(C-11)-L-Methionine Positron Emission Tomography of Human Lung Cancers

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Introduction

Recently, positron emission tomography(PET) with (C-11)-labeled-L-methionine(C-11-MET) has been reported to be useful for study of human cancer. The increase in methionine incorporation into tumor tissue was experimentally demonstrated using C-14[1] and C-11[2] labeled amino acids. And human brain glioma[3] and lung cancer[4] were also studied by PET using C-11-MET.

In this work, we have investigated the histological dependence of C-11-MET uptake in human lung cancer.

Materials and Methods

C-11-MET was synthesized by the modified method of Comar et al.[5] Quality assurance tests of C-11-MET for clinical use were performed according to the safety guidelines of the clinical research committee of our institution. The specific activity of C-11-MET varied from 5 to 10 mCi/μmol at the time of injection and its radiochemical purity was 96 % to 99 %.

As shown in the Table 1, twelve patients with histologically proven were studied using PET(ECAT II). All patients were clinically evaluated in detail by x-ray CT to determine the scan level for PET study. Written informed consent was obtained in all patients.

After transmission scanning, using a Ge-68 ring source for the attenuation correction, 5 to 16 mCi of C-11-MET were injected intravenously as a bolus. Serial tomographic scans were performed at the slice level through the tumor as determined by x-ray CT and transmission scans. The sequences of emission scans varied from 2 to 10 min depending on the injected dose and the time after injection. Scans were finished 30 or 40 min after injection. The spacial resolution was 1.8 cm FWHM at a medium resolution shadow shield. The scans were corrected for decay and attenuation.

Quantitation of C-11-MET uptake was attempted using mean pixel counts in the region of interest of the PET image. In each patient, whose tumor size was more than 3 cm in diameter, to obtain the differential absorption ratio (DAR), counts per pixel data were calibrated by the injection dose, body

weight, scan time, and ECAT II - auto well counter calibration factor.[6)]

$$DAR = \frac{\text{mean ECAT count per pixel volume}}{\text{injected dose / body weight} \times \text{scan time}} \times \text{calibration factor}$$

Results

All twelve patients had very high accumulation of C-11-MET in lung tumors in early scans. For example, in case 6, with squamous cell carcinoma, very high radioactivity appeared in the tumor(Fig. 1,2). Figure 3 shows the time-activity curves of case 6. C-11-MET in the aorta decreased rapidly by 20 min after injection, and radioactivity in the muscle, in the lung, and in the tumor was almost constant from 10 min after injection. Figure 4 shows the time-activity curves for each tumor except case 2 and case 4, whose sequential emission scans were performed at another levels. The DARs of tumors were almost constant during scan period in all cases. The highest value of DAR was seen in the case of large cell carcinoma(case 8), and the case 12, with adenocarcinoma, showed the lowest uptake of C-11-MET. The DARs of tumor, muscle, and lung in all patients at 30 min after injection are shown in Table 1. Although injected dose of C-11-MET per body weight varied from 0.08 to 0.30 mCi/kg, the DARs of the muscle of each patient remained constant with a 12 % variation(0.750 ± 0.086 mean ± S.D.). Thus the DARs were considered to be reliable markers for C-11-MET accumulation of human study. The average DAR value in squamous cell carcinoma was 2.36 ± 0.24 at 30 min, whereas that of large cell carcinoma was 3.63 ± 0.31. The DAR of adenocarcinoma was 1.38.

Discussion

In this study, all cases of tumors were clearly visualized by PET using C-11-MET, and the uptake of C-11-MET in the tumors and normal tissues were semi-quantitatively evaluated by DARs. Since the patterns of the DAR curves during scan period showed that C-11-MET distribution in the tumor had no significant change from 10 to 40 min, the uptake of C-11-MET in the tumor was expressed by the DAR at 30 min. The results suggested that the DARs of large cell carcinoma were higher than those of squamous cell carcinoma($p<0.01$). Methionine is one of the essential amino acids. Busch et al.[1)] showed that Walker tumor incorporated C-14-Methionine into the nuclear protein 1 hour after injection. In our preliminary experiment using s.c. rat ascitic hepatoma, trichloroacetic acid insoluble fraction of the tumor was more than 60 % of whole homogenate activity of the tumor 30 min after injection of C-11-MET. So it is probable that the uptake of C-11-MET in the tumor may be explained on the increased demand of amino acids for protein synthesis. Although it is not known what makes difference of DARs among tumors, the

characterization of the tumor in accordance with the C-11-MET uptake may be useful to classify the tumor and to predict a tumor's response to therapy in future.

