IV. 2 Radiotherapeutic Effects on the Tumor Uptake of $^{11}$C-L-Methionine

Kubota K., Matsuzawa T., Fujiwara T., Ishiwata K.*, Sato T. and Kubota R.
Department of Radiology and Nuclear Medicine, Research Institute for TB and Cancer, Tohoku University
Cyclotron and Radioisotope Center, Tohoku University*

Introduction

Malignant tumors are generally characterized by uncontrolled cell proliferation which requires increased metabolic activity. Recently, positron emission tomography (PET) has been demonstrated as a unique method for in vivo assessment of metabolic activity in tumor. We have experimentally and clinically shown the usefulness of $^{11}$C-L-methionine ($^{11}$C-Met) for the detection and grading of lung cancers using PET.\(^1\text{--}^3\) It may be a great help of individual therapy control for cancer patients. But the evaluation of cancer treatment with $^{11}$C-Met has never studied.

The assessment of radiotherapeutic effects on experimental tumors using $^{18}$F-2-fluoro-2-deoxy-D-glucose ($^{18}$FDG) and $^{13}$N-glutamate has been reported. In this study, the uptake of $^{11}$C-Met against volume changes in rat tumor model AH109A after single dose irradiation of Cobalt-60 has been sequentially studied to evaluate the tumor response to radiotherapy.

Materials and Methods

Transplantable ascitic hepatoma AH109A cells were inoculated s.c. in the thigh of young male Donryu rats (weighing from 180 to 250 g). Tumors were exposed to single dose of $^{60}$Co γ-ray 5-20 Gy (50 rad/min, SSD 65 cm, depth 1 cm with 5 mm sheet of bolus). Rats were anesthetized with sodium-pentobarbital 10 mg i.p. and fixed with adhesive tape so that only the thigh with tumor was in the field of irradiation but body shield was not used (Fig. 1). Tumor sizes were measured everyday with vanier-caliper, and the product of three diameters was designated as tumor volume. $^{11}$C-Met was synthesized from $^{11}$CH$_3$I and homocysteine following the modified method of Comer et al.\(^4\), using an automated synthesis system of Iwata et al.\(^5\) Radiochemical purity was over 96 %. At various time after the radiation, the animals were fasted for 8 hours, injected about 100 μCi of $^{11}$C-Met i.v. through the tail vein and sacrificed by cervical dislocation 30 after. Tissue samples were excised and weighed and radioactivity was counted by auto-gamma counter. Radioactivity of the tissue was expressed as Differential absorption ratio (DAR).\(^6\)

\[
\text{DAR} = \frac{\text{Counts of tissue/Sample weight}}{\text{Injection dose counts/Buff weight}}.
\]
Results

After single dose of 20 Gy radiation, tumor volume kept on increasing until one day after. There were no significant differences in the tumor volume between the control and the irradiated tumor (n=8 each) at the day one. Then, the volume of irradiated tumor was decreasing gradually, became significantly smaller than that of before radiation at the day 6 (76±16 %, n=8, p<0.05), and decreased to 48±12 % volume of before radiation at the day 10.

Figure 2 showed $^{11}$C-Met uptake by the tumor, bone with marrow (femor of the tumor leg), muscle (thigh of the non-tumor leg), and blood after the 20 Gy radiation. $^{11}$C-Met uptake by the tumor started to decrease at 6 hr, but the standard deviation was too large to be significant. Significant differences were observed at 12 hr and after, 54±19 % and 51±14 % of before radiation at 12 hr and 24 hr respectively (both p<0.001). At the day six, $^{11}$C-Met uptake by the tumor was 30±5 % of before radiation and almost the same as the muscle. Bone with marrow showed almost the same pattern as the tumor, but there was a recovery at the day six. Blood activity was very low and constant.

Dose-response effects of radiation on the tumor uptake of $^{11}$C-Met was studied at 48 hr after radiation. There were significant difference in the tumor uptake of $^{11}$C-Met among the control, 5 Gy and 10 Gy each other, but not significant between 10 Gy and 20 Gy.

Percent changes of tumor volume and $^{11}$C-Met uptake were plotted on the same graph (Fig. 3).

Discussion

The tumor uptake of $^{11}$C-Met clearly showed very sensitive response to radiation, but the tumor volume response was very slow. There was large dissociation between the tumor volume curve and the $^{11}$C-Met tumor uptake curve. Also at the 48 hours after radiation, dose-responsive effects of radiation on the tumor uptake of $^{11}$C-Met was clearly observed. These results suggest that $^{11}$C-Met uptake by the tumor may be more sensitive indicator for the evaluation of radiotherapy than the measured tumor volume.

Recently, studies about the tracer uptake correlation to radio or chemotherapy have been reported using various tumor-tracer combination. Abe et al. demonstrated good correlation of $^{18}$FDG uptake to tumor volume reduction and to regrowth after single dose of radiation. Knapp et al. showed that $^{13}$N-glutamate uptake by tumor was dropped 30 min after radiation and recovered 48 hr after and that these were not coupled with the changes of blood flow. Also Kallman et al. showed that tumor blood flow was decreased 3 hr after radiation, but significantly increased at 3 to 4 days. Then, the possibility that the decrease of $^{11}$C-Met uptake was induced by blood flow reduction is remote. Probably, the decrease of $^{11}$C-Met uptake by the tumor may reflect its membrane transport damage or inactivation of enzymes for
amino acid metabolism.

References

Fig. 1. Illustration of experimental setting of rats with AH109A tumor for $^{60}$Co-radiation.
Fig. 2. Effects of $^{60}$Co-radiation on the tissue uptake of $^{11}$C-Met.

Fig. 3. Comparison of the tumor growth curve and $^{11}$C-Met uptake curve of the tumor.