Published in final edited form as:

Clin Imaging. 2018 ; 52: 193–199. doi:10.1016/j.clinimag.2018.08.002.

MRI Liver fat quantification in an oncologic population: the added value of Complex Chemical Shift-Encoded MRI.

Giuseppe Corrias, MD^{1,2}, Simone Krebs, MD¹, Sarah Eskreis-Winkler, MD¹, Davinia Ryan, MD¹, Junting Zheng, MS³, Marinela Capanu, PhD³, Luca Saba, MD², Serena Monti, MS⁴, Maggie Fung⁵, Scott Reeder, MD, PhD⁶, and Lorenzo Mannelli, MD, PhD¹

¹Department of Radiology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA

²Department of Radiology, University of Cagliari, Via Università, 40, 09124 Cagliari CA, Italy

³Department of Statistics, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA

⁴IRCCS SDN, Naples, Italy

⁵Global MR Applications and Workflow, GE Healthcare, New York, NY, United States

⁶Department of Radiology, University of Wisconsin-Madison, Madison, Wisconsin, USA.

INTRODUCTION

Chemotherapy prolongs the survival of patients with advanced and metastatic tumors and is often used to reduce tumor staging before surgical resection [1]. Since the liver plays an active role in the metabolism of chemotherapy agents, hepatic injury is a common adverse effect [1–3]. Chemotherapy-induced liver injury (CALI) [4, 5] is a collective term to indicate different hepatic insults such as steatosis, steatohepatitis (Chemotherapy associated steatohepatitis, CASH), and sinusoidal obstruction syndrome, each resulting from any of the known cellular injury pathways: vascular injury, necrosis, fibrosis, and cholestasis [6]. An expert consensus of the Hepato-Pancreato-Biliary Association (HPBA) recently stated that hepatic steatosis and steatohepatitis correlate with poor postoperative outcomes after liver resection, such as longer operating times, longer hospitalizations, post-operative complications[7]. The earliest imaging feature of liver damage is an abnormal accumulation of intracellular fat within hepatocytes (i.e.: steatosis) [8]. Correspondingly, quantification of

G.C., S.E.-K., S.R., and L.M., conceived and planned the study. G.C., S.K., D.R., and S.M. planned and carried out the experiments. J.Z., M.C., L.S., S.R., contributed to the statistical analysis and to the interpretation of the results. G.C., and L.M. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. **Corresponding Author:** Lorenzo Mannelli, MD, PhD, 300 East 66th Street, New York, NY, 10021, USA, Tel. +1 646-888-5411 Fax. +1 929-321-5013, mannellilorenzo@yahoo.it.

The authors were equally involved in acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, technical, or material support of this study.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors disclose no conflict of interest. Our institutional review board approved the study with a waiver for informed consents.

intrahepatic fat can be used to grade the level of hepatic damage [9, 10]. While biopsy remains the gold standard for liver fat quantification [11], its superiority on non-invasive quantification methods has been recently questioned due to its invasiveness, sampling bias such as limited biopsy volume (1/50000 of the whole liver) [12] and subjective variability. Furthermore, biopsy is not indicated in patients who need long-term clinical follow-up and observations[13]. Ultrasonography (US), Computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive imaging techniques and are widely used to qualitatively measure liver steatosis. However, non-invasive quantification of hepatic steatosis has always presented challenges.

CT is the most widely used imaging technique to investigate liver metastasis but is only reliable to detect steatosis only when more than 30% of hepatocytes contain macrovesicular droplets of fat [14]. Thus, CT is not well suited for detecting the initial “stages” of liver steatosis. Moreover, intrahepatic fat makes a characterization of hypo-vascular liver lesions on CT more difficult, and there is a reported reduced sensitivity for detecting metastases when steatosis is present [9, 15]. This could alter diagnostic accuracy in detecting liver lesions, particularly in an oncologic population.

Multiple MR techniques have been developed to quantify steatosis. T1-weighted In-Phase and Opposed-Phase imaging (IOP), is a conventional MRI method for fat quantification. IOP provides a qualitative assessment of liver fat content and has been included in most MR protocols for the last several decades. With IOP, images are acquired at two different echo times: (1) when water and the signal from the methylene peak of fat are out of phase (i.e. the total signal is fat signal minus the water signal), and (2) when water and the signal from the methylene peak of fat are in phase (i.e. the total signal is fat signal plus water signal). The difference between the in-phase and out-of-phase signals can be used to calculate an apparent fat fraction. However, IOP imaging is confounded by several factors [16, 17], including T2* decay, T1 bias, T2 relaxation, the spectral complexity of fat, noise bias and eddy currents [18–20]. In oncologic patients, T2* decay is of particular concern, since these patients often receive blood transfusions due to bone marrow failure during chemotherapy, which can lead to liver iron overload. Elevated liver iron increases T2* decay, causing MR signal to drop at the second (later) echo time when water and fat are in phase, leading to a marked underestimation of fat fraction [21].

