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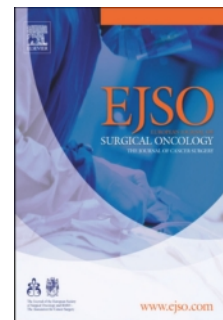
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Accuracy of liver-specific magnetic resonance imaging as a predictor of chemotherapy associated hepatic cellular injury prior to liver resection.

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Abstract

Background/aims: To evaluate the diagnostic precision of chemical shift imaging MRI and ferucarbotran-enhanced MRI for hepatic parenchymal injury prior to hepatic resection for colorectal metastases.

Methods: Preoperative MRI criteria were used to score 37 patients with colorectal liver metastases by two independent radiologists, blinded to outcomes, for signal drop-out on chemical shift imaging MRI and ferucarbotran uptake and compared to blinded standardized histopathological endpoints of steatosis, steatohepatitis and sinusoidal dilatation. Sensitivity, specificity, predictive values and the area under the receiver operating characteristic curve (AUC) were calculated for the MRI sequences.

Results: On histology, severe steatosis, steatohepatitis and sinusoidal dilation were evident in 6 (16.2%), 4 (10.8%) and 9 (24.3%) patients respectively. Chemical shift imaging MRI had a positive predictive value (PPV) of 100% for severe steatosis, 80% for steatohepatitis and zero for sinusoidal dilatation, with an AUC of 1.0, 0.99 and 0.36 respectively. Ferucarbotran-enhanced MRI had a 100% PPV for the detection of severe sinusoidal dilatation, with an AUC of 0.61.

Conclusions: This study demonstrates that liver-specific MRI can accurately predict the severity of pre-existing hepatic injury. Moreover, it may play a key role in planning the timing and extent of chemotherapy and hepatic resection for colorectal metastases.

Word Count: 198

Key words: MRI, hepatectomy, chemotherapy, hepatotoxicity, sensitivity, specificity

Introduction:

Over 50% of patients with colorectal cancer will develop liver metastases [1]. Resection of colorectal liver metastases (CRLM) offers the best outcome, with 25-44% five-year survival after curative resection [2,3,4]. However, only 20-30% of patients with CRLM will be candidates for this [2,3,4].

Advances in surgical and anaesthetic techniques have expanded the indications for liver resection. New chemotherapeutic agents such as oxaliplatin and irinotecan in the management of CRLM have resulted in response rates of 50% [5,6], increasing to 70-80% with additional biologic agents such as cetuximab or bevacizumab [7]. Neoadjuvant chemotherapy can downsize some patients with otherwise unresectable CRLM and increase the percentage of operable patients. Furthermore, Bismuth demonstrated that 16% of previously inoperable patients who underwent neoadjuvant chemotherapy and subsequent liver resection with curative intent, had a 39% five year survival [8]. These findings have subsequently been widely validated.

It is clear however, that chemotherapy can damage the hepatic parenchyma, with consequent increased surgical morbidity and mortality [9-15]. The parenchymal injury can include steatosis, steatohepatitis and sinusoidal dilatation. Oxaliplatin-based chemotherapy has the highest incidence of sinusoidal dilatation [9], whilst irinotecan can lead to steatohepatitis [10]. Currently, it is debated whether preoperative imaging can reliably predict these parenchymal changes [10,15,16]. The ability to predict hepatic steatosis has been most widely studied and there is emerging evidence that magnetic resonance imaging (MRI) using chemical-shift imaging (CSI) is predictive [17]. CSI-MRI exploits the characteristic differences in the resonant frequencies of

water and fat. T1-weighted images can be acquired in two different phases, so that water and lipid protons are either 'in phase' or 'out of phase' (opposed phase). In an 'in phase' image, the fat and water signals within a voxel are added and in an 'out of phase' image, they are subtracted from one another. Thus the signal drop-out from an 'in phase' to an 'out of phase' image is a measure of fat content of that voxel. However, a recent study has reopened the debate by concluding that conventional cross-sectional imaging using contrast-enhanced computed tomography (CT) or MRI does not consistently permit accurate identification of steatosis [18].

