# 18F-Fluoro-2'-Deoxyuridine and Experimental Brain Tumor

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| 著者 | Tsurumi Y., Kameyama M., Shirane R., Katakura R., Suzuki J., Ishiwata K., Ido , T. |
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# III. 7 $^{18}$F-Fluoro-2'-deoxyuridine and Experimental Brain Tumor

Tsurumi Y., Kameyama M., Shirane R., Katakura R., Suzuki J., Ishiwata K.* and Ido T.*
Division of Neurosurgery, Institute of Brain Diseases, Tohoku University School of Medicine
Cyclotron Radioisotope Center, Tohoku University*

We have already reported the usefulness of $^{18}$F-fluoro-2'-deoxyuridine ($^{18}$FdUrd) as a brain tumor-detecting agent from the view points of nucleic acid metabolism for positron emission computed tomography (PECT).[1] In this experiment, the characteristics of FdUrd was investigated more in detail by using multiple labeled autoradiographic(ARG) technique recently we reported.[2]

## Materials and Method

C6 rats glioma cells ($1\times10^5$) were implanted semistereotaxically into the brains of 27 Wistar rats weighing about 200 gm. About three weeks later, under the sodium pentobarbital anesthesia, 2-4 mCi of $^{18}$FdUrd and 100 μCi/kg of (2-$^{14}$C) thymidine ($^{14}$C-dThd) were injected i.v. into 6 rats simultaneously. In other 10 rats simultaneous injection of 2-4 mCi of $^{18}$FdUrd and 125 μCi/kg of 2-amino[1-$^{14}$C]isobutyric acid ($^{14}$C-AIB) were done. Animals were decapitated 30 minutes after the injection, and frozen brains were cut 30 μm thickness in a cryostat. The multiple-labeled autoradiographic study was performed according to the method previously reported.[2] In brief, sections were exposed to a X-ray film twice; for the first six hours to get the image of $^{18}$F, and for following seven days to get the image of $^{14}$C. Brain sections used for processing autoradiography were subsequently stained by hematoxylin. The autoradiographic images of $^{18}$FdUrd were compared with those of $^{14}$C-thymidine, $^{14}$C-AIB and hematoxylin-stained sections.

In other group of rats, pieces of the brain tumor were sampled for analyzing the uptake of $^{18}$FdUrd in each 3 rats sacrificed at 30 min. and 2 hours after the administration. Also the accumulation of $^{18}$F in the acid-insoluble and acid soluble nucleotide fractions was examined in 2 rats sacrificed at 30 min, 2 rats at 2 hours and one rat at 7 hours after the administration of $^{18}$FdUrd.

## Results

ARG of the $^{14}$C-dThd showed the accumulation of $^{14}$C only in the periphery of the experimental brain tumor (Fig. 1). And $^{14}$C-AIB ARG revealed the homogenous accumulation of $^{14}$C not only in the periphery of the tumor but also in the part of central necrosis (Fig. 2). On the other hand, $^{18}$FdUrd ARG demonstrated the high accumulation of $^{18}$F mainly in the periphery of the brain tumor, however, the low accumulation was also recognized in the part of central necrotic tissue.

The uptake of $^{18}$FdUrd was 0.47% dose/g in both groups of rats sacrificed at 30 min. and 2 hours after the administration. Nevertheless, the accumulation of $^{18}$F in the acid-insoluble and acid soluble nucleotide fractions were 9.3% at 30 min, 25% at 2 hours and it increased up to 44% at 7 hours.

## Discussion

It is of no doubt that the three-dimensional in vivo representation of nucleic acid metabolism will surely give us important informations to treat the yet unbeatable foe for mankind - malignant neoplasms. $^{11}$C-dThd, which is a precursor of DNA synthesis, is expected to be the most effective tracer to reveal the nucleic acid metabolism for PECT. However, the complicated and poorly efficient biosynthetic method of $^{11}$C-dThd[4] makes the routine clinical use difficult. On the other hand, fluorinated pyrimidines are known to reflect also the nucleic acid metabolism[5], and among those, it was reported that the tumor uptake of $^{18}$FdUrd was higher than those of $^{18}$F-fluorouracil (5-FUra) or $^{18}$F-fluorouridine (5-FUrd).[6] FdUrd is one of the intermediates of 5-FUra and is a precursor of 5-fluoro-2'-deoxyuridine-5'-monophosphate which is a competitive blocking agent to thymidyrate synthetase[7], and also 5-FUrd is incorporated into RNA.