Recently, quantitative confounder-corrected CSE-MRI methods have emerged as methods capable of quantifying liver proton density fat fraction (PDFF). PDFF has emerged as a standardized, reproducible and promising biomarker for quantification of hepatic steatosis and is increasingly considered as an alternative to biopsy for chronic patients, as in the case of patients exposed to chemotherapy who need a chronic follow-up of the liver functionality [20, 22–28]. PDFF has the advantage of complete mapping of the whole liver, addressing sampling bias that is typical of biopsy. One commercial implementation of CSE-MRI is Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation (IDEAL-IQ), a novel MRI technique that is highly precise and accurate for quantifying PDFF as a biomarker of hepatic steatosis [20, 29]. In IDEAL-IQ, images are acquired at multiple echo times, and an iterative least-squares decomposition algorithm is employed to simultaneously solve for an iron-corrected PDFF map and a fat-corrected R2*

($=1/T2^*$) map. By incorporating a field map variable into the algorithm, IDEAL-IQ accounts for $T2^*$ effects/field inhomogeneity and yields estimates of PDFF not-confounded by iron overload. Thus IDEAL-IQ presents a more sophisticated fat quantification approach that corrects for the confounding factors of IOP outlined above. IDEAL-IQ has already been validated experimentally, in phantoms and in mice, and clinically, in patients with nonalcoholic fatty liver disease [20, 30]. More recently, IDEAL-IQ has been shown to be highly reliable in fat quantification in patients with iron overload [31] with level of evidence 1. Two recent studies proved the accuracy of CSE-MRI both in an ex-vivo and in an animal model [32,33].

The aim of this study is to compare a novel quantitative chemical shift encoded magnetic resonance imaging (CSE-MRI), namely IDEAL-IQ, with conventional T1-weighted In and Out of phase (T1 IOP) MR for evaluating the reproducibility of the methods in an oncologic population exposed to chemotherapy. This would allow to implement this novel sequence in clinical practice instead of the older IOP-MRI.

MATERIALS AND METHODS

Study population

This retrospective study was approved by the institutional review board with a waiver of informed consent. The study population consisted of consecutive patients who had no suspected liver iron overload and who underwent upper abdomen MRI at our tertiary oncologic center between March and June 2017, for different clinical reasons. All patient had been previously diagnosed by any type of malignant cancer. All patients underwent at least 2 cycles of chemotherapy before being scanned. Only liver MRI exams with T1-weighted-in-phase (IP) out-of-phase (OP) and CSE-MRI acquisitions were included in the study. Patients with known liver metastatic disease, viral hepatitis, cholestasis were excluded from the study.

MR image parameters

All studies were performed on a 1.5 T MRI imaging system (OptimaMR450w, GE Healthcare, Waukesha, WI) with a 32 Channel Torso Array Coil. The protocol included: 1) CSE-MRI (IDEAL IQ, GE Healthcare, Waukesha, WI) to produce simultaneous iron-corrected PDFF and fat-corrected $R2^*$ maps; 2) conventional IOP MRI. Acquisition parameters for IDEAL IQ were as follows: single breath hold acquisition lasting less than 30 seconds, TR 10 ms, TE 4.7 ms, FOV 35–40 cm, matrix 128×128 , pixel bandwidth 395 kHz, flip angle 6° , slice thickness 10 mm, and space between slices 5 mm. We acquired six different echoes ranging from 1.1 ms to 6.38 ms. Post processing was performed with a software provided by the manufacturer to create $R2^*$ and PDFF maps. Acquisition parameters for IOP T1 were as follow: single breath hold acquisition lasting 15 seconds, TR: 150 ms, out-of-phase TE 2.115 ms, in-phase TE: 4.252, FOV: 35–40 cm, matrix 320×192 , slice thickness 7 mm, space between slices 1 mm.

Image Analysis

Using a dedicated workstation (Centricity PACS, RA1000 Workstation and Exam Manager, GE Healthcare, Chicago, IL), two radiologists (respectively with 4 and 5 years of experience) reviewed the images and placed 3 circular (10 mm diameter) regions of interest (ROIs) in the liver on a plane passing through the main portal vein division: (1) in the right lobe of the liver (Segment 6), (2) in Segment 4 of the liver and 3) in the left lobe of the liver (Segment 2\3) as demonstratively shown on Figure 1. These ROIs were drawn in sequences with anatomical landmarks such as T1 IOP. On traditional IOP images, three circular (10mm diameter) ROIs were also drawn in the paraspinal muscles and used as a reference for fat fraction calculation. ROIs were placed in the same positions on map images such as fat fraction maps and R2* maps. The paraspinal ROIs were marked only on the IP and OP images. All ROIs were placed in the liver avoiding major vessels, ligaments and bile ducts, making sure that each ROI was surrounded by liver parenchyma (Figure 1). In order not to lose any signal intensity due to different distances from the receiving coil, all ROIs were drawn at the same distance from the coil isocenter on a circular band extending from 10 to 15 cm from the isocenter, according to the anatomic landmark specified above. The fat fraction was calculated from IOP imaging and measured from IDEAL-IQ fat fraction maps. Since a recent study from Roberts et al.[34] has shown that median is superior to mean for reporting PDFF measurements, we used median values taken from all the measured ROIs.