This study aimed to evaluate the predictive power of preoperative liver-specific MRI using pre-contrast CSI-MRI and contrast-enhanced MRI for hepatic parenchymal injury, compared to standardized histological criteria for hepatic cellular injury, in patients undergoing hepatic resection for CRLM.

Patients and Methods:

Study design and subjects: This was a blinded study of consecutive patients undergoing hepatic resection for CRLM at a single tertiary referral centre between January 2005 and January 2007. Informed consent was obtained from each patient and the study conformed to the Helsinki Declaration. All patients underwent pre-operative MRI using two intravenous contrast agents, gadolinium and ferucarbotran. Histopathological correlation with hepatic parenchymal injury was performed after surgery as the reference standard. The study was conducted in accordance to the STARD criteria (Standards for the Reporting of Diagnostic Accuracy studies).

Patient inclusion criteria were age over 18 years, a confirmed primary colorectal cancer with at least one resectable CRLM and no general contra-indications to MRI. Patients with and without neoadjuvant chemotherapy prior to liver resection were included. Patients were excluded if the MRI protocol could not be met, or if there was insufficient “normal” liver tissue for representative histology.

Data Collection: Patient data were collected prospectively on a database (Access®, Microsoft Corporation, Redmond, Washington, USA) comprising 268 data fields. These included the type and duration of chemotherapy, type of resection, intraoperative blood loss, postoperative liver function tests, significant comorbidity [body mass index (BMI), diabetes mellitus], morbidity and mortality.

Data definitions: Resectable disease was defined as the ability to completely remove all CRLM, regardless of size, number, distribution or width of resection margin, whilst preserving sufficient volume of functioning hepatic parenchyma [usually 25-

30%, estimated by CT or MRI], portal venous and hepatic arterial inflow, hepatic venous outflow and biliary drainage. The surgical and anaesthetic techniques used have been previously reported by this unit [3,19]. No patients underwent additional removal of “normal” liver tissue for this study. Perioperative mortality was defined as death during the same admission or within 90 days of surgery. Postoperative complications were classified as minor, relevant (delayed discharge) or major (requiring urgent medical or surgical intervention). The extent of hepatic resection was recorded using the IHPBA terminology [20].

MRI Imaging: In all patients, pre-contrast in and opposed phase CSI-MRI and post-contrast imaging using two different contrast agents, ferucarbotran and gadolinium, were acquired to aid the detection of liver lesions and assess vascular anatomy prior to resection. A 1.5 Tesla (Siemens AG, Munich, Germany) Symphony™ MRI machine was used. Each set of images was acquired during a breath-hold to reduce movement artefact. The following MRI sequences were initially performed (pre-contrast): TRUE FISP (TR 5.39ms, TE 2.7ms, FOV 400, Slice thickness 10mm); T1-weighted FLASH In-Phase (TR 191ms, TE 4.7ms, FOV 400, Slice thickness 10mm); T1-weighted FLASH Opposed Phase (TR 144ms, TE 2.39ms, FOV 400, Slice thickness 10mm) and T2-weighted HASTE (TR 1100ms, TE 93ms, FOV 400, Slice thickness 4mm). All sequences were acquired in the axial plane.

Ferucarbotran (Resovist®, Schering, Berlin, Germany) is an organ-specific contrast agent consisting of super-paramagnetic iron oxide nanoparticles, taken up by Kupffer cells, causing decreased signal intensity of normal liver. It can define small focal liver lesions as they do not take up ferucarbotran and therefore appear bright on T2*-

weighted images, compared to normal liver and thus increases detection of liver metastases [21]. Ferucarbotran (0.05mmolmL^{-1}) was administered as a bolus hand injection according to patient weight. For patients weighing $<60\text{Kg}$, a 0.9ml injection was given. For patients weighing 60Kg or more, a 1.4ml injection was given, as per the manufacturers prescribing information. The following sequences were then performed at 10 minutes from injection: dynamic T1-weighted Fat Saturated Volume Interpolated Breath Hold-VIBE (TR 3.38ms , TE 1.52ms , FOV 400 , Slice thickness 2.5mm) at 40 seconds and T2*-weighted axial images (TR 148ms , TE 14ms , FOV 320 , Slice thickness 6 mm)

