Annals of Nuclear Medicine Vol. 18, No. 8, 669–674, 2004

^{18}F-FDG and ^{11}C-methionine PET for evaluation of treatment response of lung cancer after stereotactic radiotherapy

Takayoshi Ishimori,* Tsuneo Saga,* Yasushi Nagata,** Yuji Nakamoto,* Tatsuya Higashi,* Marcelo Mamede,* Takahiro Mukai,* Yoshiharu Negoro,** Tetsuya Aoki,** Masahiro Hiraoka** and Junji Konishi*

*Department of Nuclear Medicine and Diagnostic Imaging, Graduate School of Medicine, Kyoto University
**Department of Therapeutic Radiology and Oncology, Graduate School of Medicine, Kyoto University

This study was performed to investigate the feasibility of FDG- and L-[methyl-^{11}C]methionine (Met)-PET for the follow up of lung cancer after stereotactic radiotherapy (SRT). Nine patients (pt) with solitary lung cancer underwent SRT. Met- and FDG-PET studies were performed one week before SRT and from one week to 8 months after SRT. Responses to SRT were complete in 2 pt and partial in 7 pt. Met- and FDG-PET scan showed high tracer uptake in all tumors before SRT. After SRT, standardized uptake values (SUV) of FDG and Met changed concordantly. Both decreased with time in 5 pt but did not decrease steadily in 4 pt, where 2 pt showed an increase at 1 to 2 weeks after SRT and 2 pt showed an increase at more than 3 months after SRT. The former appears to reflect the acute reaction to SRT and the latter radiation-induced pneumonitis. Although the addition of Met-PET did not provide additional information over FDG-PET, FDG- and Met-PET could be used to evaluate the treatment effect of SRT.

Key words: PET, lung cancer, stereotactic radiotherapy, FDG, methionine

INTRODUCTION

Positron emission tomography (PET) with ^{18}F-labeled fluorodeoxyglucose (FDG) has recently been applied widely in clinical oncology.[1–3] However, FDG is not a cancer-specific agent and is known to accumulate in acute inflammation as well as granulomatous and autoimmune diseases.[4–6]

PET with L-[*S*-methyl-^{11}C]methionine (Met) has been used to evaluate the treatment response of lung cancer after conventional irradiation, since Met accumulates less in inflammatory lesions than FDG.[7]

Stereotactic radiotherapy (SRT), which can localize a single high dose selectively to the target, was first applied to the treatment of malignant intracranial tumors, and its feasibility has been reported.[8] Recently, SRT was adopted for lung cancer as an alternative to surgery in patients with solitary lung cancer who did not meet the indications for surgery.[9–11]

The response of a tumor to treatment was conventionally evaluated by measuring the tumor size using morphological imaging modalities such as CT and MRI. However, distinguishing viable residual tumors from fibrotic scars after irradiation is always difficult. Aoki et al. evaluated the CT appearance of tumors and lung injury after SRT, and reported that it was difficult to distinguish residual tumor from radiation fibrosis.[12] For precise differentiation, metabolic imaging such as FDG- and Met-PET may play a major role. Although the feasibility of CT and FDG-PET image fusion in the treatment planning of SRT of lung cancer was reported,[13] there has been no reported study concerning the follow up of lung cancer patients after SRT by PET. The aim of this study was to investigate the feasibility of FDG- and Met-PET for the follow up of lung cancer after SRT.

Received February 25, 2004, revision accepted August 4, 2004.

For reprint contact: Tsuneo Saga, M.D., Department of Nuclear Medicine and Diagnostic Imaging, Graduate School of Medicine, Kyoto University, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606–8507, JAPAN.

E-mail: saga@kuhp.kyoto-u.ac.jp

PATIENTS AND METHODS

Patients

The study group comprised 9 patients (age range, 64–86 years), who had histologically-confirmed solitary lung cancer less than 4 cm in diameter without distant metastasis and underwent SRT between May, 1999 and February, 2000. The histological diagnoses were: 6 squamous cell carcinomas (SqCC) and 3 adenocarcinomas (Adeno). Details of the individual patients are shown in Table 1. Before being enrolled in this study, each patient gave written informed consent, as required by the Kyoto University Human Study Committee.

