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Introduction

Lung cancer is the most common malignant disease in many countries. The most curative treatment for patients continues to be surgical resection. With current imaging procedures, candidates for surgical resection are still limited. Radiotherapy and chemotherapy continue to play an important role in the treatment ¹⁾. Various combinations of treatment regimen have been developed and tested. Although the final evaluation of treatment regimen is the survival rate, in the selection of the best treatment for each patient, prediction and early evaluation of the outcome are the most important. Various factors of tumor-related such as histology, size, TNM stage, and of host-related such as performance status, age are known to be clinical prognostic parameters. Also various in vitro cell culture techniques for predicting the probability of tumor control have been reported but required biopsied tumor samples²⁾. Investigations of metabolic parameters of tumor with positron emission tomography (PET) is expected to apply for treatment evaluation.

In the experimental study, L-[methyl ^{11}C]methionine (^{11}C -Met) uptake by AH109A tumor showed a rapid decrease after 20 Gy irradiation which precede the extension of necrosis and the tumor volume decrease³⁾. Also comparative study of five tracers showed that the responses of thymidine (Thd) and Met to tumor radiotherapy are faster and more sensitive than [^{18}F]-2-fluoro-2-deoxy-D-glucose (^{18}FDG) and [^{67}Ga]-citrate⁴⁾. In this paper, in order to demonstrate the possible unique role of PET in monitoring the radiotherapeutic effect and the recurrence of lung cancer, ^{11}C -Met PET study before and on the way or after radiotherapy were compared to the computed tomography (CT) and to the clinical evaluation of treatment results.

Materials and Methods

Patients

Thirteen patients of lung cancer (from 39 to 82 yr old, 3 women and 10 men) were studied. Histological diagnosis of five patients of large cell carcinoma, four adenocarcinoma, two squamous cell carcinoma, a small cell carcinoma, a malignant fibrous histiocytoma were obtained by transbronchial biopsy or needle biopsy. TNM staging following the 1987 edition of UICC was performed using chest CT, bone scan, brain CT and abdominal ultrasound or CT. A patient of adenocarcinoma stage 1,74 y.o. woman refused operation. Operation was not indicated to all other patients due to its advanced stage (stage 3a, 3b or 4) or inadequate pulmonary function test. All patients had radiotherapy by cobalt-60 standard 2 Gy/fraction, 10 Gy/week schedule with the total dose from 50 Gy to 70 Gy depending on the tumor size and location, and on the physical condition. Four patients had a course of chemotherapy simultaneously. A patient of Pancoast type (superior pulmonary sulcus) tumor had second radiotherapy for the pain relief, 14 month after the first radiotherapy. The investigation was approved by the clinical research committee of our university and informed consent was obtained from every patient.

PET and CT

^{11}C -MET was synthesized using automated synthesis system as described previously⁵). Radiochemical purity was over 99 %. Quality assurance tests for clinical use were performed according to the safety guidelines of our university. In 8 patients, PET study was performed before and after a course of radiotherapy. In two patients, second PET studies were performed during the course, at the dose of 10 Gy. A patient had five studies along the two courses of radiotherapy. A patient had 5 studies along the radiotherapy, follow-up and recurrence. Total 33 PET studies were performed with the mean injection dose of ^{11}C -MET was 14.8 ± 6.9 mCi (548 ± 255 MBq). Ten studies were performed with ECAT II (EG & G, Ortec, Oak Ridge, USA), 23 studies were performed with PT931/04 (CTI, Knoxville, USA).

After the transmission scan using a external ring source for the attenuation correction, ^{11}C -MET was injected intravenously as a bolus. When the PT931/04 scanner was used, eight or nine dynamic scan of 5 min each were performed over the seven slice levels covering a 5 cm width of the cross sections. When the single slice scanner ECAT II was used, three to five step-wise scan of 5 min each were performed from 25 min post injection as described previously⁶). The PET images were reconstructed using a measured attenuation correction and were corrected for the decay. CT was performed on the day before every PET study. CT was used to determine the image level of the greatest tumor diameter using identical positioning supports for both CT and PET.

Evaluation

PET images obtained from 30 to 40 min after injection were used for evaluation because of low blood-pool activity and constant activities of tumor and muscle⁷⁾. The tumor area including the highest activity point was used for the tumor region of interest (ROI), mean ROI size was 4.4 cm². Eight muscle ROIs were placed in the paravertebral, shoulder, and anterior chest muscle bilateral in the same slice as the tumor. Mean muscle counts was obtained with averaging the six ROIs, neglecting the maximum and minimum. Both of muscle ROIs and tumor ROI were copied to the corresponding transmission image with the same dimension in the display and checked carefully to avoid the partial volume effect and the contamination from other tissues as previously⁶⁾. Then tumor/muscle radioactivity (T/M) ratio was obtained. The tumor area on the hard copy of sequential CT images were measured by the planimeter and multiplied by the scan interval (10 mm), and calibrated by the matrix size. Tumor volume was obtained by the summation of each slice of tumor. Clinical evaluations of treatment results were performed following the method standardized by WHO⁸⁾. Also data of local recurrence were decided using chest X-ray or CT.