Gadolinium (Omniscan[™], GE Healthcare AS, Oslo, Norway) is a paramagnetic ion, producing positive enhancement on T1 images and widely used as an MRI contrast agent, for both lesion characterisation and to delineate vascular anatomy. Following the ferucarbotran sequences, gadolinium was administered via a pump injection at 0.1mmol/Kg with a 20ml saline flush and the following sequences obtained: dynamic T1 weighted Fat Saturated Volume Interpolated Breath Hold-VIBE (TR 3.38ms , TE 1.52ms , FOV 400 , Slice thickness 2.5mm), in arterial, portal venous and equilibrium phases.

Quantitative MRI scoring

The MRIs were scored by two independent radiologists, expert in liver-specific MRI, blinded to all other aspects of the study. Any discrepancies in scoring the MRIs were resolved by consensus.

The degree of liver steatosis was assessed from the signal drop-out between the “in phase” and the “opposed phase” T1 CSI-MRI. The ratio of the signal on the “opposed phase” over the “in phase” images was taken in order to produce the “CSI-MRI ratio”, a quantitative assessment of liver steatosis.

Qualitative MRI scoring

The degree of hepatic steatosis was also scored subjectively using CSI-MRI as absent (0), mild (1), moderate (2) or severe (3) (Figure 1b and 1c). The uptake of ferucarbotran at the 10 minute point on T2* weighted axial images was subjectively scored as normal (0), mildly abnormal (1), moderately abnormal (2) and severely abnormal (3) (Figure 3b and 3c). The MRI sequences used in the study are widely available, with no additional software required for image analysis.

Pathologic Analysis (reference standard): Tissue samples were obtained from the surgical specimens. Slides were prepared from formalin-fixed, paraffin-embedded tissue, stained with haematoxylin and eosin. One pathologist (AM), blinded to all clinical data, evaluated the resected specimens. Pathologic findings of the “normal” liver tissue remote from the tumour were assessed for presence or absence of one of three types of hepatic cellular injuries:

- (1) Steatosis, recorded as: 0=nil, 1=mild (<30%), 2=moderate (30-60%), 3=severe (>60%) (Figure 1a).
- (2) Steatohepatitis, graded as defined by Kleiner [22] based on steatosis (0≤ 5%, 1= 5%-33%, 2= 33%-66%, 3 ≥66%), lobular inflammation (0=nil, 1 ≤2 foci, 2 =2-4 foci, 3 ≥4 foci per x200 field) and ballooning (0=nil, 1=few balloon,

2=prominent ballooning). A score of ≥ 4 was considered significant steatohepatitis [10] (Figure 2a).

- (3) Sinusoidal dilatation, scored as: 0=nil, 1=mild (centrilobular to 1/3), 2=moderate (extending to 2/3), 3=severe (complete lobular involvement) [9] (Figure 3a).

Statistical Analysis: Data were entered in a Statistical Package for the Social Sciences (version 14) software package (SPSS Inc, Chicago, IL). Linear regression analysis was used to evaluate the association between the CSI-MRI ratio and the qualitative steatosis score. Multifactorial regression analysis was used to identify independent histopathological factors associated with a low CSI-MRI ratio.

Sensitivity, specificity, predictive values and the mean area the receiver operating characteristic curve (AUC) were calculated for the MRI sequences, on a patient by patient basis. Given that these methods become inaccurate when sample sizes are small, exact binomial confidence intervals were therefore calculated for sensitivity, specificity, predictive values and the AUC. Interobserver variability for scoring MRI images was calculated using the Kappa statistic. A p-value of <0.05 was considered to indicate a statistically significant difference between groups.

