^{19}F metabolite imaging for 5-FU dynamics and tissue characterization at 9.4T

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Introduction The target compounds for *in vivo* clinical evaluation of 5-FU by ^{19}F MRS should be the anabolites Fnuc, F-nucleosides/F-nucleotides, effective species as well as the cause of side effects. To cover wide range of body besides the tumor or related organs for drug dynamics, chemical shift image has advantage over localized MRS.[1, 2] However, pH dependence of T_2(^{19}F) [2-4] sometimes makes echo acquisition difficult. This work reports the simultaneous ^{19}F chemical shift images of such compounds and T_2(^{19}F) distribution of Fnuc by modified fast spin echo. The usage of T_2 images for the metabolite quantification and the tissue characterization is discussed.

Method Experimental tumor (MH134) was transplanted to C3H mice at the shoulder. 5-FU was orally administrated as CMC suspension under the dose of 1 - 2 mmol/kg after 4 hrs of fasting. NMR measurements were performed under halothane anesthesia. A 9.4T vertical bore magnet NMR system (Varian, INOVA) with 38mm clear bore probe with ^{1}H/^{19}F tunable Litz coil and actively shielded gradient system (Doty Scientific) was used. Two kinds of chemical shift selected ^{19}F images were acquired by fast spin echo in acquisition matrix size 32(ro)x16(pe), ETL=16 for the FOV of coronal 8x4cm without slice selection: (1) modified 2-shot fast spin echo with simultaneous (interleave) 4 signal selection with TE=6ms, and (2) the one under single line excitation with TE=3.2ms. The modified 2-shot fast spin echo consists of 2 trajectories as shown in Fig.1. Data handling: the first halves of trajectories f(+) and f(-) give short TE image A, and the later parts give long TE image B. The ratio A/B= exp(8TE/T_2) is used as true T_2 map of the compounds. The simple sum image, f(+) + f(-), gives best S/N. Final metabolite concentration was determined by high resolution ^{19}F NMR with excised tissue.

Results The multi-line ^{19}F images by chemical shift selective modified 2-shot fast spin echo [f(+) + f(-)] in 20 min are shown in Fig. 2-Top. Within 1 hour of oral 5-FU administration, Fnuc were observed on the image as well as the catabolite, F-β-alanine+FUPA, and 5-FU in stomach. T_2 maps are shown for FBAL (Fig. 1. multi-line excitation, 40 min) and Fnuc (Fig.2-Bottom. single excitation, 80 min acquisition). T_2(Fnuc) was shorter in liver (40 ms) than tumor (100 ms), both being long enough for quantitative imaging. The concentration of Fnuc determined *ex vivo* immediately after the imaging was 0.7 mM in the tumor.

Discussion A fast image acquisition is the requirement for the rapidly changing drugs. The gain in the sensitivity and signal separation at high field with fast spin echo enabled us to obtain simultaneous chemical shift selective ^{19}F images of the anabolites from 5-FU as well as the catabolites semi-quantitatively. In comparison to the strong pH dependent T_2(5-FU) which makes 5-FU image almost impractical except in the stomach [2, 4], T_2(Fnuc) has pH dependence in appropriate range for imaging by echo acquisition and for T_2 evaluation Longer T_2(Fnuc) in tumor than liver suggests lower pH in the tumor if the compositions of 'Fnuc' are similar in these tissues. The method will be used for the simultaneous evaluation of individual drug dynamics and tumor characterization.

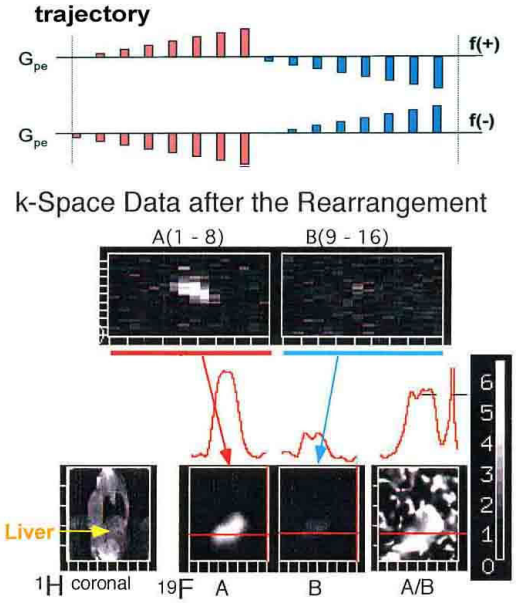

Fig.1. Sequential order, rearranged k-space data, ^{1}H and ^{19}F images of FBAL. Multi line excitation, esp=6ms, A/B=exp(48/T_2)

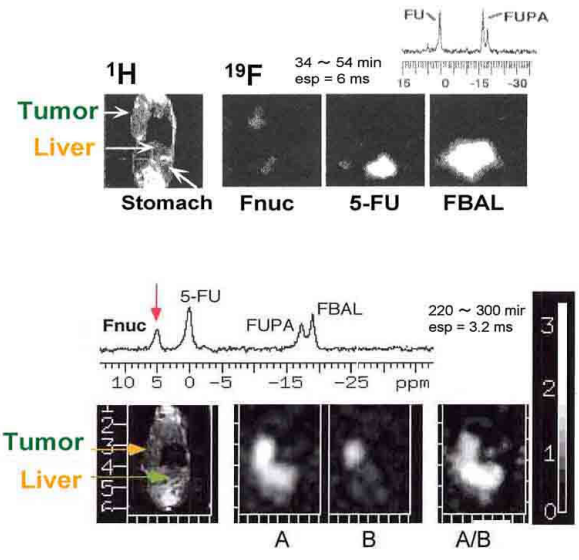

Fig.2. Top: ^{19}F images of Fnuc, 5FU, FBAL+FUPA with esp 6ms in 20 min. Bottom: Images by Fnuc excitation. esp=3.2ms, 80 min. T_2(TU)=100ms, T_2(LI)=40ms

Conclusion At 9.4T, the F-images of Fnuc and catabolites below 1mM are obtained from mice. ^{19}F T_2 map gives pH information. The present imaging method will be used for quantification of anabolites and for tumor characterization. Extended to clinical use, it will serve as the tool for the individual drug efficacy.

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