References

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Table 1. Uptake of ^{11}C-Methionine in Clinical study

Patients	Diagnosis	DAR (30 min) tumor	muscle (tumor/muscle)	lung (Tumor/lung)	Dose (mCi/kg)
1. K W	lung cancer (squamous cell)	2.76	0.68 (4.06)	0.35 (7.89)	0.13
2. K S	lung cancer (squamous cell)	3.00	0.76 (3.95)	0.54 (5.56)	0.19
3. T S	lung cancer (squamous cell)	2.36	0.90 (2.62)	0.73 (3.23)	0.17
4. S H	lung cancer (squamous cell)	2.86	0.72 (3.97)	0.28 (10.21)	0.30
5. K Y	lung cancer (squamous cell)	2.33	0.71 (3.28)	0.24 (9.71)	0.25
6. G T	lung cancer (squamous cell)	2.44	0.64 (3.81)	0.39 (6.26)	0.15
7. H O	lung cancer (squamous cell)	2.66	0.85 (3.13)	0.37 (7.19)	0.16
8. K T	lung cancer (large cell)	4.06	0.68 (5.97)	0.42 (9.67)	0.12
9. H Y	lung cancer (large cell)	3.43	0.71 (4.83)	0.42 (8.17)	0.19
10. S O	lung cancer (large cell)	3.40_a	0.70_a (4.86)	0.52_a (6.54)	0.08
11. S S	lung metastasis (thyroid cancer)	3.20	0.92 (3.48)	0.32 (10.00)	0.24
12. H S	lung cancer (adenocarcinoma)	1.38	0.68 (2.03)	0.31 (4.45)	0.17

a : 20 min after injection

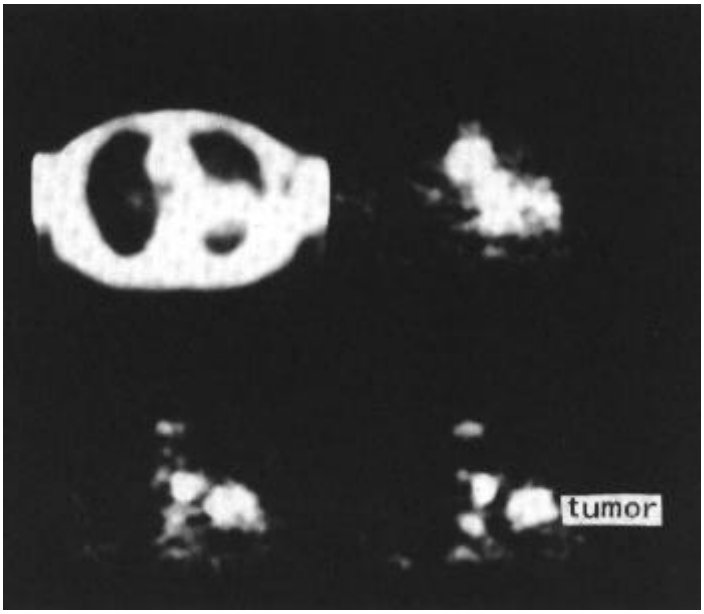

Fig. 1. Lung squamous cell carcinoma images obtained with transmission (upper left), 2 min (upper right), 10 min (lower left), and 30 min (lower right) after injection of C-11-MET. (Case 6)

