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Hepatic steatosis in patients undergoing resection of colorectal liver metastases: A target for prehabilitation? *A narrative review*

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ABSTRACT

The prevalence of elevated intra-hepatic fat (IHF) is increasing in the Western world, either alone as hepatic steatosis (HS) or in conjunction with inflammation (steatohepatitis). These changes to the hepatic parenchyma are an independent risk factor for post-operative morbidity following liver resection for colorectal liver metastases (CRLM). As elevated IHF and colorectal malignancy share similar risk factors for development it is unsurprisingly frequent in this cohort. In patients undergoing resection IHF may be elevated due to excess adiposity or its elevation may be induced by neoadjuvant chemotherapy, termed chemotherapy associated steatosis (CAS). Additionally, chemotherapy is implicated in the development of inflammation termed chemotherapy associated steatohepatitis (CASH). Following cessation of chemotherapy, patients awaiting resection have a 4–6 week washout period prior to resection that is a window for prehabilitation prior to surgery. In patients with NAFLD dietary and pharmacological interventions can reduce IHF within this timeframe but this approach to modifying IHF is untested in this population. In this review, the aetiology of CAS and CASH is reviewed with recommendations to identify those at risk. We also focus on the post-chemotherapy washout period, reviewing dietary interventions applied to the metabolic population and suggest this window may be used as an opportunity to optimise IHF with such a regime as part of a pre-operative prehabilitation programme to produce improved patient outcomes.

1. Introduction

Hepatic resection alone, or in combination with chemotherapy, for colorectal liver metastases (CRLM) is associated with a five-year survival of approximately 40% [1]. Whilst improvements in surgical technique and post-operative care have resulted in decreased mortality, post-operative morbidity remains high (22–33%) [2–4]. Strategies to reduce post-operative complications are therefore of interest.

Excess intra-hepatic fat (IHF), termed hepatic steatosis (HS), occurs in up to 40% of patients [5,6] undergoing liver resection and is associated with increased post-operative morbidity [7–10]. Trials of dietary and pharmacological intervention in patients with hepatic steatosis secondary to obesity or type 2 diabetes mellitus (T2DM) demonstrate that a significant reduction in IHF can be achieved within 8 weeks [11–16]. Therefore, hepatic steatosis may be a modifiable risk factor for morbidity and a potential target for pre-operative intervention.

This narrative review appraises the current literature on HS in patients with resectable CRLM. Firstly, we discuss the aetiology of HS. We discuss clinical features associated with the presence of HS and techniques used to quantify HS and make recommendations for future studies.

We discuss the role of neoadjuvant chemotherapy in the aetiology of chemotherapy associated hepatic steatosis (CAS) and steatohepatitis (CASH). We review the patterns of hepatic parenchymal injury described and implicated chemotherapeutic agents. Here we highlight the typical 4–8 week washout period observed following the cessation of neoadjuvant chemotherapy and surgery, citing it as a window to optimise CAS and CASH.

Next, this review addresses the body of literature that has reported on the relationship between HS and peri-operative outcomes. Finally, we discuss evidence of dietary and pharmacological interventions that may modify this fat store pre-operatively. We conclude by outlining areas where research is required to investigate the effect of targeted intervention in HS as part of a pre-operative prehabilitation programme.

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Abbreviations

5-FU	5 Fluorouracil
5 YS	five year survival
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASH	alcoholic steatohepatitis
AST	aspartate aminotransferase
Bili	bilirubin
BMI	body mass index
CAS	chemotherapy associated steatosis
CASH	chemotherapy associated steatohepatitis
CE-MR	contrast enhanced magnetic resonance
CHO	carbohydrate
CRLM	colorectal liver metastases
CS-MR	chemical shift magnetic resonance
GI	glycaemic index
ICG	Indocyanine green
ICG-PDR	Indocyanine green plasma disappearance rate
IHF	intra-hepatic fat
ITU	intensive therapy unit
ICU	intensive care unit
HbA1c	glycated haemoglobin
HFF	hepatic fat fraction
HS	hepatic steatosis
kCal	kilocalorie
MJ	mega Joule
MUFA	mono-unsaturated fatty acids
MRS	magnetic resonance spectroscopy
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
OR	odds ratio
PCOS	polycystic ovary syndrome
PT	prothrombin time
PUFA	polyunsaturated fatty acids
RCT	randomised control trial
SFA	saturated fatty acids
SOS	sinusoidal obstruction syndrome
SS	severe steatosis
T2DM	type 2 diabetes mellitus