Fat fractions from IOP imaging were calculated using the average of the three ROIs using two different methods:

IOP-Method 1[21]:

$$Fat\ fraction(1) = \frac{InPhase_{liver}}{InPhase_{spleen}} - \frac{OutofPhase_{liver}}{OutofPhase_{spleen}} \bigg/ 2 * InPhase_{liver}$$

IOP-Method 2 [21]:

$$Fat\ fraction(2) = \frac{InPhase_{liver}}{InPhase_{spleen}} - \frac{OutofPhase_{liver}}{OutofPhase_{spleen}} \bigg/ 2 * \frac{InPhase_{liver}}{InPhase_{spleen}}$$

We used literature-based proposed PDFF intervals for each histological steatosis grade in nonalcoholic fatty liver disease are: 0–6.4 % for grade 0 (normal); 6.5–17.4% for grade 1 (mild); 17.5–22.1 % for grade 2 (moderate); and 22.2 % or greater for grade 3 (severe) [26, 35, 36]. Liver iron quantification was also performed using the average of three ROIs on IDEAL-IQ R2* maps. There is a linear correlation between R2* values and liver-iron-concentration (LIC) [37][37]. Since R2* values are directly proportional to iron concentration, they were used as a primary intrahepatic iron concentration measurement [38]. An increased iron concentration was based on an R2* cutoff value that was arbitrary and approximately considered above 71 s⁻¹ based on previous literature, since the only

conversion software, approved and commercially available is a proprietary software which was not available at the time of the study[37–39].

Statistical methods

Intra-class correlation coefficient (ICC) and repeatability coefficient (RC) were estimated to evaluate agreement between the two readers on fat fraction (conventional IOP and IDEAL IQ) and on iron level (only IDEAL IQ) measurements. The bias-corrected 95% confidence intervals (CI) for RCs were estimated using nonparametric bootstrapping method with 2000 replicates. The Bland-Altman plots of fat fraction measurement were presented for between reader measurements. Kappa statistic was used to assess agreement between iron level groups (normal: <71 (1/s); high: ≥71(1/s) [39]) between two readers. Exact Wilcoxon signed rank test was used to compare the fat fraction between IOP and IDEAL IQ in patients with normal and high iron levels, and in all patients, for each reader separately.

Kappa (k) values were interpreted as follows: 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement. A test with a p -value < 0.05 was considered statistically significant. No adjustment on multiple testing was applied considering the hypothesis-generating purpose of the study. All statistical analyses were performed in software packages R version 3.3 (The R Foundation for Statistical Computing).

RESULTS

A total of 55 consecutive patients were included in the study. Five patients were excluded for poor image quality, specifically on the IDEAL-IQ sequence, due to reconstruction problems: the reconstruction software failed, probably due to some motion artifacts in the original acquisition. Only really blurry images, with band artifacts or not visible liver were excluded. None of the patients was excluded for artifacts among the IOP sequences. The final patient population consisted of 50 patients (24 males, 26 females), mean age 59 years ($M=65$; $F=57$). Individual patient tumor characteristics are detailed in Table 1. None of the patients previously had blood transfusion. IDEAL-IQ was acquired during one breath hold.

Based on the thresholds given in the materials and methods, we found an abnormal fat fraction (>6.5%) in 14 patients (28%) for reader 1 and 15 patients (30%) for reader 2.

$R2^*$ maps values ranged between 26.1 and 113.7 s^{-1} for reader 1 and between 24.7 and 120.6 s^{-1} for reader 2 (Table 2). Using IOP method 1, which had a higher ICC than IOP method 2, as shown later, a higher fat concentration was found in 16 patients (32%) for Reader 1 and 19 patients (38%) for Reader 2.

The inter-reader agreement of fat fraction measurements using conventional IOP MRI was moderate using method 1 (ICC=0.737, 95%CI: 0.566–0.845) and poor using method 2 (ICC=0.372, 95% CI: 0.106–0.588). The inter-reader agreement of IDEAL IQ fat fraction measurements was high (ICC=0.961, 95%CI: 0.932–0.978) (Table 3a). The repeatability coefficient of fat fraction measurements was also much better using IDEAL IQ (RC=3.9,

95%CI: 2.1–7.5) than conventional IOP (method1 RC=9.7, 95%CI: 6.2–16.0 and method 2 RC=20.4, 95%CI: 12.6–34.6) (Figure 2).

According to $R2^*$ cutoff value of 71 s^{-1} , patients were divided into two groups: a low iron level group with an $R2^*$ less than 71 s^{-1} , $n=44$ patients; a high iron level group with an $R2^*$ higher than or equal to 71 s^{-1} , $n=6$ patients. The agreement on $R2^*$ grouping between the two readers was almost perfect ($\kappa=0.811$, Table 3).