Results

Patient characteristics: 239 consecutive patients underwent hepatic resection for colorectal liver metastases during the study period. 202 patients were excluded either because the MRI protocol could not be met in its entirety (n=130), or there was insufficient liver tissue for representative histology to be undertaken (n=72). Thus 37 patients were recruited and their demographics outlined in Table 1. At the time of liver resection, the patients' mean age was 60 years (range 21-79) with a male to female ratio of 1.6:1. Thirty patients had a major hepatectomy. The median blood loss was 410mls (range 30–1050mls), which did not differ significantly between patients with or without hepatic parenchymal injury. There were two diabetic patients and five who were clinically obese ($\text{BMI} > 30 \text{ kg/m}^2$). Patients with a $\text{BMI} > 30 \text{ kg/m}^2$ had a significantly higher incidence of severe steatosis (80% vs. 6%; $p < 0.001$) and steatohepatitis (80% vs. 0%; $p < 0.001$) compared to patients with a $\text{BMI} \leq 30 \text{ kg/m}^2$, on histological analysis.

Chemotherapy details: Twenty-four patients had pre-operative chemotherapy. Twenty patients had neoadjuvant chemotherapy for known liver metastases, nine for resectable disease and eleven for initially unresectable disease who were subsequently downsized. The most common regime was oxaliplatin and 5-fluorouracil (5-FU) (n=19) and the majority of patients (n=18) had 3-6 months of chemotherapy. The median time interval between cessation of chemotherapy and liver resection in this group was six weeks. Four patients had adjuvant chemotherapy following resection of their primary colorectal tumour.

Clinical Outcome: There was no in-patient or 90-day mortality. Nine patients had complications including four minor (wound infection n=2, chest infection n=1, hepatic insufficiency n=1), four relevant (hepatic insufficiency n=3, chest infection n=1) and one major complication, a bleed from a branch of the left portal vein requiring re-operation to achieve haemostasis.

Histological analysis: Histological analysis for parenchymal injury showed that 27 patients had nil or mild steatosis (Figure 1), 4 moderate and 6 severe steatosis (Figure 1a). Thirty patients had a Kleiner score of <4 and 7 scored ≥ 4 , indicating moderate-severe steatohepatitis. Four patients had severe steatohepatitis (Figure 2a). Twenty-three patients had no or mild sinusoidal dilatation, 5 had moderate and 9 severe sinusoidal dilatation (Figure 3a). No patient had cirrhosis.

Diagnostic precision of CSI-MRI versus histology:

There was 100% agreement in the CSI-MRI ratio and scoring between the two radiologists. Moreover, there was a significant inverse association between the quantitative CSI-MRI ratio and the qualitative score of signal drop-out between the “opposed” and “in” phases on MRI ($p<0.001$, $r^2=0.786$). The diagnostic performance of CSI-MRI for detection of grades of steatosis, steatohepatitis and sinusoidal dilatation are shown in Table 2.

Univariate and multivariate analysis were used to determine the independent predictors of CSI-MRI ratio. On univariate analysis, all three histological criteria (steatosis, lobular inflammation and hepatocyte ballooning) were predictors of a low CSI-MRI ratio ($p<0.001$, $p=0.001$, $p=0.028$ respectively). However, on multivariate

analysis, only histological steatosis and ballooning were found to be independent predictors of the CSI-MRI ratio, with steatosis being the most important factor ($p < 0.001$ versus $p = 0.03$). Because of this, CSI-MRI was not able to satisfactorily distinguish between steatosis and steatohepatitis. However, histologically, moderate or severe steatosis was found to occur with a CSI-MRI ratio of ≤ 0.6 .

Diagnostic precision of ferucarbotran-enhanced MRI versus histology:

Contrast administration was well tolerated and no patient had significant adverse events following MRI. In three cases there was disagreement between the two radiologists in the reporting of ferucarbotran uptake, resolved by consensus (k-statistic for inter-observer variation = 0.946; standard error = 0.030). The diagnostic performance of ferucarbotran-enhanced MRI for detection of grades of steatosis, steatohepatitis and sinusoidal dilatation is shown in Table 2. The ferucarbotran-enhanced MRI demonstrated little diagnostic value for the histological diagnosis of steatosis or steatohepatitis. However, it had 100% specificity and 100% PPV for moderate or severe sinusoidal dilatation. The sensitivity however, was low (Table 2).