2. Methods

A systematic search was performed across the databases of EMBASE, MedLine, CINAHL and Google Scholar. Key terms included 'hepatic steatosis', 'intra-hepatic fat', 'liver resection', 'colorectal cancer', 'liver metastasis', 'dietary intervention', 'dietary alteration', 'nutrition therapy', 'non-alcoholic fatty liver disease', 'NAFLD', 'non-alcoholic steatohepatitis', 'steatohepatitis', 'neoadjuvant chemotherapy', 'chemical shift magnetic resonance', 'magnetic resonance spectroscopy', 'MRI' and 'magnetic resonance imaging'. The search included articles published in English up to July 2018.

Abstracts of generated articles were reviewed prior to selection. Further cross-referencing of these articles was also conducted for citation of relevant articles. Articles were included which discussed the impact of HS or IHF on liver resection for colorectal cancer, dietary interventions to reduce IHF, the association of chemotherapy and IHF in patients with CRLM and articles that discussed quantification of IHF by magnetic resonance techniques.

3. Aetiology of intra-hepatic fat in patients with colorectal liver metastases

The excess accumulation of triglycerides is related to a spectrum of disease states on a continuum from steatosis alone, to steatohepatitis and cirrhosis. HS is commonly defined as the accumulation of greater than 5% triglycerides within the liver [17]. The most common cause of HS worldwide is non-alcoholic fatty liver disease (NAFLD), a diagnosis made in the absence of significant alcohol consumption, competing causes of HS (e.g. chemotherapy) or other causes of chronic liver disease (e.g. viral hepatitis) [17,18]. The combination of steatosis and inflammation on histology is termed steatohepatitis and the progression from steatosis to steatohepatitis is associated with an increase in the risk of developing cirrhosis, liver failure, and hepatocellular carcinoma [18]. The progression of steatosis to steatohepatitis to cirrhosis is poorly understood. Histologically steatohepatitis is graded by the degree of steatosis, lobular inflammation, hepatocellular ballooning and fibrosis which correlate with clinical outcomes [17]. However, non-alcoholic steatohepatitis (NASH) and alcoholic steatohepatitis (ASH) are almost indistinguishable histologically [18].

As obesity is a risk factor for both CRLM and HS [19], and chemotherapy is associated with steatosis, it is unsurprising that HS is present in the post-operative biopsies of 30–39% of patients undergoing resection for CRLM [5,6]. Hepatic steatosis is present in patients with CRLM due to either; steatosis independent of their treatment (i.e. associated with obesity, metabolic syndrome or insulin resistance (NAFLD)) or chemotherapy associated steatosis (CAS) or steatohepatitis (CASH) (Fig. 1).The quantity of IHF will vary for a single patient during treatment as IHF is influenced by diet, chemotherapy, cancer associated cachexia and the fluctuations in weight associated with time, treatments and changes in lifestyle.

3.1. Non-alcoholic fatty liver disease

Due to the lack of widespread screening studies, the prevalence of HS within the general UK population is unknown. Studies of Mediterranean populations suggest a prevalence of up to 33% in the general population [20,21]. The conditions of NAFLD, T2DM, metabolic syndrome, obesity and cancer are considered products of industrialisation and their increase in prevalence over the last 30 years mirrors the dietary trends observed involving increasing consumption