Stereotactic Radiotherapy (SRT)

The SRT procedures were previously reported in detail.[11] In brief, radiation therapy was delivered using a 6-MV Linear Accelerator (Clinac 2300C/D Varian Associates, Palo Alto, CA, USA) with the 6 to 10 fields non-coplanar 3D conformal technique. A total tumor isocenter dose of 48 Gy (12 Gy/fraction) was administered in 12 or 13 days. CT (SCT700 TX/TH, Shimadzu Co., Kyoto, Japan) and the three-dimensional treatment planning system (CADPLAN R.6.0.8, Varian Associates, Palo Alto, CA, USA) were used for treatment planning. The Stereotactic Body Frame (Elekta Instrument AB, Stockholm, Sweden) was used for patient fixation.

FDG and Met Preparation

Both FDG and Met were synthesized at the in-house cyclotron facility at Kyoto University Hospital. Fluorine-18 [^{18}F] and carbon-11 [^{11}C] were produced with a cyclotron, CYPRIS-325R (Sumitomo Heavy Industries, Co. Ltd., Tokyo, Japan). ^{18}F-FDG was synthesized by the nucleophilic substitution method with an ^{18}F-FDG-synthesizing instrument, F-100 (Sumitomo Heavy Industries, Co. Ltd., Tokyo, Japan).[14–16]

Met was synthesized by reaction of L-homocysteine thiolactone and [^{11}C]methyl iodide.[16] [^{11}C]Carbon dioxide, produced by a ^{14}N(p, α)^{11}C reaction, was transported into an automated [^{11}C]methyl iodide synthesis system (C-11-BII; Sumitomo Heavy Industries, Co. Ltd., Tokyo, Japan). [^{11}C]Methyl iodide was prepared as previously described,[17] then trapped in a mixture of acetone (500 μl) and 100 mg/ml L-homocysteine thiolactone solution (50 μl). After the addition of 0.2 M NaOH (500 μl), the reaction mixture was heated at 80°C for 3 min. The solution was neutralized with 0.2 M HCl, and evaporated. The resulting residue was then dissolved in sterile saline and passed through a sterile 0.22-μm filter. Radiochemical purity was >97% as determined by analytical HPLC using a Partisil 10-SCX column (4.6 × 250 mm; Whatman, Clifton, NJ, USA) eluted with 50 mM citric acid/trisodium citrate (10/1).

PET Imaging

One week before SRT, initial Met- and FDG-PET studies were performed on the same day with a dedicated PET scanner (PCT3600W; Hitachi Medical, Tokyo, Japan). This scanner had 8 rings and provided 15 tomographic sections at 7 mm intervals. We certified the scan range, which was marked on the body surface, by referring to CT images previously obtained. All patients fasted for at least 4 hours and underwent a 10-min transmission scan of the lung before Met injection. At the same body position, a Met-PET image was obtained 20 min after intravenous injection of 768.2 ± 224.5 MBq of Met. Sixty min after Met injection, 370.0 ± 37.5 MBq of FDG was intravenously injected and FDG-PET images were obtained 60 min later. At the time of FDG-PET scan, the residual radioactivity of Met was estimated to be 4.6% ± 1.4% of FDG activity. Although Met radioactivity could not be completely eliminated, it was substantially low compared with FDG activity. The emission scan time for both Met- and FDG-PET was 10 min. Attenuation corrected PET images were reconstructed by the filtered back projection method. The tumor uptake of FDG and Met was evaluated semiquantitatively as a standardized uptake value (SUV) in the regions of interest (ROIs) placed over the treated lesion. The ROI placed over the lesion was 10 × 10 mm

Table 1 Patient characteristics

Pt #	Age/Sex	Histology	Local response	Time interval*	Tumor size before SRT**	Tumor size at the maximum response**
1	68/M	SqCC	PR	4 months	3.4 × 3.3	2.1 × 2.1
2	74/M	SqCC	PR	2 months	3.2 × 2.8	2.2 × 1.8
3	77/F	Adeno.	PR	17 months	2.4 × 1.7	0.8 × 0.7
4	77/F	SqCC	CR	3 months	1.7 × 1.4	0.0 × 0.0
5	86/M	Adeno.	PR	6 months	2.9 × 2.7	1.9 × 1.3
6	70/M	SqCC	CR	11 months	2.1 × 1.5	0.0 × 0.0
7	72/M	SqCC	PR	10 months	3.4 × 1.7	1.0 × 0.8
8	71/M	SqCC	PR	16 months	3.3 × 3.1	1.0 × 1.0
9	71/M	Adeno.	PR	16 months	3.1 × 2.5	2.6 × 0.6