Result

Details of patients' data, histology, irradiation dose at the second PET study, T/M ratio and the tumor volume are shown in Table 1. The distributions of the T/M ratio were 6.2 ± 1.5 (n=14) for before therapy and 3.0 ± 1.7 (48 % of before) both after and on the way of 14 radiotherapy in 13 patients. The T/M ratio of after the completion of radiotherapy was 2.6 ± 1.6 (n=12), which was 42 % of before. Tumor volume of each patient showed wide variation, then, percent volume of after therapy compared to before was shown as 74.1 ± 21.5 % (n=14) both after and on the way of therapy and 70.5 ± 21.1 % (n=12) after the therapy. The percent values of T/M ratio and tumor volume after radiotherapy (42 % vs 70.5 %) clearly showed that ¹¹C-MET uptake reduction was significantly larger than the volume reduction after radiotherapy. Figure 1 showed individual correlations of percent uptake and tumor volume after therapy. A 45° line indicate parallel decrease of both value. Every patient data except Pt. No. 10 distributed below the line showed the same results. Fig. 2 showed the irradiation dose-response of ¹¹C-MET uptake by the tumor. The patients responding to therapy showed large decrease of ¹¹C-MET uptake after therapy. And the studies at 10 Gy, 30 Gy and 40 Gy plotted on the line of decrease suggested that ¹¹C-MET uptake showed linear decrease dose-dependently in the course of radiotherapy. Two patients showed high residual uptake after radiotherapy 84 % and 64 % of before, and showed early local recurrence by 3 month and 1 month respectively. These two patients were clearly differentiated from the others by the ¹¹C-MET uptake after therapy, but not by the percent

tumor volume after therapy (49 % and 80 % respectively). After radiotherapy, the T/M ratio of patients responding to therapy was 2.0 ± 0.7 (n=10).

Discussion

Clinical PET study with ^{18}F FDG monitoring radio-chemotherapy of head and neck cancer⁹⁾, lung cancer¹⁰⁾, and liver tumor¹¹⁾ have shown that the changes of ^{18}F FDG uptake before and after tumor therapy were correlated with the clinical evaluation of treatment responding and resisting tumors. But the tumor volume changes by X-ray or CT, a standard of treatment evaluation have not been correlated to the PET measurements in the previous studies. The superiority of metabolic evaluation by PET over the anatomic volume measurement by CT in treatment evaluation has not yet been demonstrated.

In this study, ^{11}C -Met uptake reduction was larger than the volume reduction. In two cases of early recurrence, high residual ^{11}C -Met uptake after treatment was clearly differentiated from large decrease of ^{11}C -Met uptake in the responding group. But the volume changes were almost similar in the both. It suggested that ^{11}C -Met tumor uptake with PET is more sensitive indicator for treatment evaluation than the tumor volume with CT.

Experimentally, ^{11}C -Met tumor uptake by AH109A tumor was reduced to 50 % of control at 12 hr after 20 Gy irradiation while tumor volume reduced to 50 % at 10 day. Transplanted AH109A tumor in the rat with the volume doubling time 1.2 day was quite different from slow growing spontaneous human lung cancer. Different response speed can be explained by the different growth rate. Radiotherapy was performed with the 2 Gy fractions in clinically, and with single dose of 20 Gy in experimentally. The linear decrease of ^{11}C -Met uptake dose-dependently in Fig. 2 can be explained by the effect of fractional radiotherapy. In spite of these differences, both experimental and clinical study showed similar results. ^{11}C -Met tumor uptake representing amino acid metabolism with strong correlation to protein synthesis¹²⁾, seems to monitor tumor viability more directly than the tumor volume.

In our previous studies, ^{11}C -Met uptake by lung cancer was correlated to the prognosis¹³⁾. But in this study, we cannot differentiate the early recurrence group from the responding group with ^{11}C -Met uptake before therapy. Further study is necessary to draw a conclusion at this point.

Four patients received a chemotherapy and the radiotherapy simultaneously. That may have some effects on the tumor viability and ^{11}C -Met uptake, but no significant differences were observed between the radiotherapy alone and the combination in this study.

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Table 1. PET and CT pre and post radiotherapy of lung cancer.