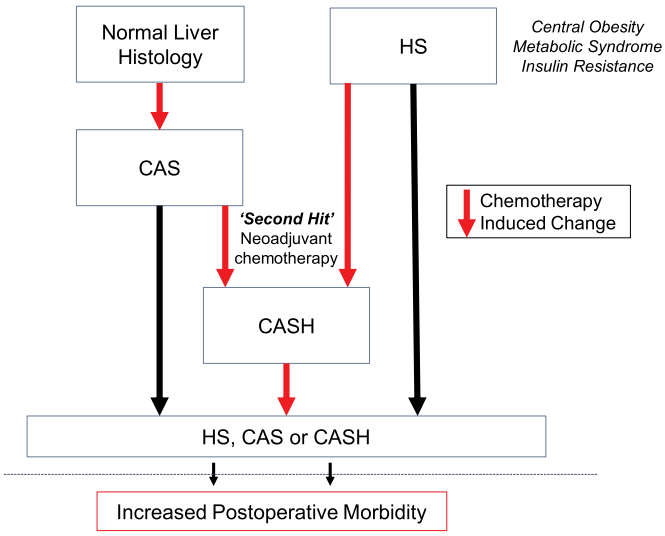

Fig. 1. Schematic diagram illustrating aetiology of hepatic steatosis, chemotherapy associated steatosis and chemotherapy associated steatohepatitis.*HS hepatic steatosis; CAS chemotherapy associated steatosis; CASH chemotherapy associated steatohepatitis.*

of refined carbohydrates and consequent insulin resistance [22–25].

3.2. Chemotherapy associated steatosis and chemotherapy associated steatohepatitis

Patients with CRLM may receive chemotherapy prior to liver resection either for treatment of the primary colorectal cancer or as part of treatment of the CRLM. This treatment is associated with the development of CAS and chemotherapy associated steatohepatitis (CASH) [26]. It is worth noting that in much of the literature the terms HS and CAS are used interchangeably.

Chemotherapy for CRLM may be given either in the neo-adjuvant or adjuvant setting [27–29]. Typical chemotherapy regimens are based on a combination of irinotecan, leucovorin, fluorouracil (5-FU) and oxaliplatin. The use of chemotherapy improves the progression-free survival at 3 years by 9.2%, from 33.2% to 42.4% [28,30]. Chemotherapy may also be used to downstage disease and may facilitate resection in some patients with metastases initially considered to be unresectable [31]. However, the impact of this systemic treatment spreads beyond the target lesions and some regimens are associated with changes within the non-tumour liver parenchyma. Chemotherapy may induce steatosis and it is hypothesised that it may provide an inflammatory hit inducing the progression of pre-existing HS or CAS to CASH [32,33].

The literature describes the differing aetiologies for elevated IHF in patients undergoing hepatic resection of CRLM. HS may be due to the excess adiposity, insulin resistance and metabolic syndrome as seen with increasing frequency in the general population. Unique to this group, this process may be exacerbated by neoadjuvant chemotherapy regimens, with the most implicated agent being irinotecan [26,34]. The association with CAS and CASH varies with different chemotherapeutic agents. Irinotecan is associated with the development of CAS and CASH independent of BMI [26,34,35]. Additionally, 5-FU alone or in combination with Leucovorin is associated with the development of CAS independent of Irinotecan [36] although the addition of Irinotecan increases further the frequency of steatosis [37]. In contrast, Oxaliplatin-based regimens have been shown to cause Sinusoidal Obstruction Syndrome (SOS) rather than steatotic changes [26,36]. SOS involves the loss of sinusoidal wall structure, sinusoidal congestion and fibrosis. Although discussion of SOS is beyond the scope of this review, it is important to note that SOS too has been implicated in increasing post-operative morbidity [36,38].

Following the completion of chemotherapy, it is accepted practice that a period of 4–6 weeks (6–8 weeks in patients receiving regimes containing becuzimab) should precede resection to allow some resolution of chemotherapy-induced liver injury [39,40]. This 'washout' period reduces the risk of post-operative complications [39].

This time period provides a window for intervention to optimise this modifiable risk factor before surgery (Fig. 2). Gaps remain in the literature, however, and although improvements in surrogate markers of hepatic function (Indocyanine Green Clearance (ICG)) have been observed after completion of chemotherapy [41], histological or imaging evidence of an improvement in steatosis or steatohepatitis are lacking. Imaging studies examining the change in the quantity of IHF between the completion of chemotherapy and resection have not been performed. Therefore, one key question when considering pre-operative interventions that take place in this same window is whether changes in intra-hepatic fat are intervention related or due to cessation of chemotherapy. To provide this information, chronological assessment using imaging should first be performed.

