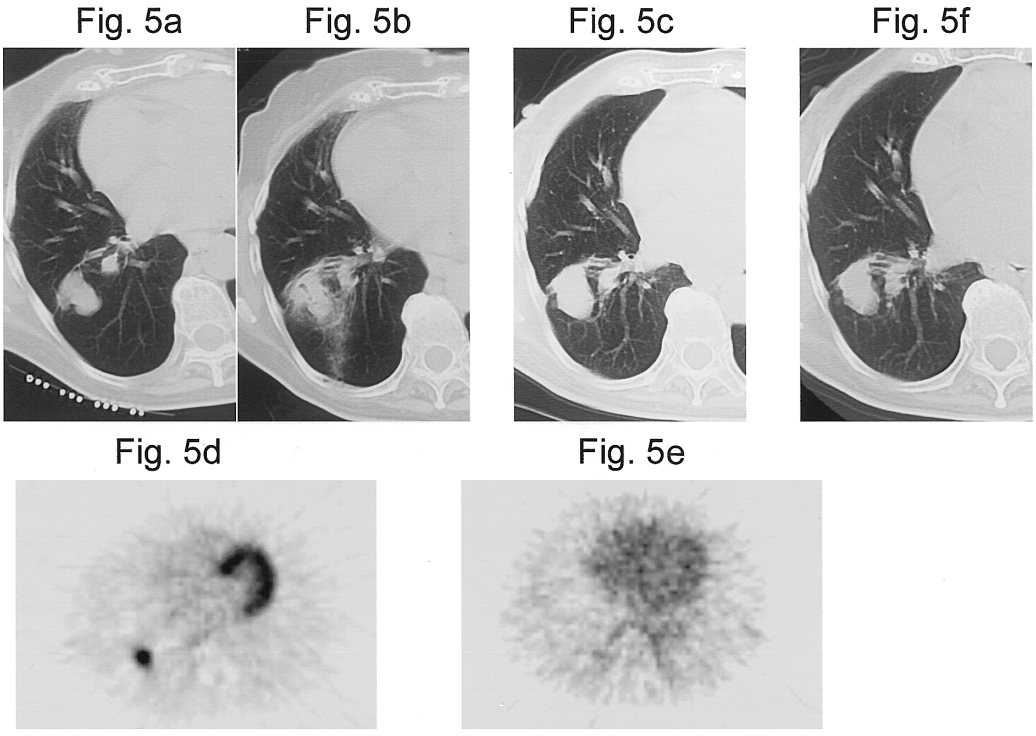

Fig. 5 Illustrative case in which FDG-PET at 2 months after RFA was better than CT at 2 months at predicting response to RFA at 6 months. (a) Transverse CT image obtained before RFA in a 68-year-old woman (Patient 3) with a right lower lobe tumor (metastatic renal cell carcinoma, tumor diameter 26 mm). (b) Immediately after RFA. Note the ground glass opacities around the lesion. A pneumothorax occurred during RFA but did not require insertion of a thoracostomy tube. (c) CT at 2 months after RFA showed no marked change in size and was considered stable disease. (d) FDG-PET before RFA shows FDG uptake with SUV of 4.2. (e) SUV decreased to 1.2, and the nodule was categorized as a partial response according to FDG-PET at 2 months after RFA. (f) CT at 6 months after RFA shows nonprogressive disease.