The IOP methods 1 and 2 were statistically different from IDEAL IQ (Table 4) in the group with low iron level from reader 1; this was true especially when using IOP method 2 ($p < 0.001$). Considering all patients, IOP method 2 was statistically different from IDEAL-IQ fat fraction quantification (Table 4) for both readers ($p < 0.001$).

DISCUSSION

Many studies have investigated the use of PDFF techniques in patients with non-alcoholic fat liver disease (NAFLD) [25, 40], but this is the first study to focus on oncologic patients specifically. This particular subset of patients would benefit from a more accurate liver fat quantification. Chemotherapy of any kind is particularly hepatotoxic, and early findings of this hepatotoxicity would increase clinical care of these patients helping to stratify who is at higher risk of hepatic injury and who should suspend treatments. Furthermore, oncologic patients are at risk for bone marrow failure, often necessitating repeat blood transfusions. This can cause a higher incidence of elevated liver iron, an important confounding factor for MRI fat quantification techniques. For all these reasons oncologic patients would benefit from a highly reproducible, not invasive and consistent way to quantify hepatic fat and iron content (Figure 3 and 4).

In this study evaluated the reproducibility of a confounder-corrected CSE-MRI method (IDEAL IQ) for simultaneous quantification of liver iron and fat content in patients exposed to chemotherapy-induced liver injury. In comparison to conventional IOP imaging, we found that IDEAL IQ has a higher inter-reader agreement for fat and iron measurements taken with IDEAL-IQ, whereas the conventional IOP shows a much lower agreement between readers. This could have important clinical implications, making IDEAL-IQ a more suitable technique to follow-up liver fat and iron content in patients undergoing chemotherapy.

Furthermore, our results show that fat fraction calculated from IDEAL-IQ maps and IOP are significantly different in an oncologic population that includes many patients with iron overload. This could be due to the many factors that confound the fat-fraction signal in IOP methods [16, 18, 21, 31, 41, 42]. Since many studies have demonstrated that IDEAL-IQ is more highly correlated with actual liver fat content (i.e. biopsy, MR Spectroscopy) than conventional IOP methods [25, 43], we considered IDEAL IQ as the best commercially available reference standard for this study.

IDEAL IQ simultaneously generates fat-corrected $R2^*$ maps as a biomarker of liver iron content and iron-corrected PDFF maps. Further, it provides volumetric whole-liver coverage in a single breath hold and can be performed in a relatively short time, even in patients with difficulties holding breath. IDEAL-IQ addresses confounding factors such as T1 bias, $T2^*$

decay, eddy currents and noise bias. Correcting for these confounders, IDEAL-IQ MRI produces an accurate estimation of both iron-corrected PDFF and fat-corrected R2* [44, 45].

Previous studies have already confirmed that MRI-PDFF is accurate for quantifying liver fat in phantoms, animals and clinical settings. PDFF is increasingly accepted as the standard of reference for liver fat quantification in clinical trials, and since then its reproducibility compared to histopathological analysis has been established in many studies [46, 47].

PDFF has several advantages compared to liver biopsy. First, it is noninvasive. Second, PDFF measures fat fraction on a continuous scale while histological grading uses discrete ordinal categories. Third, PDFF provides a regional map of liver fat while a biopsy only samples a very small quantity of tissue.

IOP methods allow a fat estimation limited to a fat concentration of 0% to 50%; however, in our population, the sample fat fraction obtained with IOP methods never exceeded 30%. Thus the discrepancy in fat fraction estimation in these patients is probably due to another known possible cause (i.e. liver fibrosis, noise bias, T1 and T2 bias, eddy currents) [21].

One of the most important results of our study is that IDEAL IQ showed a higher reliability in fat fraction quantification compared with both IOP methods, with a substantially higher inter-reader agreement. This has important clinical implications; IDEAL IQ provides increased reproducibility and confidence in diagnosing hepatic steatosis in clinical settings.

A recent meta-analysis by Bohte et al. [48] demonstrated that conventional MRI and ¹H-MRI spectroscopy are more accurate than ultrasonography and CT for the quantification of liver steatosis, especially in patients with low liver fat content. However, they excluded all triple-echo, multi-echo and multi-interference techniques because of lack of comparison with the gold standard pathologic evaluation; they concluded the meta-analysis stating that “consensus on the role of ¹H-MRS as the reference standard needs yet to be established”; for this reason, and since most clinically approved protocols consider only conventional fat quantification MRI, we did not use ¹H-MRS as reference standard in this study. Indeed, Yokoo et al recently demonstrated, in a large meta-analysis of 28 studies comparing ¹H-MRS with CSE-MRI that PDFF measured by MRS and CSE-MRI are equivalent [49].