Patient ID	Age	Sex	Histology	Dose(Gy)	¹¹ Cmet tumor uptake(T/M)		Tumor volume (cm ³)		
					Pre	Post	Pre	Post	
1. KS 582	76	M	Adeno	10	8.6	5.0	28	25	91
2. YY 606	61	F	Small	60+C	7.8	2.6	41	30	73
3. KH 626	60	M	Large	50+C	5.8	2.7	100	56	56
4. MK 724	69	M	Large	60	5.0	2.0	55	51	93
5. KI 792	82	M	Large	10	6.7	5.7	4.5	4.5	100
6. ST 858	74	F	Adeno	64	3.4	1.6	47	1.1	52
7. IK 923	68	M	Adeno	66+C	5.2	1.6	30	2.1	57
8. TT 984	49	F	M.F.H.	68	7.7	4.9	64	173	80
9. SH 1105	66	M	Squamous	50+C	7.4	1.4	19	67	33.5
10. TK 54	64	M	Large	70	7.5	6.3	84	121	59
11. ST 590	39	M	Adeno	42	6.4	3.0	47	68	41
				69		1.6	25	35	51
12. SI 769	71	M	Squamous	59	4.8	2.0	42	46	36
						2.7	56	53	115
13. NY 964	52	M	Large	30	6.2	3.6	58	87	85
				64	4.8	1.3	27	41	44.5
						1.7	35	36	88
						2.6	54	33	80
						5.6	117	32	78

Mean and SD (n=14) 6.2±1.5 3.0±1.7 47.1±20.7 74.1±21.5

per cent of pre therapy

+C chemotherapy

R early recurrence

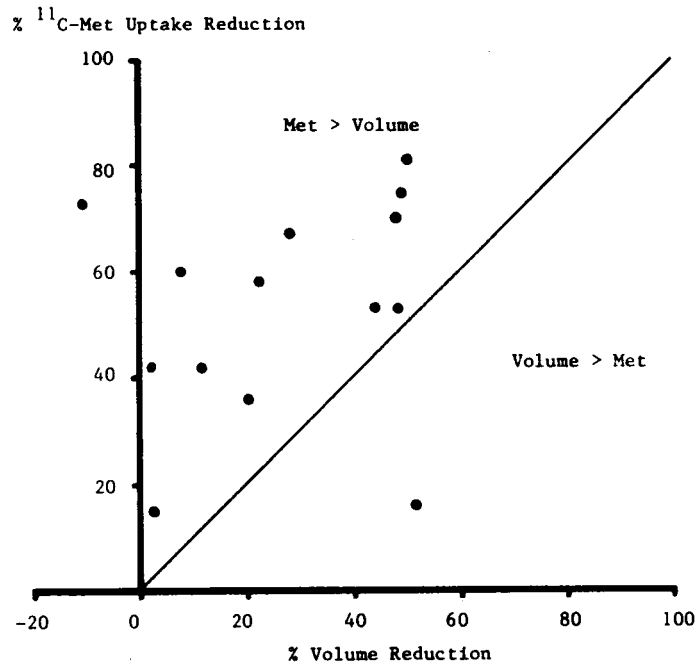


Fig. 1. Comparison of the ¹¹C Met uptake reduction and the tumor volume reduction after radiotherapy. Abscissa is % ¹¹C Met uptake reduction. Ordinate is % tumor volume reduction. A 45 degree line indicate the parallel change of both parameters.

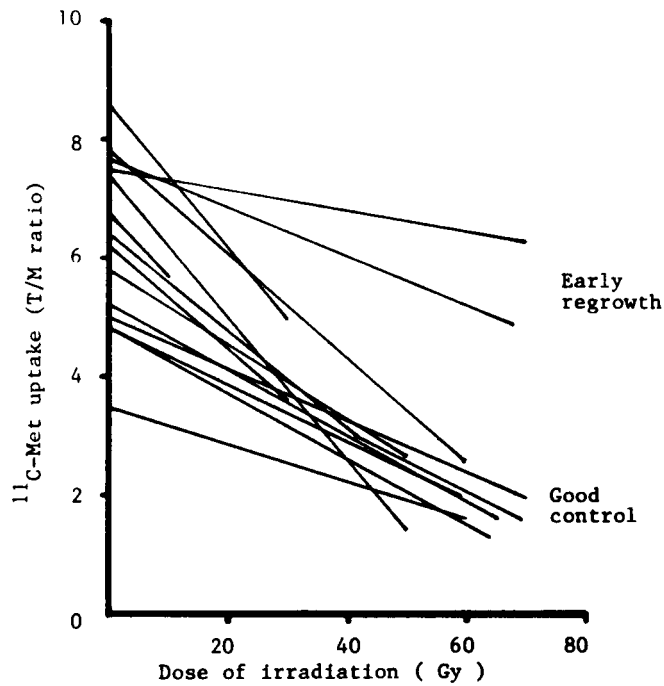


Fig. 2. Irradiation dose-response of ¹¹C Met uptake and treatment results. Abscissa is ¹¹C Met uptake (T/M) ratio by the tumor. Ordinate is the dose of irradiation in the 2Gy fractional radiotherapy course.