4. Intra-hepatic fat, mortality and morbidity following hepatic resection of colorectal liver metastases

An association between grade of steatosis (mild (< 30%), moderate (30–60%) or severe (> 60%)) and post-operative complications has been reported in the majority of studies (Table 1). In a study of 325 patients, steatosis in over 30% of hepatocytes was associated with significantly more infectious, wound, hepatobiliary (including cholangitis, biliary obstruction, liver failure, ascites, peri-hepatic abscess and fluid collection or hepatic artery pump failure) and gastrointestinal complications. Severe steatosis (fat inclusions present in > 60% of hepatocytes) increased the probability of developing a single complication by threefold [7]. This finding was replicated using the same categorisations of HS in a retrospective analysis of 135 patients [8]. An association between increasing steatosis and peri-operative complications was seen (10%, 14% and 29% for no steatosis, mild steatosis and severe steatosis respectively). Additionally, operative time and transfusion requirements were increased and the post-operative rise in bilirubin and aspartate aminotransferase (AST) was greater in patients with severe steatosis [8]. Significant associations were found on univariate analysis between severity of steatosis and frequency of intensive care unit (ICU) admission, infectious complications and post-operative biochemical marker derangement. Multivariate analysis demonstrated that the extent of hepatic resection, requirement of blood transfusion and severity of steatosis were independent risk factors for post-operative morbidity. Post-operative complications occurred in 22.4% of patients without steatosis, 42.6% with mild steatosis, 62% with moderate steatosis and 58% with severe steatosis. There was also an increased incidence of in-hospital mortality in patients with steatosis, although this was not statistically significant [42]. In a cohort of 58 patients, steatosis was found to be an independent risk factor for post-operative complications and associated with rises in post-operative liver function tests [43].

A meta-analysis of these studies confirmed that steatosis of all levels was associated with increased morbidity and mortality. The relative risk of a post-operative complication compared to a non-fatty liver was 1.53 (1.27–1.85) for patients with < 30% steatosis, and 2.01 (1.66–2.44) for patients with ≥30%. Additionally, ≥30% steatosis increased post-operative mortality (RR 2.79; 1.19–6.51) [9]. A large prospective international study of 949 patients undergoing hepatectomy (57% for CRLM) demonstrated that steatosis in operative specimens conveyed an increased risk of post-hepatectomy liver failure. However, steatosis was not defined or graded [44]. A single study has associated pre-operative MR quantified IHF with post-operative morbidity and mortality. When IHF was quantified using CS-MR in 84 patients undergoing major liver resection, increased IHF was associated with greater frequency of post-operative complications, and more severe complications, including organ failure and sepsis. Patients with over 10% IHF content had a significantly longer ICU and hospital stay [10].

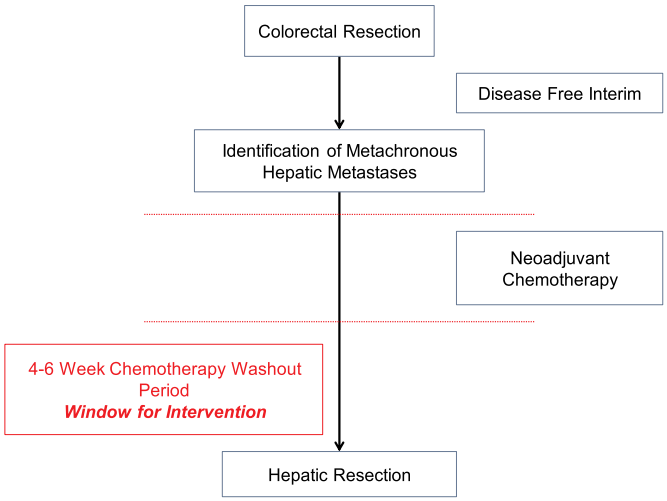

Fig. 2. Schematic diagram illustrating metachronous colorectal liver metastases chronology with a potential window for pre-operative intervention highlighted.

Table 1
Summary of studies assessing impact of intra-hepatic fat on post-operative outcomes following hepatic resection of colorectal liver metastases.