IDEAL-IQ method should have an advantage in terms of reproducibility when measuring liver fat-fraction in patients with concurrent liver iron overload. However, this was not the case in our population where there are some differences but not for both readers and not for both IOP methods vs IDEAL-IQ. This might be due to the fact that the iron overload population was too small to obtain any statistical results (six patients). Our study had several limitations. First, it was a retrospective study. Second, the study lacked a pathologic or MRS as standard of reference, although IDEAL-IQ has already been compared to those standards of reference and it has been proved to be highly accurate, and many clinical trials are starting to use this sequence as gold standard for quantifying drug induced liver injury [20, 21, 49, 50]. Furthermore, it is not clear whether a previous hepatic injury is present in an oncologic population, given the high prevalence of NAFLD, and to which extent these pre-existent conditions can influence the treatment course. Given the rapidity of CSE-MRI and the possibility to be acquired in a single breath-hold, a diffusion of these techniques would allow

a better stratification of risk patients before they undergo a chemotherapy treatment, and a better understanding of any liver-fat accumulation complication.

In conclusion our study demonstrated that IDEAL IQ has a higher reproducibility and a higher inter-reader agreement than conventional IOP imaging, with many advantages over the conventional sequence such as a shorter acquisition time in a single breath hold (giving the possibility to measure $R2^*$ values within the same acquisition) a higher accuracy in quantifying fat fraction. More consistent liver fat quantification may have clinical implications in therapy management of oncologic patients.

Acknowledgments

Grant support was provided by MSK Cancer Center Support Grant/Core Grant P30 CA008748 Work by GC was partially supported by a scholarship awarded by ISSNAF Imaging Scienc Chapter. Work from SK was partially supported by NIH grant K12 CA184746.

References

1. Grigorian A, O'Brien CB. Hepatotoxicity Secondary to Chemotherapy J Clin Transl Hepatol. 2014; 2:95–102. [PubMed: 26357620]
2. King PD, Perry MC. Hepatotoxicity of chemotherapy. Oncologist 2001; 6:162–176 [PubMed: 11306728]
3. Maor Y, Malnick S. Liver injury induced by anticancer chemotherapy and radiation therapy. Int J Hepatol 2013; 2013:815105 [PubMed: 23970972]
4. Stravitz RT, Sanyal AJ. Drug-induced steatohepatitis. Clin Liver Dis 2003; 7:435–451 [PubMed: 12879993]
5. Patel V, Sanyal AJ. Drug-induced steatohepatitis. Clin Liver Dis 2013; 17:533–546, vii [PubMed: 24099016]
6. Ishak KG, Zimmerman HJ. Morphologic spectrum of drug-induced hepatic disease. Gastroenterology clinics of North America 1995; 24:759–786 [PubMed: 8749898]
7. Schwarz RE, Berlin JD, Lenz HJ, Nordlinger B, Rubbia-Brandt L, Choti MA. Systemic cytotoxic and biological therapies of colorectal liver metastases: expert consensus statement. HPB (Oxford) 2013; 15:106–115 [PubMed: 23297721]
8. Cho CS, Curran S, Schwartz LH, et al. Preoperative radiographic assessment of hepatic steatosis with histologic correlation. J Am Coll Surg 2008; 206:480–488 [PubMed: 18308219]
9. Dioguardi Burgio M, Bruno O, Agnello F, et al. The cheating liver: imaging of focal steatosis and fatty sparing. Expert Rev Gastroenterol Hepatol 2016; 10:671–678 [PubMed: 27027652]
10. Hamer OW, Aguirre DA, Casola G, Lavine JE, Woenckhaus M, Sirlin CB. Fatty liver: imaging patterns and pitfalls. Radiographics 2006; 26:1637–1653 [PubMed: 17102041]
11. Angulo P Treatment of nonalcoholic fatty liver disease. Ann Hepatol 2002; 1:12–19 [PubMed: 15114291]
12. Ratzliff V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005; 128:1898–1906 [PubMed: 15940625]
13. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012; 142:1592–1609 [PubMed: 22656328]
14. Kodama Y, Ng CS, Wu TT, et al. Comparison of CT methods for determining the fat content of the liver. AJR Am J Roentgenol 2007; 188:1307–1312 [PubMed: 17449775]
15. Vilgrain V, Ronot M, Abdel-Rehim M, et al. Hepatic steatosis: a major trap in liver imaging. Diagn Interv Imaging 2013; 94:713–727 [PubMed: 23751229]