The tumor image of $^{18}$FdUrd we obtained through the multiple labeled ARG study was clearly different from that of $^{14}$C-AIB, but was rather similar to the $^{14}$C-dThd ARG image. The $^{14}$C-dThd ARG showed the localized accumulation of $^{14}$C in the periphery of the brain tumor and $^{18}$FdUrd also revealed the higher $^{18}$F distribution at the same region. On the other hand, the homogeneous tumor image of $^{14}$C-AIB ARG, which has been used for demonstrating the blood brain barrier (BBB) impairment[8], probably indicates the absence of BBB in the brain tumor. And this BBB dysfunction in the brain tumor seems responsible to the accumulation of $^{18}$F even in the central necrotic tissue.

It is also of great interest that the uptake of $^{18}$FdUrd in the brain tumor did not show remarkable change from 30 min. to 2 hours after the administration, while the percentage of acid-insoluble and acid-soluble nucleotid fractions increased with time. It points out the possibility that $^{18}$F existed in the acid-soluble nucleoside fraction which plays an important role as a precusor pool of nucleic acid metabolism, might be much higher even 30 min. after the administration of $^{18}$FdUrd. If so, even the PECT image taken within one hour after the injection of $^{18}$FdUrd would mostly reflect nucleic acid metabolism.

There still remains some problems need further investigation, however, these results suggest that $^{18}$FdUrd distribution pattern closely correlates with nucleic acid metabolism of brain tumor with high tumor/brain ratio and could be a useful tracer for PECT.

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References


1) Kameyama M., Tsurumi Y., Katakura R. et al., CYRIC Annual Report (1982) 156.
2) Kameyama M. and Ido T., Jap. J. Nucl. Med. 19 (1982) 1233.
3) Ishiwata K., Ido T., Murakami M. et al., CYRIC Annual Report (1982) 150.
4) Christman D., Crawford E., Friedkin M. et al., Proc. Nat. Acad. Sci. 69 (1972) 988.
5) Heiderberger C., in : Holland JF, Frei III(eds), Cancer Medicine 2nd ed. Philadelphia Lea & Febiger (1982) 801.
6) Abe Y., Fukuda H., Ishiwata K. et al., Eur. J. Nucl. Med. 8 (1983) 258.
7) The Chemistry of Radiopharmaceuticals, Masson publishing USA, Inc., New York, (1978) pp 205-213.
8) Blasberg R., Jenstermacher J. and Patlak C., J. CBF Metabol, 3 (1983) 8.


Fig. 1. $^{18}$FdUrd ARG (left), $^{14}$C-AIB ARG (center) and hematoxylin-stained section (right).

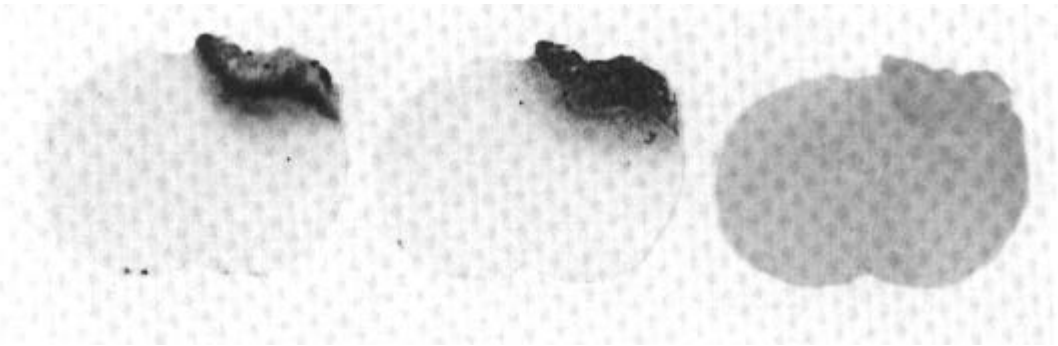

Fig. 2. $^{18}$FdUrd ARG (left), $^{14}$C-AIB ARG (center) and hematoxylin-stained section (right).