*: time interval between SRT and maximum response on CT

**: long axis × short axis (cm) on CT images

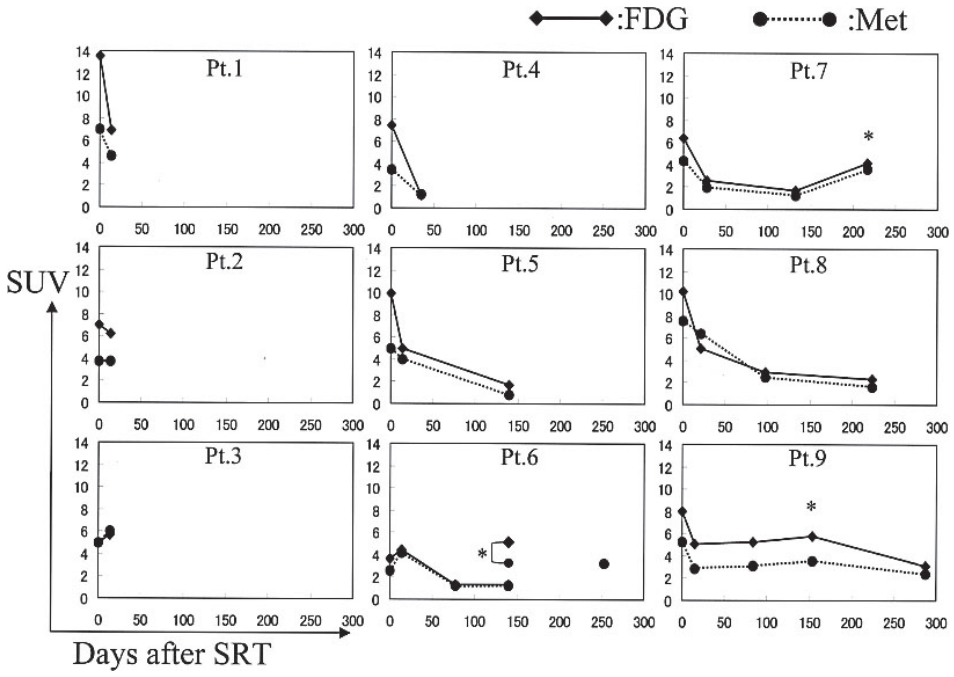

Fig. 1 The temporal changes in SUV in 9 patients are shown. (◆—◆ FDG, ●---● Met) In pt. 6, increased uptake of FDG and Met are observed (*) corresponding to the SRT-induced pneumonitis separated from the treated tumor. In pt. 7 and pt. 9, increased uptakes (*) are observed because the treated tumors are involved in SRT-induced pneumonitis.