The AUC for ferucarbotran-enhanced and CSI-MRI for detection of severe hepatic parenchymal injury is shown in Table 3. CSI-MRI had a high predictive power for the detection of severe steatosis or steatohepatitis, reflected in the area under the ROC curve (1.000 and 0.985, respectively). Ferucarbotran-enhanced MRI had had little diagnostic discrimination for steatosis or steatohepatitis, but provided moderate predictive power for the detection of severe sinusoidal dilatation, with an area under the ROC curve of 0.611.

Discussion

Neoadjuvant chemotherapy is an integral part of the multidisciplinary management of metastatic colorectal cancer. Its benefits are well documented and include the potential to downsize disease and thus improve hepatic resection rates [8], to simultaneously treat hepatic and systemic micro-metastases early and to provide in-vivo assessment of tumour chemo-responsiveness, allowing clinicians to continue treatment for responders or change treatment for non-responders. Furthermore, there is evidence that response to chemotherapy is a prognostic indicator of survival, even when subsequent liver resection is performed with curative intent [23]. However, there is strong evidence that modern chemotherapeutic regimens are associated with hepatic parenchymal injury including steatosis [24,25], steatohepatitis [10] and sinusoidal dilatation [9]. More recently, studies have confirmed an increase in surgical morbidity and mortality in the presence of chemotherapy-associated parenchymal injury [10-15]. Indeed, some investigators suggest liver biopsy in high-risk patients [10, 26] to evaluate the “normal” liver parenchyma prior to major hepatectomy.

Currently, the gold standard for pre-operative diagnosis of hepatic parenchymal injury is liver biopsy. However, the parenchymal changes are often patchy, which may lead to sampling error. To overcome this, Vauthey has suggested laparoscopy, combining direct inspection with biopsy as a useful method of evaluation [10,15]. This technique clearly poses increased patient risk and clinical costs. In addition, a biopsy that inadvertently samples tumour can result in tumour dissemination and consequent reduced survival [27].

This study demonstrates that MRI may predict parenchymal damage prior to surgery. Specifically, qualitative CSI-MRI scores show a high sensitivity and specificity for steatosis. The qualitative CSI-MRI scores correlate well with the quantitative CSI-MRI ratio and a ratio of ≤ 0.6 accurately predicts moderate or severe steatosis on histology. CSI-MRI also shows a high sensitivity and specificity for steatohepatitis. This is largely due to the ability of CSI-MRI to predict steatosis, a component of steatohepatitis. Indeed, given the fact that steatohepatitis by its definition includes steatosis (along with inflammation and ballooning), a single modality imaging technique is unlikely to distinguish between steatosis or steatohepatitis.

This study has shown that ferucarbotran-enhanced MRI is associated with a high specificity for moderate or severe sinusoidal dilatation and moderate predictive power for severe sinusoidal dilatation (AUC=0.61). This finding has recently been confirmed by Ward and coworkers [28], who showed that ferucarbotran-enhanced MRI had an 83% PPV for the detection of moderate to severe sinusoidal dilatation, largely associated with oxaliplatin-based chemotherapy. They suggest that locally impaired Kupffer cell function is responsible for the patchy iron uptake observed. Certainly, the clinical implications of abnormal iron uptake on imaging warrant further exploration.

Despite a recent publication to the contrary [18], the role of imaging for the evaluation of hepatic steatosis is established. Specific criteria for grading of steatosis are available for CT [29], ultrasound [30] and MRI [17,30]. However, this current study is unique in that it correlates MRI grading of steatosis, steatohepatitis and sinusoidal dilatation with histological analysis and shows that the CSI-MRI score accurately predicts the extent of steatosis and steatohepatitis. Whilst the numbers in this study

