Dynamic Human Imaging using 18F-FRP170 as a New PET Tracer for Imaging Hypoxia

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The 2-nitroimidazole analogs are known to have an interesting property, namely, they accumulate selectively in hypoxic tissue. The mechanism for the intracellular retention in hypoxic cells is not fully understood. It is believed that 2-nitroimidazoles undergo nitro-reduction with the formation of products that bind to intracellular elements and remain trapped in hypoxic tissues[1)]. ^{18}F-Fluoromisonidazole (^{18}F-FMISO) was the first such radiopharmaceutical developed, and was used most widely for imaging hypoxia. However, misonidazole is a rather lipophilic compound, and the images of ^{18}F-FMISO may have a low target-to-background ratio. Therefore, there is ongoing research to develop better compounds for clinical use. ^{18}F-FRP170, 1-(2-fluoro-1-[hydroxymethyl]ethoxy)- methyl-2-nitroimidazole, is a new hypoxia imaging agent for positron emission tomography (Fig. 1). This compound was synthesized by ^{18}F-labeling of RP170, which was developed as a new hydrophilic 2-nitroimidazole analog[2,3)]. In the present study, we analyzed dynamic whole-body imaging in healthy volunteers and dynamic tumor imaging in three patients with lung cancer.

Methods

Four healthy male volunteers and three lung cancer patients were enrolled in this study. Volunteers underwent dynamic whole-body scans just after injection of ^{18}F-FRP170 for about 90 min, while the lung cancer patients underwent dynamic tumor imaging for about 60 or 120 min. Data are expressed as standardized uptake values (SUV). Regions of interest were placed

over images of each organ or tumor to generate time–SUV curves.

Results

The series of dynamic whole-body scans showed rapid elimination of ^{18}F-FRP170 from the kidneys following elimination from the liver. Figure 2 shows a series of dynamic whole-body images of a 32-year-old male volunteer. Very low physiological uptake was observed above the diaphragm. ^{18}F-FRP170 uptake in the lung cancer lesion could be visualized clearly from early after injection. The changes of tumor SUV, tumor/blood ratio, or tumor/muscle ratio about 30 min. after injection or later were small. Figure 3 shows ^{18}F-FRP170 images acquired 1 hr and 2 hr after injection in patient with lt. lung cancer. The tumor/muscle ratio and tumor/blood ratio were 1.69 and 1.09 at 1 h after injection, and 1.96 and 1.24 at 2 h, respectively.

Discussion

Since the 1990s, there have been many intensive studies using ^{18}F-FMISO, and a great deal of research effort has been directed toward synthesizing new hypoxia markers that overcome the limitations of ^{18}F-FMISO. Compounds characterized by high hydrophilicity were thought to be better for imaging hypoxia because of rapid blood clearance and high target-to-background ratio. Therefore, many 2-nitroimidazole analogs have been developed by changing the side chain of the drug. ^{18}F-FRP170 is designed as a hydrophilic 2-nitroimidazole analog, and is also expected to yield images with high contrast and a low background level. In the volunteer study, ^{18}F-FRP170 showed rapid elimination from almost all organs *via* excretion through the urinary pathway. In addition, its excretion into the bile was delayed. These observations were thought to be due to the high degree of hydrophilicity of the tracer. ^{18}F-FRP170 uptake in the lung cancer could be visualized clearly from early after injection. The tumor/muscle ratio tended to decrease slightly prior to 45-60 min after injection, but then tended to increase slightly. On the other hand, the tumor/blood ratio showed a rapid increase prior to about 30 min after injection, after which it increased gradually with time. The tumor/muscle ratio and tumor/blood ratio in Fig 3 were 1.69 and 1.09 at 1 h after injection, and 1.96 and 1.24 at 2 h, respectively. Both the tumor/muscle and tumor/blood ratios were higher 2 h than 1 h after injection, although the differences were too small to detect visually. The images obtained about 60 min after injection may be of sufficient quality to allow evaluation of tumor uptake in a clinical setting. However, considering the recent advances of

PET technology, the images of ^{18}F-FRP170 demonstrated in the present study may have room for improvement. For example, increasing injected doses, longer emission-scan time, or using the latest PET/CT scanner may improve the image quality. The 2-nitroimidazoles are known to enter the cells by passive diffusion; therefore, their intracellular uptake is thought not to be particularly high. It may be necessary to administer a larger amount of radioactivity than that used in the present study. From the standpoint of estimated radiation dose[4], about 370–555 MBq of ^{18}F-FRP170 may be considered safe for use in adults.

Conclusions: We analyzed dynamic ^{18}F-FRP170 images obtained in healthy volunteers and in three patients with lung cancer. Rapid elimination of the tracer from the kidney was seen in the volunteers, supporting the strong hydrophilicity of ^{18}F-FRP170. The images obtained in the cases of the lung cancer patients demonstrated good image contrast even at 1 h after injection. ^{18}F-FRP170 could be expected to yield good tumor images and allow scanning to begin early, but further investigations are warranted to clarify these points.