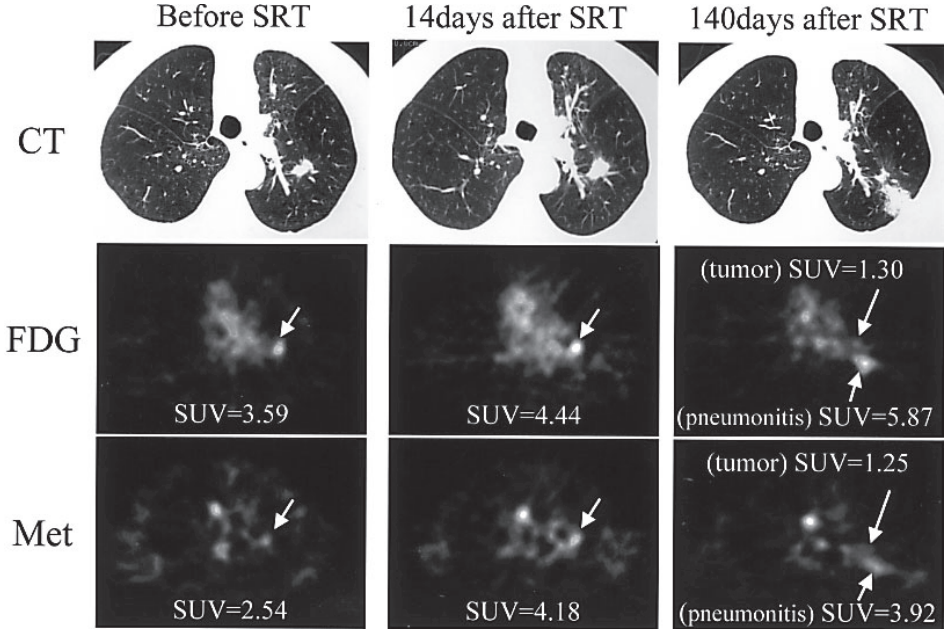

Fig. 2 (patient #6). (*Left*) Before treatment, CT shows a mass lesion (1.5 cm) in the left lower lung (S6). FDG- and Met-PET show high tracer uptake in the tumor. (*Middle*) Fourteen days after SRT, both FDG- and Met-PET show higher uptake in the tumor than in the pre-treatment study. The corresponding CT shows slight enlargement of the treated tumor. (*Right*) One hundred and forty days after SRT, the uptake of FDG and Met to the tumor is decreased, while both FDG- and Met-PET show higher uptake in the peripheral lung field. CT shows a decrease in tumor size. Furthermore, CT reveals a new consolidation in the peripheral lung field suggestive of radiation-induced pneumonitis, corresponding to the high uptake of FDG and Met. One year later, follow-up CT showed a decrease in size of this opacity (not shown).

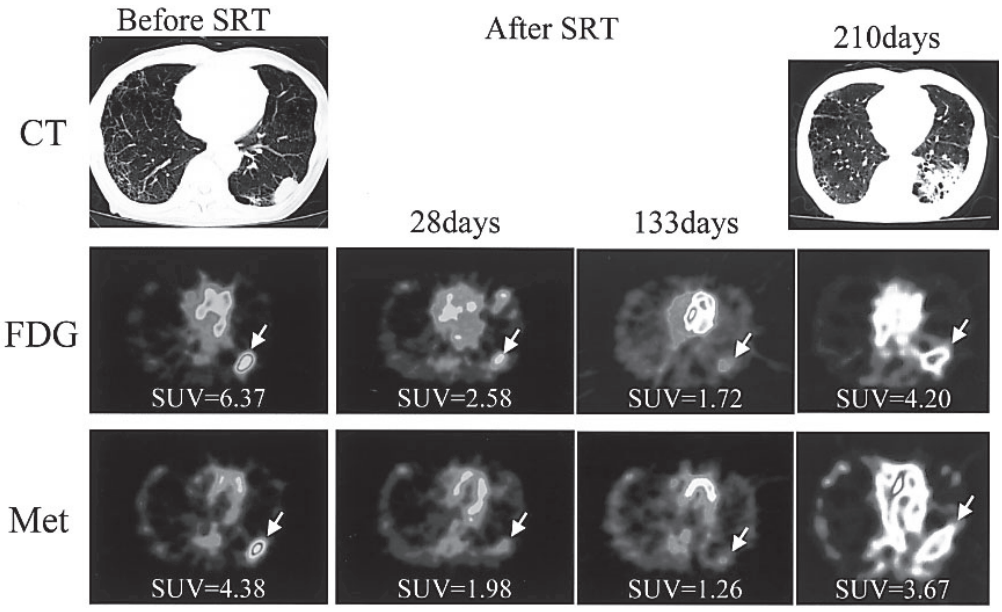

Fig. 3 (patient #7). (*Left*) Before treatment, CT shows a mass (3 cm) in the left lower lung (S9). FDG- and Met-PET show high tracer uptake in the tumor. (*Middle*) Both at 28 and 133 days after SRT, the uptakes of FDG and Met in the tumor have decreased steadily. (*Right*) Seven months after SRT, CT shows consolidation surrounding the tumor area, consistent with radiation-induced pneumonitis. FDG- and Met-PET show higher uptake in the corresponding area. The uptake of the tumor cannot be separated from that of inflammation.

(independent of tumor size) and was placed in tumor areas that showed the highest tracer activity. The SUV was calculated as the mean value in this ROI. Follow-up PET studies were performed in the same manner from 2 weeks to 8 months after SRT. Overall, 56 (28 Met- and 28 FDG-) PET examinations were conducted for these 9 patients.

