In vivo Chemical Shift Imaging of 5-Fluorouracil and it's Metabolites

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Purpose: After several decades of use, 5-Fluorouracil (5-FU) remains one of the most heavily used cytotoxic drugs for treatment of cancer. Over the last 20 years, increased understanding of 5-FU's mechanism of action has led to an increase in its anticancer activity. Despite these advances, drug resistance remains a significant limitation in clinical use.[1] 5-FU is converted intracellularly into multiple fluorinated metabolites, each displaying a unique resonance chemically shifted from that of 5-FU. Metabolites of interest include fluorinated nucleotides (Fnuc.) and fluoro-β-alanine (FBAL). Fnuc. actively inhibits RNA synthesis and key enzyme function. As the active metabolites of 5-FU, they are essential when assessing drug efficiency[1]. Metabolite distribution images obtained using MRI, promise to yield substantial information on drug uptake and resistance. Therefore monitoring 5-FU using fluorine-19 (^{19}F) CSI may lead to a decrease in clinical response times, facilitating personalized cancer treatment.[2] ^{19}F is highly MR sensitive and has almost no endogenous signal. Differences in bulk and local perfusion will affect the amount of measurable signal from 5-FU and its metabolites. Furthermore, variations in resonance of each metabolite, allows for the differentiation of metabolites with the use of MR Chemical Shift Imaging to create distribution maps of each metabolite. Previous work demonstrating imaging 5-FU in-vivo utilized specialized high-field animal MRIs to achieve sufficient chemical shift dispersion to form CSI maps[3]. In this study, a 3 T clinical whole-body scanner was used to obtain distribution images of 5-FU and its metabolites in a live rat.

Methods: All animal experiments were conducted in accordance with the Canadian Council on Animal Care (CCAC) and with approved Lakehead University animal-use protocols. MR experiments were performed using a Philips 3T Achieva whole body scanner with a custom quadrature birdcage coil tuned to 120.15 MHz for the 19F nuclei. Rats (487g ± 26.7 g) were initially anaesthetized by isofluorane induction, followed by a 50 mg/kg injection of ketamine. A 26 g tail-vein catheter was inserted and a constant infusion of ketamine/propofol (1:10) was delivered using a syringe pump at a rate of 1.9 mL/hr for the remainder of the experiment. Coronal ^{1}H gradient-echo multi-slice images were acquired using a FOV of 150 mm^2, a slice thickness of 5 mm with a slice gap of 0.5 mm, a 15° flip angle, an acquisition matrix of 128 x 128, and a reconstruction matrix of 256 x 256. A dose of 200 mg/kg of 5-FU (2 mL bolus) was injected into the tail vein over a 5-minute period. CSI maps were then acquired at continuous intervals up to 113 minutes after injection at which point the session was concluded and the animals were euthanized. CSI maps were acquired using a FOV of 150 mm^2, a matrix size of 16 x 16, a bandwidth of 32 kHz, a slice thickness of 300mm, a TR/TE of 2000 ms/0.32 ms , 47° flip angle and 6 averages. All CSI maps were then overlaid onto their corresponding ^{1}H image to give an accurate biodistribution of 5-FU and its metabolites.

Results and Discussion: Figure 1a displays a 19F spectrum from a distribution map acquired at 113 minutes after the injection of 5-FU (our reference signal). Two other resonances were detected (-18.9 ppm and 5.2 ppm) which are believed to be that of FβAL and Fnuc. It is to be noted that signals found at 82.89 ppm and 88.8 ppm are due to the isoflurane used during initial anaesthetization. Figure 1b shows the time courses of 5-FU, FβAL, and Fnuc. distribution images overlaid onto a corresponding ^{1}H image. 5-FU signals were seen mainly in the areas of the liver and bladder, and decreased gradially (with the exception of the bladder). FβAL signals were obtained mainly within the liver, kidney, and bladder regions where signal was found to increase gradually. Fnuc. signals were obtained primarily in the bladder and liver regions. These findings agree with previously published work in a 7T animal MRI.[3] The present study sucsessfully demonstrates that sufficent chemical shift dispersion is attainable using a clinical whole-body scanner to acquire distribution maps of 5-FU and its metabolites. The use of animal models will aid in the understanding of 5-FU metabolisim, allowing for direct comparison of imaging 5-FU in future preclinical experiments.

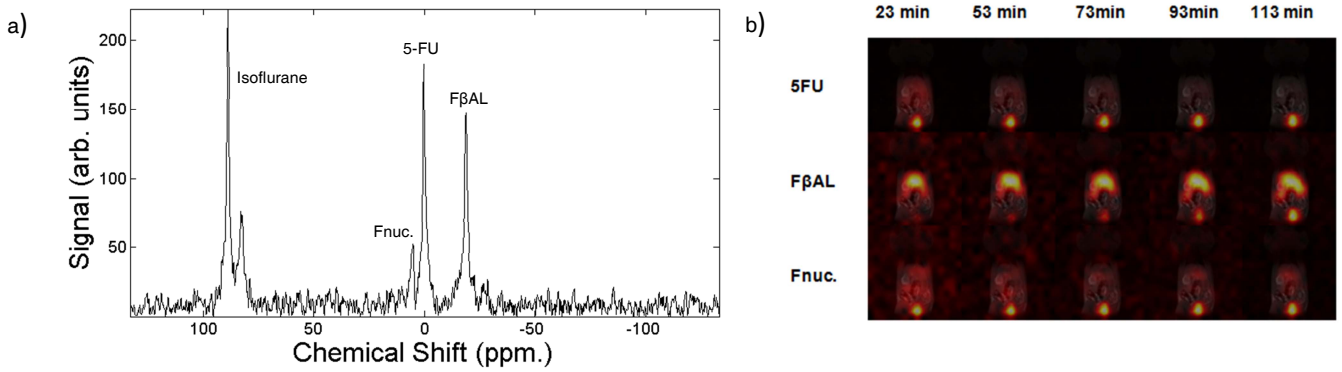

Figure 1: Panel a) depicts a typical ^{19}F spectrum showing 5-FU and its metabolites as well as residual isoflurane signal. b) displays the CSI maps of 5-FU, FβAL and Fnuc. at 23, 53, 73, 93, and 113 minutes after injection of 5-FU. Changes CSI signals were found to follow similar trends when compared to previous spectroscopic time-course data[3].

Conclusion: Distribution maps of 5-FU, FβAL, and Fnuc. were acquired at continuous intervals until 113 minutes after the injection of 5-FU. Thus, sucessfully demonstrating the ability of ^{19}F CSI to monitor metabolisim of 5-FU. To our knowledge, this is the first report of CSI mapping of 5-FU in a rat using a clinical 3T system. This proof-of-principle study demonstrates sufficient chemical shift dispersion laying the groundwork for future preclinical animal trials, and subsequent clinical imaging trials of patients administered with 5-FU as part of their cancer therapy. The results of such studies promise to facilitate improvements in personalized therapy for cancer.

References:

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