Serial $^1$H magnetic resonance spectroscopy detects liver steatosis associated with chemotherapy in advanced colorectal cancer patients

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OBJECTIVES: Although modern combination chemotherapy has achieved a substantial survival benefit for advanced stage colorectal cancer, there has been growing concern about potential liver toxicity, particularly in the adjuvant setting. High rates of steatosis and steatohepatitis have been observed in patients treated with irinotecan and/or oxaliplatin based chemotherapy (1). Severe steatosis may relate to perioperative mortality, so detection of chemotherapy-associated liver steatosis is of great importance to properly adjust the treatment regime. Since liver steatosis is a very prevalent condition among the general population, it is essential to evaluate the mobilization of liver fat in a longitudinal fashion (2). The purpose of this study was to monitor hepatic triglyceride contents (HTGC) before and during combination chemotherapy to detect lipid changes using non-invasive serial $^1$H MRS.

METHODS: A total of 27 patients with colorectal cancer receiving FOLFOX (5FU+folinic acid +oxaliplatin) (n=16) or hepatic arterial infusion of FUDR with systemic irinotecan (n=11) were studied prospectively. Three $^1$H MRS studies were performed on each patient: at baseline (before treatment), after 3 cycles (early follow up), and after 12 cycles (post treatment in FOLFOX patients). 17 patients completed all 3 examinations. There were 7 men and 10 women. Median patient age was 62 years (range 29 to 77 years), median patient BMI was 25.2 kg/m$^2$ (range 16.7 to 36.9 kg/m$^2$). All scans were performed on a 1.5 Tesla General Electric Electric Signa scanner using a 4-channel torso phased-array coil (G.E., Milwaukee, WI). After a T2-weighted, fat-suppressed fast-spin echo liver scan, a single voxel non-water-suppressed $^1$H MRS was acquired from the right liver during a breath-hold using a point resolved spectroscopy sequence (PRESS) with the following parameters: TR=5s, TE=40ms, spectral width (SW) = 2000 Hz, points = 512, 4 acquisitions. The water and methylene fat peaks were calculated using JMRUI. Singular Value Decomposition (SVD) was applied to remove water signal to find optimal lipid fitting (Fig.1). Measured peak areas were corrected for T2 relaxation times calculated from 10 subjects. HTGC was reported as: $\text{FFW} = \text{fat/(water +fat)}$.

RESULTS: In Figure 1, an increase in liver lipid detected in one patient who underwent HAI-FUDR/Iri is shown. Fig. 2 shows the FFW change from baseline to 12 cycles in patients receiving FOLFOX (Fig. 2a) and HAI-FUDR/irinotecan (Fig. 2b). Based on MRS and histologic data obtained by our group (not shown), a cutoff value of FFW = 0.025 has sensitivity of 86% for detecting clinically relevant steatosis (>25% of hepatocytes involved). Of the 17 patients who finished 12 cycle treatment, 7 patients had MRS steatosis at baseline (FFW range from 0.029 to 0.336). In the FOLFOX group (Fig. 2, left), 5 patients had increased FFW after 12 cycles, 2 patients showed no significant change, and 4 patients showed decreased FFW. In the HAI-FUDR/Iri group (Fig. 2, right), 4 patients had increased FFW, 1 patient showed no significant change, and 1 patient showed decreased FFW. Overall, 53% of patients showed a significant increase in HTGC over the course of the study. The limited number of patients in the HAI-FUDR/Iri group precludes a comparison of steatosis rates in the two groups at this time. Changes in FFW did not correlate with changes in BMI (R = -0.21) or with serum liver function markers. MRS steatosis at baseline did not correlate with an increase in liver fat during treatment (R = -0.08). One FOLFOX patient experienced a remarkable increase in HTGC from 0.04 to 0.23. However, his condition was complicated by HIV controlled on HAaRT. His dramatic liver steatosis could be related to the combination of FOLFOX and HIV therapy. A followup study at one year showed an FFW increase to 0.30 suggesting a slower rate of increase in liver lipid once FOLFOX was concluded.

CONCLUSIONS: Serial $^1$H-MRS can quantitatively monitor HTGC changes during chemotherapy, offering an accurate way to detect chemotherapy-associated steatosis. The study is ongoing and the comparison of the steatosis rates between the two specific chemotherapy regimes will be made when more data are available.