16. Meisamy S, Hines CD, Hamilton G, et al. Quantification of hepatic steatosis with T1-independent, T2-corrected MR imaging with spectral modeling of fat: blinded comparison with MR spectroscopy. *Radiology* 2011; 258:767–775 [PubMed: 21248233]
17. Yu H, Shimakawa A, Hines CD, et al. Combination of complex-based and magnitude-based multiecho water-fat separation for accurate quantification of fat-fraction. *Magn Reson Med* 2011; 66:199–206 [PubMed: 21695724]
18. Reeder SB, McKenzie CA, Pineda AR, et al. Water-fat separation with IDEAL gradientecho imaging. *J Magn Reson Imaging* 2007; 25:644–652 [PubMed: 17326087]
19. Hussain HK, Chenevert TL, Londy FJ, et al. Hepatic fat fraction: MR imaging for quantitative measurement and display - Early experience. *Radiology* 2005; 237:1048–1055 [PubMed: 16237138]
20. Idilman IS, Aniktar H, Idilman R, et al. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. *Radiology* 2013; 267:767–775 [PubMed: 23382293]
21. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. *J Magn Reson Imaging* 2011; 34:729–749 [PubMed: 21928307]
22. Kukuk GM, Hittatiya K, Sprinkart AM, et al. Comparison between modified Dixon MRI techniques, MR spectroscopic relaxometry, and different histologic quantification methods in the assessment of hepatic steatosis. *Eur Radiol* 2015; 25:2869–2879 [PubMed: 25903702]
23. Leiber LM, Boursier J, Michalak S, et al. MRI versus histological methods for time course monitoring of steatosis amount in a murine model of NAFLD. *Diagn Interv Imaging* 2015; 96:915–922 [PubMed: 25934180]
24. Leporq B, Lambert SA, Ronot M, et al. Hepatic fat fraction and visceral adipose tissue fatty acid composition in mice: Quantification with 7.0T MRI. *Magn Reson Med* 2016; 76:510–518 [PubMed: 26527483]
25. Nouredin M, Lam J, Peterson MR, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. *Hepatology* 2013; 58:1930–1940 [PubMed: 23696515]
26. Tang A, Desai A, Hamilton G, et al. Accuracy of MR imaging-estimated proton density fat fraction for classification of dichotomized histologic steatosis grades in nonalcoholic fatty liver disease. *Radiology* 2015; 274:416–425 [PubMed: 25247408]
27. Zand KA, Shah A, Heba E, et al. Accuracy of multiecho magnitude-based MRI (M-MRI) for estimation of hepatic proton density fat fraction (PDFF) in children. *J Magn Reson Imaging* 2015; 42:1223–1232 [PubMed: 25847512]
28. Lin SC, Heba E, Bettencourt R, et al. Assessment of treatment response in non-alcoholic steatohepatitis using advanced magnetic resonance imaging. *Aliment Pharmacol Ther* 2017; 45:844–854 [PubMed: 28116801]
29. Chiang HJ, Lin LH, Li CW, et al. Magnetic resonance fat quantification in living donor liver transplantation. *Transplant Proc* 2014; 46:666–668 [PubMed: 24767318]
30. Idilman IS, Tuzun A, Savas B, et al. Quantification of liver, pancreas, kidney, and vertebral body MRI-PDFF in non-alcoholic fatty liver disease. *Abdom Imaging* 2015; 40:1512–1519 [PubMed: 25715922]
31. Horng DE, Hernando D, Reeder SB. Quantification of liver fat in the presence of iron overload. *J Magn Reson Imaging* 2017; 45:428–439 [PubMed: 27405703]
32. Hernando D, Sharma SD, Aliyari Ghasabeh M, et al. Multisite, multivendor validation of the accuracy and reproducibility of proton-density fat-fraction quantification at 1.5T and 3T using a fat-water phantom. *Magn Reson Med* 2017; 77:1516–1524 [PubMed: 27080068]
33. Xu L, Duanmu Y, Blake GM, et al. Validation of goose liver fat measurement by QCT and CSE-MRI with biochemical extraction and pathology as reference. *Eur Radiol* 2018; 28:2003–2012 [PubMed: 29238866]
34. Roberts NT, Hernando D, Holmes JH, Wiens CN, Reeder SB. Noise properties of proton density fat fraction estimated using chemical shift-encoded MRI. *Magn Reson Med* 2018;

35. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab* 2005; 288:E462-468 [PubMed: 15339742]
36. Tang A, Tan J, Sun M, et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. *Radiology* 2013; 267:422-431 [PubMed: 23382291]
37. Pirasteh A, Yuan Q, Hernando D, Reeder SB, Pedrosa I, Yokoo T. Inter-method reproducibility of biexponential R2 MR relaxometry for estimation of liver iron concentration. *Magn Reson Med* 2018;
38. Virtanen JM, Komu ME, Parkkola RK. Quantitative liver iron measurement by magnetic resonance imaging: in vitro and in vivo assessment of the liver to muscle signal intensity and the R2* methods. *Magn Reson Imaging* 2008; 26:1175-1182 [PubMed: 18524528]
39. Wood JC, Enriquez C, Ghugre N, et al. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. *Blood* 2005; 106:1460-1465 [PubMed: 15860670]
40. Permutt Z, Le TA, Peterson MR, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non- alcoholic fatty liver disease-MRI accurately quantifies hepatic steatosis in NAFLD. *Alimentary pharmacology & therapeutics* 2012; 36:22-29 [PubMed: 22554256]
41. Reeder SB, Pineda AR, Wen Z, et al. Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL): application with fast spin-echo imaging. *Magn Reson Med* 2005; 54:636-644 [PubMed: 16092103]
42. Reeder SB, Wen Z, Yu H, et al. Multicoil Dixon chemical species separation with an iterative least-squares estimation method. *Magn Reson Med* 2004; 51:35-45 [PubMed: 14705043]
43. Bannas P, Kramer H, Hernando D, et al. Quantitative magnetic resonance imaging of hepatic steatosis: Validation in ex vivo human livers. *Hepatology* 2015; 62:1444-1455 [PubMed: 26224591]
44. Reeder SB, Sirlin CB. Quantification of liver fat with magnetic resonance imaging *Magn Reson Imaging Clin N Am.* 2010; 18:337-357. ix. [PubMed: 21094444]
45. Hernando D, Kramer JH, Reeder SB. Multipeak fat-corrected complex R2* relaxometry: theory, optimization, and clinical validation. *Magn Reson Med* 2013; 70:1319-1331 [PubMed: 23359327]
46. Hines CD, Agni R, Roen C, et al. Validation of MRI biomarkers of hepatic steatosis in the presence of iron overload in the ob/ob mouse. *J Magn Reson Imaging* 2012; 35:844-851 [PubMed: 22127834]
47. Hines CD, Yu H, Shimakawa A, et al. Quantification of hepatic steatosis with 3-T MR imaging: validation in ob/ob mice. *Radiology* 2010; 254:119-128 [PubMed: 20032146]
48. Bohte AE, van Werven JR, Bipat S, Stoker J. The diagnostic accuracy of US, CT, MRI and 1H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis. *Eur Radiol* 2011; 21:87-97 [PubMed: 20680289]
49. Yokoo T, Serai SD, Pirasteh A, et al. Linearity, Bias, and Precision of Hepatic Proton Density Fat Fraction Measurements by Using MR Imaging: A Meta-Analysis. *Radiology* 2017:170550
50. McPherson S, Jonsson JR, Cowin GJ, et al. Magnetic resonance imaging and spectroscopy accurately estimate the severity of steatosis provided the stage of fibrosis is considered. *J Hepatol* 2009; 51:389-397 [PubMed: 19505740]

Highlights

- IDEAL-IQ has a higher reproducibility, inter-reader agreement and accuracy in quantifying fat than conventional IOP imaging
- IDEAL-IQ has many advantages over the conventional sequence in a population with a high probability of iron overload.
- It has the possibility to quickly measure the $R2^*$ values within the same acquisition.
- A more accurate quantification of fat and iron in an oncologic population can change therapy and management.

Figure 1:
ROI placement. A 5 cm thick band was placed along the bore isocenter. Readers were instructed to place 3 ROIs in the liver and 3 in the spleen, on a plane passing through the portal vein division. Readers were instructed to place the ROIs as close as possible to the midpoint of the 5 cm band, when possible, trying to avoid vessels and bile ducts.

Figure 2: Bland-Altman plots for fat fraction measurement between two readers using (a) conventional IOP method 1, (b) conventional IOP method 2 and (c) IDEAL IQ. Middle dashed line is the mean of the difference, the top and the bottom dashed lines are the limits of agreement. We expect the differences of fat fraction measurements using each method will fall within the limits of agreement between the two readers on 95% of the reads.

Figure 3:
ROIs traced in the right liver, segment VI, avoiding major vessels and bile ducts. A: IDEAL IQ- R2* MAP; B: IDEAL-IQ fat fraction MAP; C: conventional T1-in phase; D: conventional T1 out-of-phase. This patient has mildly elevated iron concentration (ROI R2* average= 152) and normal fat concentration (PDFF=2%).

Figure 4:

ROIs traced in the right liver, segment VI, avoiding major vessels and bile ducts. A: IDEAL IQ- R2* MAP; B: IDEAL-IQ fat fraction map; C: conventional T1-in phase; D: conventional T1 out-of-phase. This patient has normal iron concentration (ROI R2* average= 152) and elevated fat concentration (PDFF= 21%), quickly measured with the IDEAL-IQ fat fraction map and visible also by the drop of signal in the in and out-of-phase T1 sequences.

Table 1:

Type of tumors as proved by pathology, ordered by number of cases.

TYPE OF TUMOR	NUMBER OF CASES
Colorectal Adenocarcinoma	13
Breast Carcinoma	6
Melanoma	6
NET	5
PDAC	4
Thyroid Carcinoma	3
Prostate Adenocarcinoma	2
HCC	2
Basal Cell Carcinoma	1
Bladder Urothelial Carcinoma	1
Gallbladder Cholangiocarcinoma	1
Endometrioid Adenocarcinoma	1
Esophageal Adenocarcinoma	1
Mycosis Fungoides	1
RCC	1
SCC tonsillar	1

NET: neuroendocrine tumor; PDAC: pancreatic ductal adenocarcinoma; HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; SCC: squamous cell carcinoma

Table 2:

Summary of iron measurement and fat fraction in reader 1 and 2. Median and mean of measurements taken by both readers with ROIs.

