

Serial Proton MRS measurements of hepatic lipid alterations during chemotherapy for colorectal cancer

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OBJECTIVES: High rates of steatosis have been reported in colorectal cancer patients who have received irinotecan and/or oxaliplatin-based chemotherapy (1). However, steatosis rates have generally been reported only in post-chemotherapy populations without pre-treatment lipid information. We previously reported preliminary results in 17 patients who underwent serial ¹H-MRS while receiving adjuvant chemotherapy for colorectal cancer (2). We have now completed serial studies in 27 patients and we have assessed 1) the percentage of patients who converted to clinical steatosis during chemotherapy, and 2) the correlation between early and late changes in hepatic lipids during chemotherapy.

METHODS: Nineteen patients were treated with FOLFOX 6 (5FU+leucovorin+oxaliplatin) and one was omitted from analysis due to concurrent anti-HIV treatment. Eight patients received hepatic arterial infusion of floxuridine (HAI-FUDR) with systemic irinotecan (IRI). All scans were performed on a 1.5 Tesla scanner using a 4-channel torso phased-array coil (G.E., Milwaukee, WI). Patients underwent scanning at baseline, after 6 weeks of chemotherapy and after 24 weeks of chemotherapy. A single voxel non-water-suppressed ¹H 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. Software for combining multicoil data and peak fitting was kindly provided by Dikoma Shungu, Ph.D. (Weill-Cornell Medical College, New York, NY). Peak areas (PA) were calculated using time-domain fitting. Because the majority of our subjects were lean, fitting of lipid peaks other than the methylene peak at 1.3 ppm was unreliable due to low lipid SNR. We fit the methyl peak (0.9 ppm) when possible in order to improve the accuracy of the methylene peak fit. Water and methylene peak areas were corrected for T₂ relaxation using the mean of the measured T₂ values for 10 subjects (66 ± 6 ms for methylene lipid and 45 ± 6 ms for water). We estimated the total fat area (PA_{fat}) using the relative ratios for fat peaks given in Hamilton, et. al. and correcting the methylene and water peaks for contributions from nearby lipid peaks. Finally, the total fat fraction was calculated as: FFW=PA_{fat}/(PA_{water}+PA_{fat}). Data from a separate cohort of 18 patients who underwent *in vivo* ¹H-MRS followed by partial hepatic resection were used to assess the correlation between the *in vivo* FFW value and the grade of clinical steatosis assigned by an experienced hepatopathologist. ROC analysis was performed to yield a cutpoint value for FFW representing clinical steatosis. Patient body mass index (BMI) was recorded at all examination times.

RESULTS AND DISCUSSION:

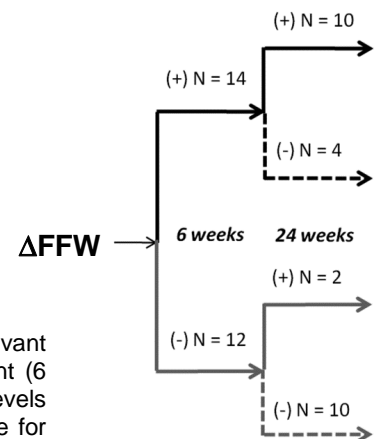
Conversion to steatosis. Table 1 illustrates the FFW data in the 8 patients whose steatosis status changed over the 24 weeks of the study. Of 26 patients, six patients converted from non-steatotic to steatotic, while 2 patients converted from steatotic to non-steatotic. Five of the 6 patients who became steatotic were treated with FOLFOX. BMI changes during the study were minimal in these patients and were not correlated with steatosis changes. **Early changes in hepatic lipids.**

Patient No.	chemo	Steatosis Change	FFW		
			baseline	24 wk	% change
11	FOLFOX	-/+	2.77E-2	5.15E-2	86%
14	FOLFOX	-/+	1.01E-2	8.93E-2	782%
18	FOLFOX	-/+	3.74E-2	1.85E-1	395%
19	FOLFOX	-/+	1.72E-2	5.64E-2	227%
21	FOLFOX	-/+	2.58E-2	7.53E-2	192%
27	FUDR/iri	-/+	1.96E-2	4.16E-2	112%
1	FOLFOX	+/-	8.08E-2	3.05E-2	-62%
30	FUDR/iri	+/-	4.51E-2	1.39E-2	-69%

Table 1. FFW values in 8 patients whose steatosis status changed after 24 weeks of chemotherapy.

Figure 1 contains a diagram which shows the separation of patients according to whether FFW increased or remained the same/decreased at 6 weeks and then at 24 weeks. After 6 weeks of chemotherapy, 14 patients had increased lipids while 12 did not. Of the 14 patients whose lipids were increased at 6 weeks, 10 had elevated lipids after 24 weeks of treatment as well. Conversely, 10 of 12 patients whose lipids did not increase at 6 weeks also showed no increase at 24 weeks. The change in FFW at 6 weeks was significantly correlated with the lipid outcome at 24 weeks (p=0.004) indicating that a lipid measurement early in treatment has predictive value for the change in lipids after 24 weeks.

Figure 1. FFW branching diagram indicating hepatic lipid changes during treatment compared to baseline. First branching is after 6 weeks of treatment. For example, after 6 weeks of treatment, 14 patients had increased hepatic lipids relative to baseline while 12 patients had unchanged or decreased lipids. The second branching is after 24 weeks.



Conclusions. *In vivo* ¹H MRS showed that approximately 20% of patients receiving neoadjuvant chemotherapy developed steatosis after 24 weeks. Changes in lipid levels at an early time point (6 weeks) were correlated with lipid levels after 24 weeks suggesting that early changes in lipid levels could predict which patients will become steatotic during chemotherapy. This technique has value for oncologists seeking to know the likelihood of steatotic changes in individual patients during chemotherapy.

References. 1. Vauthey, et. al. J Clin Oncol 24; 2065-72,2006. 2. Zakian, et. al. Proc. ISMRM 2012. # 856. 3. Hamilton, et. al. NMR Biomed 24; 784-790, 2011.