DISCUSSION

Percutaneous CT-guided RFA has been used to treat an increasing number of tumor types in recent years, including lung cancers,[1–19] but data on its effectiveness and reliability are limited. CT is usually used for evaluating the response to RFA.[8–19] The response evaluation after RFA for cancer in the lung is based on changes in tumor size as determined by CT examination. In our study, 17 nodules were evaluated by CT at 2 months and again at ≥6 months post-RFA. The CT findings of enlargement at 6 months as opposed to 2 months after RFA were considered to represent progressive disease. The ablated nodule appeared smaller in patients judged to have stable disease on CT performed at ≥6 months post-RFA, as well as those showing a partial response. The sensitivity, specificity, and accuracy of CT performed at 2 months after RFA in predicting the results at ≥6 months post-RFA were 27.2%, 66.7%, and 41.1%, respectively. Thus, the response evaluation based on CT at 2 months did not correspond to CT evaluations at ≥6 months post-RFA. The CT performed at 2 months post-RFA was considered to show surrounding parenchymal edema, inflammation, and hemorrhage caused by RFA thermal damage, resulting in a spurious increase in tumor size immediately after RFA. Follow-up CT in the early stage is often reported to show few or no short-term changes after therapy.[9–12] Atelectasis and pleural effusion may interfere with the CT measurement of tumor size.[9,10,12] Steinke et al.[12] reported that ablated lesions appeared larger on CT performed immediately after RFA because normal tissues at the lesion also are ablated. They reported that almost all lesions increased in size during the first 3 months after RFA and then gradually decrease, until follow-up CT at 6 months after RFA showed the lesion to be the same size or smaller than the size before the procedure; on the other hand, any recurrent tumor usually appeared within 6 months after RFA.[12] Needle biopsy after RFA is not always successful in obtaining residual tumor cells present in small numbers.[18] On the other hand, false-positive pathologic results, also known as the ghost phenomenon, also limit the reliability of biopsy as an evaluation method after RFA.[18]

FDG-PET is a useful noninvasive modality for evaluating neoplasm metabolism after treatment; some studies

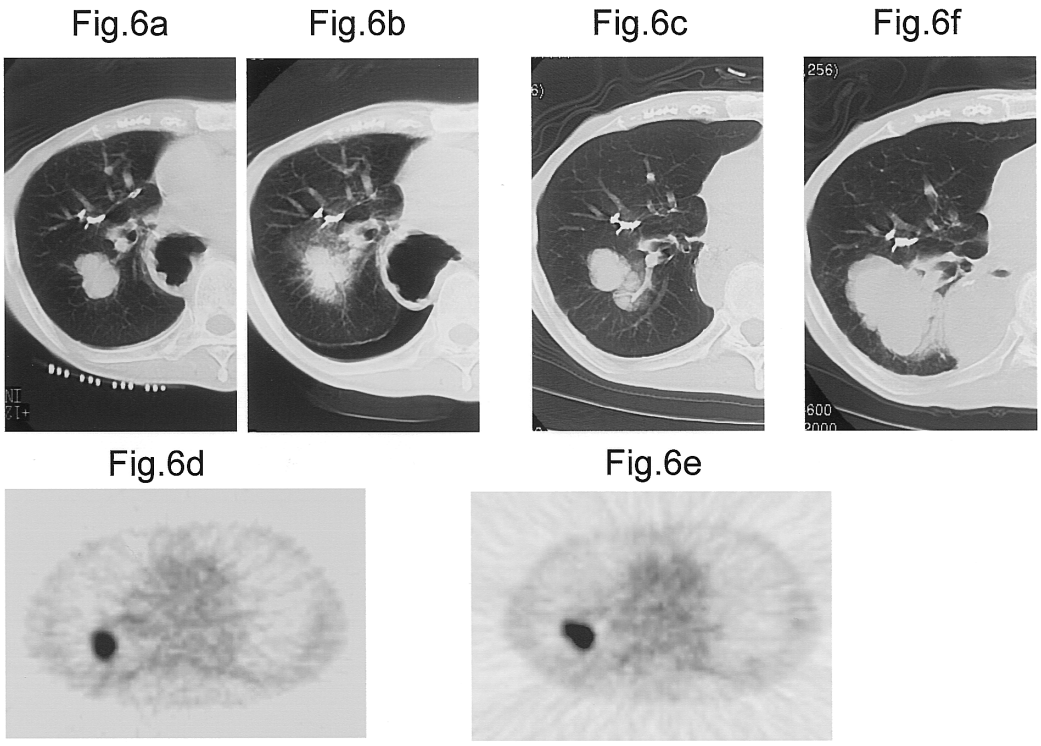

Fig. 6 Transverse CT and PET images obtained in a 71-year-old man (Patient 8b) with a metastatic right lower lobe cancer from the esophagus. (a) Transverse CT image obtained before RFA shows a tumor 30 mm in diameter. (b) CT image immediately after RFA, which shows increased opacity around the lesion. (c) CT obtained 2 months after RFA shows no marked changes in size (considered as stable disease). (d) PET before RFA demonstrates FDG uptake with SUV of 7.0. (e) SUV decreased to 4.5 on FDG-PET at 2 months after RFA. (f) CT at 6 months, however, shows increased tumor size, representing recurrence.

