^{19}F high senseitivity imaging for *in vivo* drug dynamics in mice at 7T with 5-FU

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Introduction: The evaluation of drug efficacy and safety for individuals will become more reliable by performing direct dynamical study of drug itself. This is a study towards this purpose using 5-FU in animals. CSI is often used for the metabolite distribution. However, for the compounds with metabolites in wide range of chemical shift, generation of pulse covering sufficient band width is difficult for imaging instrument. One of the best methods for the dynamical study of ^{19}F containing drug, e.g. 5-FU, has been found to be frequency selective imaging [1]. Here, we evaluate fast imaging sequences including FISP and Flash in comparison to FSE at 7T.

Material and Methods: C3H/He mice were transplanted with experimental tumor subcutaneously. 2 mmol/kg of 5-FU was administrated orally after overnight fasting as CMC dispersion. Phantoms with and without air bubbles were used for image evaluation. ^{19}F MRS and chemical shift selected imaging were taken under the anesthesia of ketamine-xylazine by 7T/400mm/SS system (NIRS/KOBELCO/Bruker) with 72mm i.d. ^{1}H/^{19}F RF coil (Bruker Biospin). ^{19}F images were obtained mainly by FISP, Flash and FSE with frequency selective pulses of 1400Hz bandwidth, FOV of 32 x 8 cm^2 with matrix size 128 x 32 without slicing, TE 3.2 (FISP), 5.1 (Flash), esp/TR 8.5/1500 ms single shot (FSE) typically under 10 min accumulation. While only single line can be selected for each run by FISP and Flash, administrated drug 5-FU, anabolites Fnuc (F-nucleosides/-tide), and catabolites FUPA and FBAL were observed simultaneously with non-sliced FSE by using interleave selection of these resonance frequencies [1]. Apparent T_2 of each metabolite was estimated by second or further echoes of FSE.

Results: Time course study of 5-FU and FUPA/FBAL is shown in Fig. 1 with whole body *in vivo* ^{19}F spectra and a plot of image intensities. The effect of the simultaneous observation of 3 lines within TR of 1.5 s on the individual intensity was negligible.

Image quality of FSE was often influenced by short T_2. For the comparison of FSE and FISP, a typical example is shown in Fig.2. FISP gives image with excellent S/N and shape (Fig. 2 top) for the compounds inside the homogeneous tissues. However, the FISP intensities of FBAL tend to be lost in the liver (Fig.2 bottom left) or sometimes even 5-FU in the stomach (not shown) supposedly due to the presence of swallowed air. Such phenomena were confirmed by the phantom study with air bubbles. No advantage of Flash was found for this system.

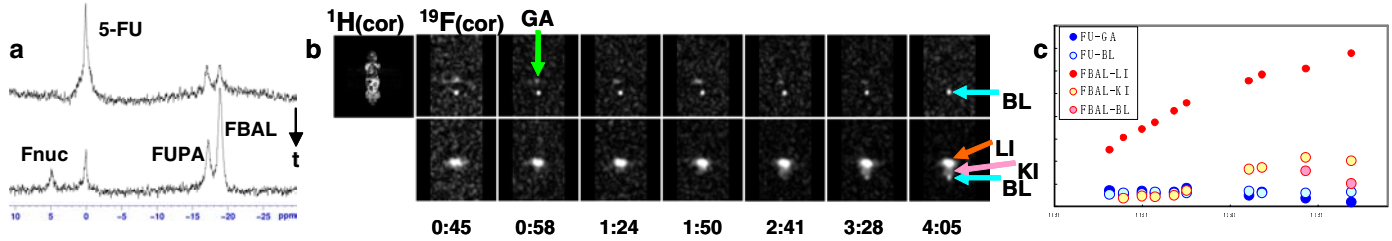

Fig. 1. (a) ^{19}F spectra (whole body) (b)^{19}F images by FSE: Interleaved selection of 5-FU(upper case) and FUPA/FBAL(lower case) (c) Plot of image intensity of b without correction for relaxation times. Blue: 5-FU, red: FUPA/FBAL

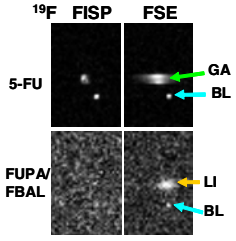

Fig.2 FISP vs. FSE

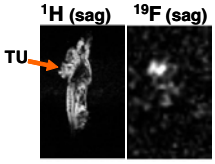

Fig.3. Fnuc image at tumor position on the back

An image of Fnuc at tumor position is demonstrated in Fig. 3. In addition to longer accumulation time of 20 min, a shorter esp (7.5 ms) under single line selection mode with non selective refocusing pulse was required to take good image of Fnuc with short T_2 (<100ms). Apparent T_2 determined from the second echo of FSE was ca. 500 ms for 5-FU in the stomach, much longer in the bladder, and that of FUPA/FBAL in the liver was shorter than 100 ms.

Discussion: The difficulty in the metabolite imaging in small animals at high field is susceptibility problem and short T_2. Imaging most of ^{19}F metabolites in mice is successful at 7T by using minimum TE of FISP and FSE under the dose of 2 mmol 5-FU/kg. The image quality by FISP is found to be excellent even in mice if the target is surrounded by the homogeneous tissues such as bladder and the stomach. The disadvantage of FISP as observed in the signal loss at the liver or sometimes at the stomach limits its use for such cases but not totally at this field strength. Single shot FSE was successfully applied to 5-FU study at 7T giving stable results as in the previous work at 9.4T irrespective of rather long TE due to large bore gradient system. For the imaging of Fnuc by FSE, however, reduction of TE is essential, and the use of smaller gradient system. **In conclusion**, FSE is the first choice as a standard method, and the use of FISP as an auxiliary tool will be a good solution to cover various cases and purposes. The analysis of Fnuc image vs. tumor species is under way.

Reference [1] Kanazawa Y and Doi Y, 12th ISMRM 2004: 2497, Kuribayashi H, Doi H et al. MRM 2001:46: 864, Narazaki M et al., 5th ICMRM 1999: O22.