The tumor size was also evaluated by CT images before and after SRT, and a local response was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) as follows[18]:

CR (complete response): no visible tumor

PR (partial response): 30% or greater decrease in tumor diameter

NC (no change): less than 30% reduction or less than 20% increase in tumor diameter

PD (progressive disease): 20% or greater increase in tumor diameter

The local response was evaluated at the time of maximum local response, and the time interval between SRT and evaluation of response was from 2 months to 17 months (Table 1).

RESULTS

The temporal changes in SUV of FDG and Met are shown in Figure 1. The local response of the treated tumor evaluated by CT images was complete response (CR) in 2 patients and partial response (PR) in 7 patients. An initial PET study showed high FDG and Met uptake to the tumors in all patients. In the follow up studies, SUV of FDG and Met had decreased gradually with time in 5 patients. In contrast, in the remaining 4 patients, SUV of FDG and Met did not decrease steadily, with 2 patients (Pt. 3 and 6) showing a temporal increase in SUV of both FDG and Met at 2 weeks after SRT, and 2 patients (Pt. 7 and 9) showing a delayed increase of both SUVs more than 3 months after SRT (Figs. 2 and 3). In the latter two patients, CT showed the presence of radiation-induced pneumonitis in the treated area. An additional patient (Pt. 6) developed radiation pneumonitis in the vicinity of the tumor site about 5 months later, which showed increased FDG uptake, although the FDG-uptake in the treated tumor remained low. In all cases, changes in the tumor uptake of Met paralleled those of FDG, and there was no discrepancy between Met and FDG uptake changes.

DISCUSSION

SRT is a new and attractive technique, which can localize a high radiation dose selectively to the target. It is reported clinically effective and can be performed safely without serious complications.[10] However, the temporal changes in tumor viability or metabolism after this treatment have not been clarified. The response of tumor tissue to SRT might be different from that to conventional radiotherapy since the single dose is higher and the overall treatment time is shorter in SRT.

In the follow up of lung cancer patients, tumor size measurements using CT have been the standard method of the evaluation of the treatment response,[18] but it could be falsely positive after treatment due to the fibrotic or necrotic tissue remaining in the tumor. Differentiating residual tumor from radiation fibrosis is also difficult in lung cancer patients after SRT.[12]

FDG-PET, which can depict tumor glucose metabolism, is widely used for the evaluation of malignant tumors in clinical oncology. Since FDG is a good marker of tumor viability, FDG-PET is also widely applied for the evaluation of lung cancer after treatment.[19,20] However, Haberkorn et al. reported the contribution of inflammatory reactions caused by radiation injury in falsely increased FDG uptake after radiation therapy.[21] FDG has some limitations in the evaluation of an irradiated tumor because it is known to accumulate not only in malignant cells but also in inflammatory reactions. Met is an essential amino acid necessary for protein synthesis. The transport and metabolism of Met are increased in malignant cells,[7] and Met-PET is useful in the evaluation of lung cancer.[22] Met uptake in tumor tissue is reported to be more specific for viable cancer cells than FDG, where granulation tissue and macrophages show lower uptake of Met.[7] Therefore, Met-PET appears to be more suitable for the monitoring of the treatment response of cancers.[23]

In the present study, all patients showed a favorable response to SRT (2 CRs & 7 PRs) with no treatment failures noted. In 5 of 9 patients, tumor uptake of both tracers (FDG & Met) decreased with time, implying the feasibility of FDG- and Met-PET in the follow up of patients after SRT. However, in the remaining 4 patients, tumor uptake of both tracers did not decrease steadily. In 2 patients, a temporal increase in SUVs of both tracers at 1 to 2 weeks after SRT appeared to reflect the acute reaction of the tumor to SRT.[24] In the other 2 patients, the delayed increase in both SUVs at more than 3 months after SRT occurred along with the appearance of radiation-induced pneumonitis at the site of the tumor. In an additional patient, pneumonitis at the vicinity of the tumor showed increased FDG and Met uptake, while FDG and Met uptakes in the treated tumor were low. In these 3 patients, therefore, it is highly likely that both FDG and Met accumulated in the inflammatory tissue of radiation-induced pneumonitis.