reported that FDG uptake could predict prognosis or likelihood of survival.[20–22] Functional biochemical imaging can also be used to evaluate the response to radiotherapy or chemotherapy.[20–22] Only a few studies have examined the usefulness of FDG-PET after RFA.[8–11] Dupuy et al.[8] reported that a tumor treated with RFA showed decreased FDG uptake on follow-up FDG-PET. Herrera et al.[10] reported that PET could confirm suspected residual tumor on CT, while FDG-PET could be used to evaluate the response to RFA; CT and FDG-PET thus complemented one another. To our knowledge, no previous study investigated the use of FDG-PET to predict recurrence after RFA tumors in the lung. RFA for cancer in the lung is relatively new, and long follow-up studies are needed to determine the treatment response after RFA. The time required for tumor shrinkage as a result of scarring has not been well established. It is important to raise the benefit of early prediction of tumor recurrence at least to offer patients with progressive disease the opportunity of alternative therapies. In the present study, we investigated the correlation between response evaluations based on FDG-PET and CT after RFA. The sensitivity, specificity, and accuracy of visual analysis of FDG-PET performed at 2 months after RFA in predicting CT findings at ≥6 months post-RFA were 100%, 83.3%, and 94.1%, respectively. Nodules later considered progressive disease showed significantly higher SUV on FDG-PET performed at 2 months after RFA than non-PD nodules. Persistent FDG uptake on PET at 2 months after RFA appeared as progressive disease on CT at ≥6 months after treatment. The percent reduction of SUV on FDG-PET at 2 months after RFA relative to the baseline correlated with responses evaluated by CT performed at 6 months. Thus, changes in percent reduction of FDG uptake after RFA of cancer in the lung correlated with subsequent CT response. Response evaluations therefore can be based on absolute SUVs on FDG-PET performed at 2 months after RFA and percent reduction of SUV after RFA relative to the baseline. Nodules with percent reduction in FDG uptake after RFA of less than 60% after RFA were considered to have been incompletely treated, probably requiring additional therapy or a second RFA. Thus, the results of FDG-PET performed at 2 months after RFA might predict progression at 6 months after RFA. One nodule (No. 1b) was considered to show CR on CT ≥6 months after RFA, though the mean absolute SUV on PET at 2 months and percent reduction of SUV were 2.4 and −33.3, respectively. This nodule shows scarring and no

local recurrence by follow up CT at 16 months after RFA. In this regard, Herrera et al.[12] reported some false-positive cases in which there was a possibility that reflective inflammatory changes due to RFA appeared on PET at 2 months. Delay of imaging until ≥2 hours after FDG injection might improve the distinction of inflammatory changes from residual tumor.[24]

Our retrospective study has certain limitations, including a relatively small number of patients and nonuniform histopathological types of cancer in the lung. A larger number of subjects and longer follow-up are desirable in further investigation of the usefulness of FDG-PET for monitoring the response to RFA. PET alone is characterized by limited spatial resolution and lack of anatomic landmarks, while PET/CT will easily localize the ablated lesion and will make possible a more accurate evaluation response after RFA.

In conclusion, the response to RFA in patients with cancer in the lung could be evaluated by FDG-PET performed at 2 months after RFA using the absolute SUV and the percent reduction of SUV post-RFA relative to the baseline. Our pilot study showed that FDG-PET at 2 months after RFA could predict tumor recurrence earlier than CT scans. Finally, nodules showing persistent uptake in the tumor and reduction of SUV from the baseline on FDG-PET at 2 months after RFA of less than 60% might require additional therapy.

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