Author	Sample Details	Quantification of Steatosis	Results Summary
Behrns et al., 1998 [8]	Retrospective analysis Major hepatic resection n = 135 53% (n = 72) mild, 42% (n = 56) moderate, 5% (n = 7) moderate to severe	Histological Assessment Graded into: a. No steatosis b. Steatosis (fat inclusions in 30% of hepatocytes) c. Severe steatosis (fat inclusions in > 60% of hepatocytes)	Significant increase in duration of surgery in SS (290 min ± 9 vs 355 min ± 24, p < 0.05) SS associated with higher rate of blood transfusion requirements (No steatosis 51%, steatosis 52%, and severe steatosis 71%; p > 0.05) Post-operative elevation of Bili significantly higher in SS (400% above normal value vs 25% above normal value, p < 0.05) Post-operative elevation of AST significantly higher in steatosis and severe steatosis (125% above normal vs 160% above normal vs 175% above normal, p < 0.05)
Kooby et al., 2003 [7]	Retrospective matched case control analysis n = 325 Mild, n = 223; Moderate, n = 64; Severe, n = 38 Moderate & severe grouped as 'marked steatosis' (n = 102)	Histological Assessment as above	Degree of steatosis correlated with significantly higher rate of infectious complications and complications overall (p < 0.01, p < 0.01) All steatosis was associated with significantly higher wound, hepatobiliary and gastro-intestinal complications (13% vs 1%, p < 0.001; 23% vs 13%; p = 0.01; 11% vs 5%, p = 0.04) No significant difference in 5 YS (No steatosis 45% ± 5, Mild 42% ± 4, Marked 30% ± 6%)
Gomez et al., 2007 [42]	Retrospective analysis n = 386 Mild, n = 122; moderate, n = 60; severe, n = 12 First hepatic resection of CRLM	Histological Assessment as above	SS associated with significant increase in post-operative complications (p < 0.001) Steatosis associated with significantly higher proportion of ITU admission, derangement of Bili and AST and infectious complications (p = 0.001, p < 0.001, p = 0.031, p < 0.001) Higher rate of in hospital death in steatotic patients (p = 0.588)
McCormack et al., 2007 [43]	Matched case control study Hepatic resection for malignant or benign lesions n = 58 44 mild steatosis, 14 moderate/severe	Histological Assessment Graded as: a. No steatosis b. Mild (10–30% of hepatocytes with fat droplets) c. Moderate (30–60% with fat droplets) d. Severe (> 60% with fat droplets)	Steatosis associated with significantly higher rates of blood loss, need for Pringle manoeuvre and ICU admission (394 ml ± 41 vs 581 ml ± 71, p = 0.044; 50% vs 67%, p = 0.09; 1.5 days vs 3 days, p = 0.01) Steatosis associated with significantly higher post-operative elevation in AST, ALT, Bili, ALP and PT (412 UI/L ± 63 vs 534.9 IU/L ± 70, p = 0.012; 410 IU/L ± 57 vs 516.9 IU/L ± 58, p = 0.041; Bili 28.8 μmol/L ± 5.2 vs 52.7 ± 10 μmol/L, p 0.032; ALP IU/L 61.3 ± 17.7 vs 93.8 IU/L ± 17, p = 0.021; PT 19.7% ± 2.1 vs 28.1 ± 2.4, p = 0.018) Steatosis associated with significantly higher levels of major and overall complications (6.9% vs 27%, p = 0.001; 15% vs 29%, p = 0.007)
Pathak et al., 2010 [49]	Retrospective analysis n = 102 Normal, n = 27; Cirrhosis, n = 1; Steatosis, n = 57 (Mild, n = 26; moderate, n = 10; severe, n = 21)	Histological Assessment Graded as: a. No fatty change (< 5%) b. Mild (5–33%) c. Moderate (> 33–66%) d. Severe (> 66%)	No significant difference in post-operative median survival (No fatty change 32.3 months; mild 37.5 months; moderate 23.3 months; severe 28.6 months; p > 0.05)
Raptis et al., 2012 [10]	Retrospective analysis n = 84 69 < 10% liver fat; 15 > 10% liver fat Major liver resections (> 3 segments)	CS-MR quantification of hepatic fat fraction	Liver fat > 10% associated with significantly higher post-operative rise in AST and ALT, longer post-operative ICU and hospital stay and increased frequency of post-operative complications (326 vs 1108, p < 0.001; 421 U/I 386 vs 1355, p < 0.001; 1 day vs 2 days, p = 0.012; 12 days vs 19 days, p = 0.006) Liver fat > 10% associated with significantly higher treatment cost (€26549 vs €45058, p = 0.027)
Pilgrim et al., 2012 [48]	Retrospective analysis n = 232 Hepatic resection for any pathology Only 49.6% had available data regarding chemotherapy	Histological assessment categories: Steatosis Grade: 1. > 0–5% 2. > 5–33% 3. > 33–66% 4. > 66% Steatohepatitis: steatosis > 5%, NAS > 2	High grade steatosis (> 33%) associated with significantly higher rate of perioperative morbidity compared to those without (51% vs. 30%; p = 0.02) Steatohepatitis and sinusoidal injury not associated with increased morbidity (p values not available)
Parkin et al., 2013 [5]	Retrospective analysis n = 5853 30.6% (n = 1793) steatosis First time liver resection w/o pre-operative chemotherapy from LiverMetSurvey	Histological assessment categories: a. Normal b. With steatosis c. Other No guidelines for classification	Significant increase in 90 day mortality in other pathologies (normal 2.8%; steatosis 2.1%; other 4.9%) Steatosis associated with higher 5 YS (Normal 43.0%; Steatosis 47.4%; Other 43.0%; p = 0.0017) and cancer specific survival (50.3%; 56.1%; 47.2%; p = 0.002)
Parkin et al., 2014 [6]	Retrospective analysis n = 4329 Steatosis, n = 1675 (39%) First time liver resection with pre-operative chemotherapy from LiverMetSurvey	Histological assessment categories: a. Normal b. With steatosis c. Other No guidelines for classification	No significant difference in 90-day mortality (2.1%, 2.3% and 3.5%; p = 0.103) No significant difference in 5 YS (39%, 42% and 36%; p = 0.363) or cancer specific survival (43%, 45% and 41%; p = 0.496)
Ramos et al., 2015 [45]	Retrospective analysis Resection of CRLM n = 935 Mild steatosis 30.2%, Moderate 10.7%, Severe 4.2% 44.2% received pre-operative chemotherapy	Histological Assessment Graded as: a. No steatosis (0–5%) b. Mild steatosis (> 5%–30%) c. Moderate (30%–60%) d. Severe steatosis (> 60%)	No significant difference in 90-day mortality (Mild 3.5%; Moderate 3%, Severe 2.6%; p = 0.931) No significant difference in post-operative morbidity (Steatosis 55.1%; without steatosis 45.2%; p = 0.006) Mild and moderate steatosis associated with significantly higher 5 YS (p = 0.048, p = 0.033)