The present results, namely the accumulation of Met in the inflammatory change evoked by SRT, were not consistent with our initial expectations of a difference between the two tracers. Only a few studies have described Met uptake in inflammatory[25] or granulomatous[26] lesions, and the exact reason why Met accumulated in SRT-induced inflammation is not clear. Higashi et al. reported from an *in vitro* study that the increased FDG and Met uptake in cancer cells observed 12 days after irradiation could be attributed to giant-cell formation and accelerated repair of cells.[27] They suggested that tumor cells themselves could transiently increase FDG and Met uptake early after irradiation. Among the present 5 patients who had a temporal increase in the uptake of FDG and Met in the tumor, this mechanism may have occurred in 2 cases in which increased tracer uptake was observed 1 to 2 weeks after SRT. However, in the 3 other patients, in whom an increase of both tracer uptakes occurred at more than 3 months after SRT, an acute reaction of cancer cells was not the likely cause and the increased uptake could only be explained by the contribution of infiltrating inflammatory cells in SRT-induced pneumonitis, which actively accumulated both tracers. In the follow up of patients after SRT, Met-PET did not provide any additional information to that obtained from FDG-PET and was not useful in distinguishing an inflammatory reaction evoked by SRT.

To evaluate the precise treatment effect by FDG- and/or Met-PET, the contribution of inflammatory reactions after SRT, which includes both the acute reaction and irradiation-induced pneumonitis, should be minimized. Aoki et al. reported that the initial changes of the irradiated lung detected by CT appeared 2–6 months after SRT.[12] In this small number of cases, no temporal increases of FDG or Met uptake were observed between 2 weeks and 2 months after SRT. FDG- and Met-PET might possibly evaluate the treatment effect without interference from inflammation during this period. However, the number of patients was quite small, and further studies are warranted to optimize the timing of the PET examination after SRT of lung cancer.

In the present study, it was not fully evaluated whether FDG- and Met-PET provided additional information over CT scan. Although PET imaging is expected to have additional value over morphological imaging such as CT or MR, further studies are needed to elucidate the impact of PET images as compared to morphological imaging modalities.

CONCLUSIONS

The present study showed, for the first time, that FDG- and Met-PET could be used for the follow up of lung cancer patients after SRT, although the addition of Met-PET did not provide additional information to that gained from FDG-PET. Further investigations are necessary to elucidate the optimal timing of FDG- and Met-PET examinations after SRT to evaluate the precise treatment effect.

REFERENCES

1. Delbeke D. Oncological applications of FDG PET imaging: brain tumors, colorectal cancer, lymphoma and melanoma. *J Nucl Med* 1999; 40: 591–603.
2. Strauss LG. Positron Emission Tomography: Current Role for Diagnosis and Therapy Monitoring in Oncology.