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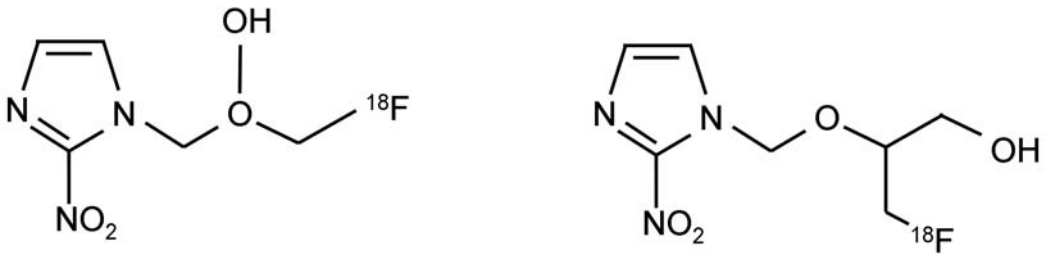

Figure 1. Chemical structures of ^{18}F-FMISO and ^{18}F-FRP170.

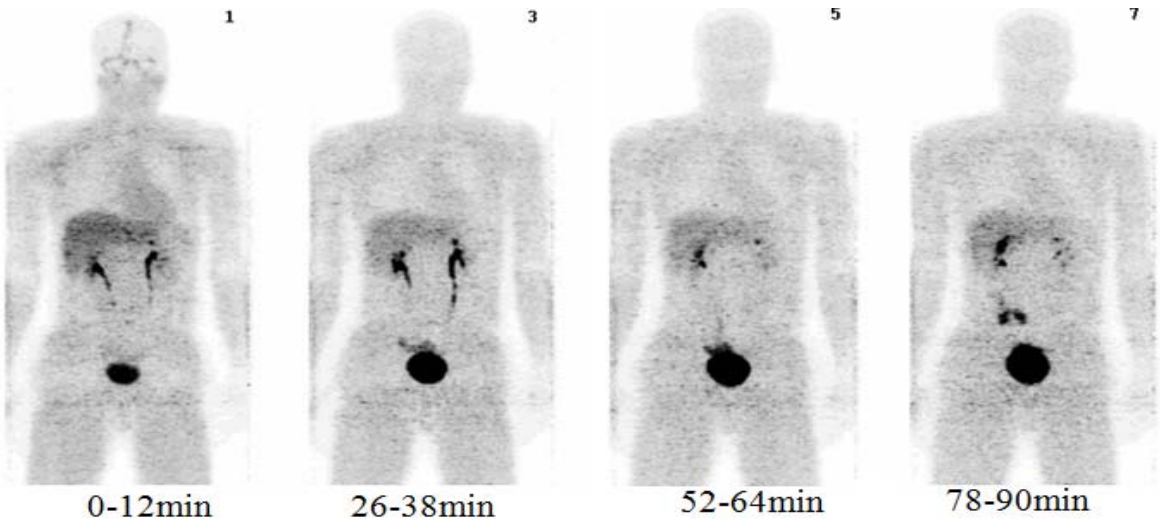

Figure 2. A series of dynamic whole-body images of a 32-year-old male volunteer.

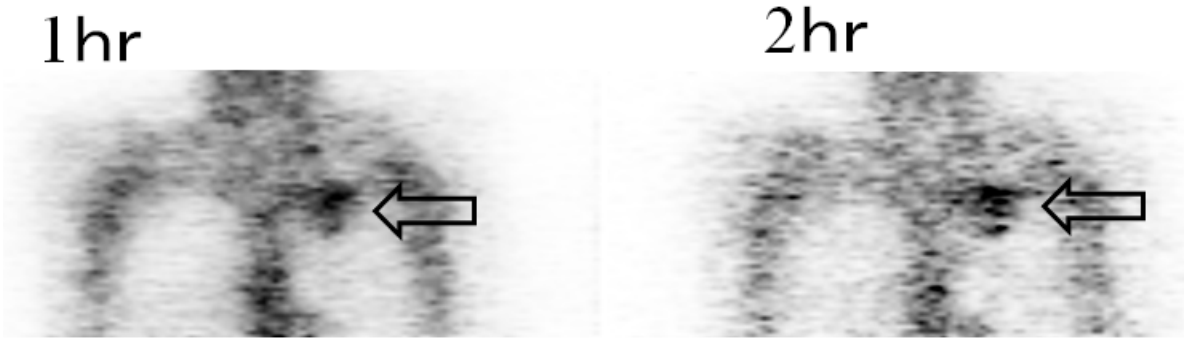

Figure 3. ^{18}F-FRP170 images of lung cancer (*arrow*) acquired 1 hr and 2hr after injection.