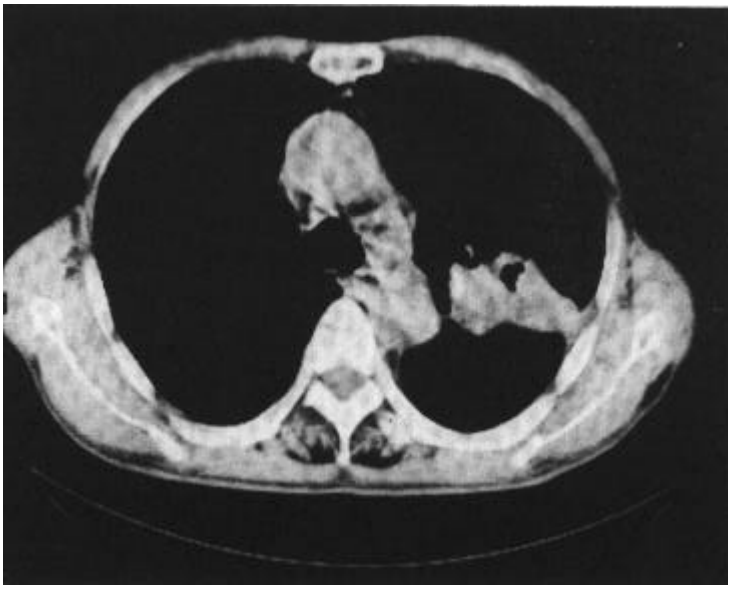

Fig. 2. Chest x-ray CT scan showing lung tumor at the same level of PET scan (Fig. 1). (Case 6)

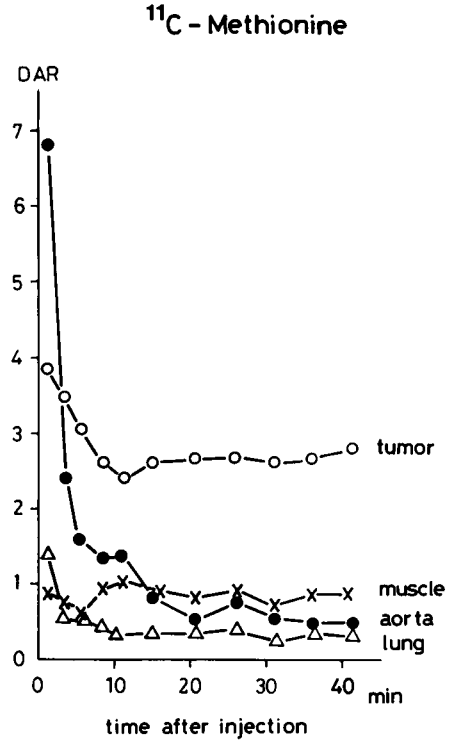

Fig. 3. Time-activity curves of Case 6, lung squamous cell carcinoma after injection of 13 mCi of C-11-MET.

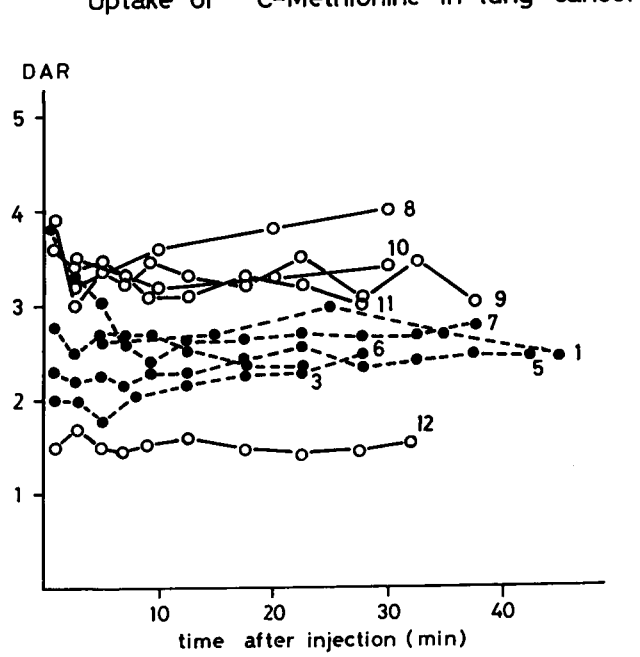

Fig. 4. Time activity curves of lung tumor. Differential absorption ratios of the tumor were calculated from PET scan data.