Oncologist 1997; 2: 381–388.
3. Inokuma T, Tamaki N, Torizuka T, Fujita T, Magata Y, Yonekura Y, et al. Value of fluorine-18-fluorodeoxyglucose and thallium-201 in the detection of pancreatic cancer. *J Nucl Med* 1995; 36: 229–235.
4. Shreve PD. Focal fluorine-18 fluorodeoxyglucose accumulation in inflammatory pancreatic disease. *Eur J Nucl Med* 1998; 25: 259–264.
5. Strauss LG. Fluorine-18 deoxyglucose and false-positive results: a major problem in the diagnostics of oncological patients. *Eur J Nucl Med* 1996; 23: 1409–1415.
6. Nakamoto Y, Saga T, Ishimori T, Higashi T, Mamede M, Okazaki K, et al. FDG-PET of autoimmune-related pancreatitis: preliminary results. *Eur J Nucl Med* 2000; 27: 1835–1838.
7. Kubota R, Kubota K, Yamada S, Tada M, Takahashi T, Iwata R, et al. Methionine uptake by tumor tissue: a microautoradiographic comparison with FDG. *J Nucl Med* 1995; 36: 484–492.
8. Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, et al. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. *Int J Radiat Oncol Biol Phys* 1996; 35: 27–35.
9. Uematsu M, Shioda A, Suda A, Fukui T, Ozeki Y, Hama Y, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys* 2001; 51: 666–670.
10. Nagata Y, Negoro Y, Aoki T, Mizowaki T, Takayama K, Kokubo M, et al. Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002; 52: 1041–1046.
11. Negoro Y, Nagata Y, Aoki T, Mizowaki T, Araki N, Takayama K, et al. The effectiveness of an immobilization device in conformal radiotherapy for lung tumor: reduction of respiratory tumor movement and evaluation of the daily setup accuracy. *Int J Radiat Oncol Biol Phys* 2001; 50: 889–898.
12. Aoki T, Nagata Y, Negoro Y, Takayama K, Mizowaki T, Kokubo M, et al. Evaluation of lung injury after three-dimensional conformal stereotactic radiation therapy for solitary lung tumors: CT appearance. *Radiology* 2004; 230: 101–108.
13. Giraud P, Grahek D, Montravers F, Carette MF, Deniaud-Alexandre E, Julia F, et al. CT and (18)F-deoxyglucose (FDG) image fusion for optimization of conformal radiotherapy of lung cancers. *Int J Radiat Oncol Biol Phys* 2001; 49: 1249–1257.
14. Kitano H, Magata Y, Tanaka A, Mukai T, Kuge Y, Nagatsu K, et al. Performance assessment of O-18 water purifier. *Ann Nucl Med* 2001; 15: 75–78.
15. Hamacher K, Coenen HH, Stocklin G. Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med* 1986; 27: 235–238.
16. Comar D, Cartron J, Maziere M, Marazano C. Labelling and metabolism of methionine-methyl-^{11}C. *Eur J Nucl Med* 1976; 1: 11–14.
17. Magata Y, Saji H, Tokui T, Ohmomo Y, Yamada Y, Hirata M, et al. High reactivity of [^{11}C]CH_3I with thiol group in the synthesis of C-11 labeled radiopharmaceuticals. *Ann Nucl Med* 1993; 7: 173–177.
18. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92: 205–216.
19. Kubota K. From tumor biology to clinical PET: A review of positron emission tomography (PET) in oncology. *Ann Nucl Med* 2001; 15: 471–486.
20. Abe Y, Matsuzawa T, Fujiwara T, Itoh M, Fukuda H, Yamaguchi K, et al. Clinical assessment of therapeutic effects on cancer using ^{18}F-2-fluoro-2-deoxy-D-glucose and positron emission tomography: preliminary study of lung cancer. *Int J Radiat Oncol Biol Phys* 1990; 19: 1005–1010.
21. Haberkorn U, Strauss LG, Dimitrakopoulou A, Engenhart R, Oberdorfer F, Ostertag H, et al. PET studies of fluorodeoxyglucose metabolism in patients with recurrent colorectal tumors receiving radiotherapy. *J Nucl Med* 1991; 32: 1485–1490.
22. Kubota K, Matsuzawa T, Fujiwara T, Ito M, Hatazawa J, Ishiwata K, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. *J Nucl Med* 1990; 31: 1927–1932.
23. Kubota K, Yamada S, Ishiwata K, Ito M, Fujiwara T, Fukuda H, et al. Evaluation of the treatment response of lung cancer with positron emission tomography and L-[methyl-^{11}C]methionine: a preliminary study. *Eur J Nucl Med* 1993; 20: 495–501.
24. Plowman PN. Stereotactic radiosurgery. VIII. The classification of postradiation reactions. *Br J Neurosurg* 1999; 13: 256–264.
25. Ishii K, Ogawa T, Hatazawa J, Kanno I, Inugami A, Fujita H, et al. High L-methyl-[^{11}C]methionine uptake in brain abscess: a PET study. *J Comput Assist Tomogr* 1993; 17: 660–661.
26. Yamada Y, Uchida Y, Tatsumi K, Yamaguchi T, Kimura H, Kitahara H, et al. Fluorine-18-fluorodeoxyglucose and carbon-11-methionine evaluation of lymphadenopathy in sarcoidosis. *J Nucl Med* 1998; 39: 1160–1166.
27. Higashi K, Clavo AC, Wahl RL. *In vitro* assessment of 2-fluoro-2-deoxy-D-glucose, L-methionine and thymidine as agents to monitor the early response of a human adenocarcinoma cell line to radiotherapy. *J Nucl Med* 1993; 34: 773–779.