	Median (Range)	Mean $\pm$ SD
Reader 1		
	4.3 (−16, 32.5)	4.3 $\pm$ 7.5
Fat fraction IOP method 1 (%)		
Fat fraction IOP method 2 (%)	2.6 (−25.7, 30.2)	1.3 $\pm$ 10.4
IDEAL IQ PDFF (%)	3.6(1,41.1)	6.1 $\pm$ 7.1
R2* IDEAL IQCs ^{−1})	39.4(26.1, 113.7)	46.7 $\pm$ 21.1
Reader 2		
Fat fraction IOP method 1 (%)	5.8 (−3.9, 28.8)	6 $\pm$ 6.6
Fat fraction IOP method 2(%)	3.4 (−16.2, 34.6)	2.2 $\pm$ 8.1
IDEAL IQ PDFF (%)	3.4(1.1,38.7)	6.4 $\pm$ 7
R2* IDEAL IQ (s ^{−1})	39 (24.7, 120.6)	47.3 $\pm$ 20.7

SD: standard deviation; IOP: In and out of phase.

Table 3:

Agreement on iron level and fat fraction between two readers. The agreement on fat fraction using conventional MRI method 1 was moderate and poor using method 2 (ICC=0.737 and 0.372, respectively). The agreement on iron level and IDEAL IQ fat fraction was excellent (ICC=0.935 and 0.961, respectively). Iron level grouping between two readers had a high kappa ($k=0.811$). High intrahepatic iron level was considered with an $R2^*$ cutoff higher than 71 s-1.

	ICC (95%CI)	RC (95%CI)
IOP Fat Fraction, Method 1	0.737 (0.566, 0.845)	9.69 (6.19, 16.02)
IOP Fat Fraction, Method 2	0.372(0.106,0.588)	20.43 (12.61, 34.62)
IDEAL IQPDFF	0.961 (0.932, 0.978)	3.86(2.14,7.48)
IDEAL IQR2*	0.935 (0.888, 0.962)	14.92 (10.71, 21.43)
Reader 2		
Reader 1	Normal Iron Level High Iron Level	
Normal R2* group	43 (86%)	1 (2%)
High R2*group	1 (2%)	5 (10%)

ICC: Intra-class correlation coefficient; RC: Repeatability coefficient; CI: confidence interval; IOP: In and out of phase.

Table 4:

Comparison of fat fraction measurements using conventional MRI and IDEAL IQ.

	IOP method 1	IOP method 2	IDEAL IQ	IOP1 vs IDEAL, P Value	IOP2 vs IDEAL, P Value
<i>Normal Iron level, $R2 < 71s^{-1}$, $n=44$</i>					
Reader 1				0.029	<0.001
Median (range)	4.3 (−16, 32.5)	3 (−25.7, 30.2)	3.6(1,41.1)		
Mean $\pm$ SD	4.1 $\pm$ 7.7	1.5 $\pm$ 10.6	6 $\pm$ 7.3		
Reader 2				0.081	0.001
Median (Range)	5.8 (−3.9, 28.8)	3.8 (−14.8, 34.6)	3.6(1.1,38.7)		
Mean $\pm$ SD	5.8 $\pm$ 6.8	2.9 $\pm$ 7.7	6.8 $\pm$ 7.4		
<i>Normal Iron level, $R2 \geq 71s^{-1}$, $n=6$</i>					
Reader 1				0.313	0.063
Median (range)	2.8 (−0.6, 16.4)	0.9 (−11.5, 11.9)	4.3 (1.3, 17.4)		
Mean $\pm$ SD	5 $\pm$ 6	−0.2 $\pm$ 8.6	6.1 $\pm$ 6		
Reader 2				0.031	0.156
Median (Range)	5.8 (2.4, 18.5)	−5.5 (−16.2, 11.1)	2.3(2.1, 7.1)		
Mean $\pm$ SD	7.5 $\pm$ 5.7	−3.2 $\pm$ 9.7	3.4 $\pm$ 2		
<i>All patients, $n=50$</i>					
Reader 1				0.017	<0.001
Median (range)	4.3 (−16, 32.5)	2.6 (−25.7, 30.2)	3.6(1,41.1)		
Mean $\pm$ SD	4.3 $\pm$ 7.5	1.3 $\pm$ 10.4	6.1 $\pm$ 7.1		
Reader 2				0.304	<0.001
Median (Range)	5.8 (−3.9, 28.8)	3.4 (−16.2, 34.6)	3.4(1.1,38.7)		
Mean $\pm$ SD	6 $\pm$ 6.6	2.2 $\pm$ 8.1	6.4 $\pm$ 7		

IOP1 = conventional IOP MRI method 1; IOP2 = conventional IOP MRI method 2.