are too small to show an association of CSI-MRI score with duration or type of chemotherapy, serial CSI-MRI could potentially guide clinical decision-making in this area. One other study has looked specifically at chemotherapy-related hepatic parenchymal changes with imaging [25]. The senior radiologist of this study (DP) was also an author of that report which examined 27 patients treated with 5-FU for advanced colorectal cancer and found that 47% developed hepatic steatosis as demonstrated by CT criteria. However, that study neither quantified the extent of injury nor did it correlate findings on CT with histopathology, unlike the current analysis. There is a well-established association of steatohepatitis and patient factors such as obesity and insulin resistance [31]. It is likely that all these factors are inter-related, for example, obesity may lead to steatosis and chemotherapy may provide the “second hit” which induces steatohepatitis [32]. Certainly, the importance of patient factors is seen in this study and in others [10,14], there being a greater incidence of steatosis and steatohepatitis in patients with a high BMI.

The MRI scoring system does not differentiate patients with steatohepatitis from those with steatosis alone. However, severe steatosis and steatohepatitis are both major risk factors for extended resection [10,26]. If the preoperative CSI-MRI suggests severe steatosis, consideration should be given to preoperative portal vein embolisation (PVE) or parenchymal-sparing surgery, to maximise postoperative liver function [33]. Moreover, the use of short-term specialised diets, exercise and drug regimes to reduce steatosis [34,35] or modulate steatohepatitis [36] may improve clinical outcomes.

In conclusion, chemotherapy-associated hepatic parenchymal injury is a reality for all hepatic surgeons. MRI can provide a non-invasive and accurate method of

determining hepatic injury. This straightforward evaluation of parenchymal damage has important implications in clinical decision-making, including the risk and extent of resection, the duration of chemotherapy and the use of PVE.

ACCEPTED MANUSCRIPT

Conflict of Interest Statement:

The authors have no financial or personal relationships with other people or organisations that could inappropriately influence or bias this work.

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Table 1: Demographic characteristics of patients (n=37) undergoing hepatic resection for colorectal liver metastases grouped by the histopathological type and grade of hepatic parenchymal injury.

	All patients	Steatosis		Steatohepatitis		Sinusoidal Dilatation	
		Nil-Mild (0-1)	Mod-sev (2-3)	Nil-Mild (0-4)	Mod-sev (4-8)	Nil-Mild (0-1)	Mod-sev (2-3)
N=	37	27	10	30	7	23	14
Mean age (range)	60 (21-79)	60 (21-79)	55.5 (30-72)	58.5 (21-79)	62 (48-71)	58 (21-76)	61 (30-79)
Gender: Male	23	19	4	20	4	13	10
Gender: Female	14	8	6	10	3	10	4
Pre-op chemotherapy: Yes	24	17	7	18	6	15	9
Pre-op chemotherapy: No	13	10	3	12	1	8	5
Liver resection: Major	30	21	9	25	5	17	13
Liver resection: Minor	7	6	1	5	2	6	1
BMI: 19-25 kg/m ²	23	19	4	21	2	13	10
BMI: 25.1-30 kg/m ²	9	8	1	8	1	5	4
BMI: >30 kg/m ²	5	0	5	1	4	5	0
Diabetes mellitus: Yes	2	0	2	0	2	2	0
Diabetes mellitus: No	35	27	8	30	5	21	14
Post-operative Morbidity	9	7	2	2	7	4	5

Table 2: Sensitivity, specificity and predictive value of Ferucarbotran-enhanced MRI and chemical shift imaging (CSI) MRI for the detection of three types of hepatic parenchymal injuries: steatosis; steatohepatitis and sinusoidal dilatation.

Ferocarbotran-enhanced MRI						CSI-MRI			
Histology	Number	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Steatosis									
Nil or Mild	27	14%	75%	43%	40%	38%	100%	100%	55%
Moderate	4	0%	93%	0%	71%	60%	100%	100%	87%
Severe	6	0%	97%	0%	83%	83%	100%	100%	97%
Steatohepatitis									
Nil or Mild	30	9%	77%	14%	67%	64%	96%	88%	86%
Moderate	3	0%	93%	0%	80%	100%	86%	100%	97%
Severe	4	0%	97%	0%	89%	100%	97%	80%	100%
Sinusoidal Dilatation									
Nil or Mild	23	22%	90%	86%	30%	11%	50%	38%	17%
Moderate	5	14%	100%	100%	66%	0%	74%	0%	55%
Severe	9	11%	100%	100%	78%	0%	82%	0%	72%

Table 3: The area under the ROC for Ferocarbوتران-enhanced and chemical shift imaging (CSI) MRI for the detection of severe hepatic parenchymal injury.

Histology	Ferocarbوتران - enhanced MRI		CSI-MRI	
	AUC	95% CI	AUC	95% CI
Steatosis	0.387	0.170 - 0.604	1.000	---
Steatohepatitis	0.394	0.140 – 0.648	0.985	0.948 – 1.000
Sinusoidal Dilatation	0.611	0.378 - 0.844	0.357	0.171 – 0.543

Footnotes to tables**Table 1:**

Mod = Moderate

Sev = Severe

BMI = Body mass index

Table 3:

AUC = area under the receiver operating characteristic curve

95% CI = 95 percent confidence interval

Legends to Figures:**Figure 1.**

Figure 1a. Severe Steatosis (Grade 3) x100. > 60% of the liver parenchyma is involved by steatosis

Figure 1b & c. MRI images of the corresponding patient demonstrating patchy severe steatosis (MRI Grade 3). T1 images in-phase (b) and out of phase (c) are illustrated. The liver appears darker on the out of phase images compared to the in-phase images (ratio = 0.26). The more marked signal indicates severe steatosis, but the changes are regional.

Figure 2.

Figure 2a. Severe Steatohepatitis x200. Shows 60% steatosis (Grade2) and lobular inflammation; >4 foci of inflammatory cell (grade3) Kleiner score =5.

Figure 2b & c. MRI images of the corresponding patient demonstrating severe steatosis (MRI Grade 3). T1 images in-phase (b) and out of phase (c) are illustrated. The liver appears much darker on the out of phase images compared to the in-phase images (ratio = 0.08). The more marked signal indicates severe steatosis.

Figure 3.

Figure 3a. Severe Sinusoidal Dilatation. (Grade 3) complete lobular involvement by sinusoidal dilatation x40

Figure 3b. A T2* image obtained 10 minutes following the administration of Ferucarbotran illustrating severely impaired iron uptake (MRI Grade 3). The liver has a heterogeneous signal and appears much lighter than expected on the post-contrast

image. This indicates that the liver tissue has not taken up the iron normally and the signal intensity has therefore not been reduced.

Figure 3c. A T2* image obtained 10 minutes following the administration of Ferucarbotran illustrating patchy moderate to severely impaired iron uptake (MRI Grade 2). The liver has a heterogeneous signal that appears much lighter in a regional distribution. This indicates that these areas of liver tissue have not taken up the iron normally due to sinusoidal dilatation.

Figure 1: Severe Steatosis.

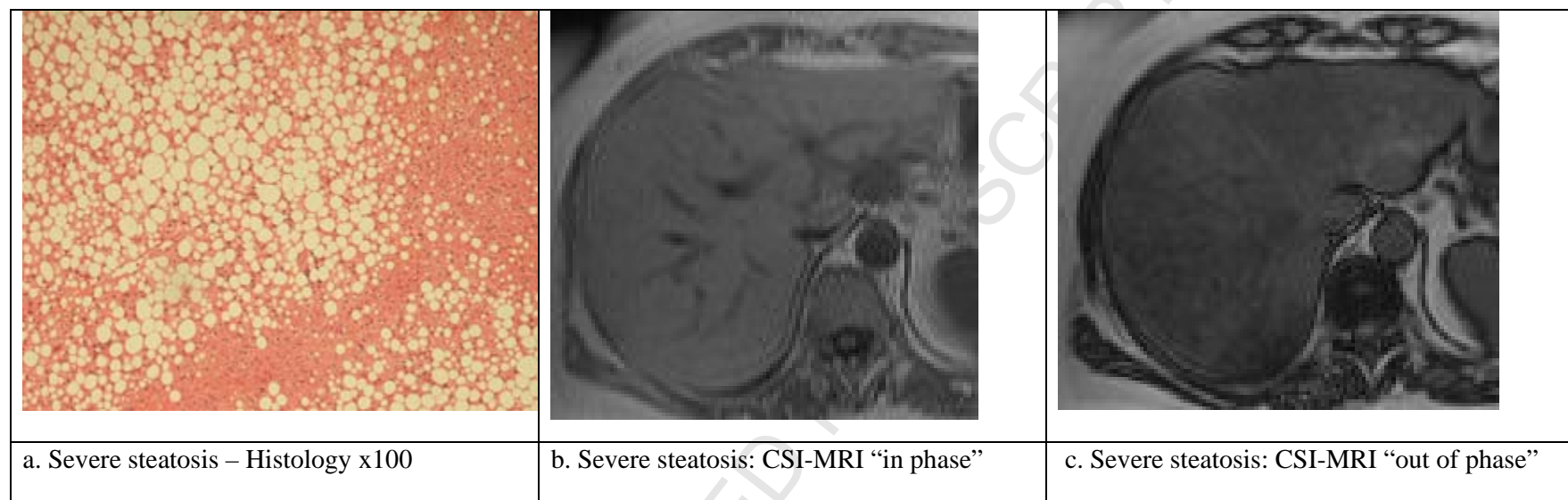


Figure 2. Severe Steatohepatitis.

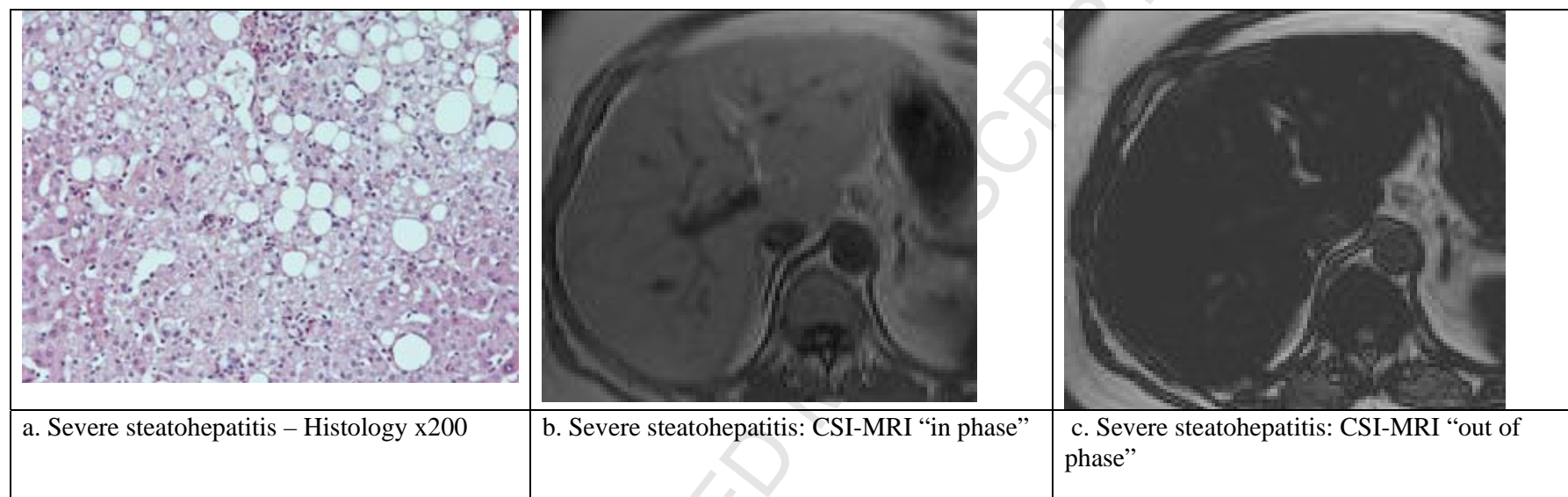


Figure 3. Severe Sinusoidal Dilatation