(*continued on next page*)

Table 1 (*continued*)

Author	Sample Details	Quantification of Steatosis	Results Summary
			No significant difference in recurrence at 5 years (steatosis 48.1%, no steatosis 44.5%; p = 0.663)
Sultana et al., 2018 [44]	Prospective analysis N = 949 57% (n = 540) Resection of CRLM 32% steatosis (n = 304)	a. Steatosis b. Fibrosis c. Blue liver	Post-hepatectomy liver failure Unadjusted risk 1.85 (1.24–2.76) (p = 0.003) Adjusted risk 2.73 (1.20–6.17) (p = 0.16)

AST aspartate aminotransferase; ALT alanine transaminase; ALP alkaline phosphatise; Bili bilirubin; CRLM colorectal liver metastases; CS-MR chemical shift magnetic resonance; ICU intensive care unit; ITU intensive therapy unit; PT prothrombin time; SS severe steatosis; 5 YS five year survival.

Table 2
NAFLD activity score [1].

Steatosis		
Grade	0	< 5%
	1	5–33%
	2	> 33%–66%
	3	> 66%
Lobular Inflammation		
Grade	0	No foci
	1	< 2 foci per 200X field
	2	2-4 foci per 200X field
	3	> 4 foci per 200X field
Liver Cell Injury (hepatocellular ballooning)		
Grade	0	None
	1	Few balloon cells
	2	Many cells/prominent ballooning

NAS < 2: no steatohepatitis; 3–4: probable steatohepatitis; ≥5: steatohepatitis.

Three studies have found no association with increased post-operative complications and steatosis. One study of 934 patients undergoing hepatic resection for CRLM found no significant difference in post-operative mortality and morbidity at 90 days between steatotic and non-steatotic groups, defined as the presence of fat vacuoles in 5% of liver cells on histological assessment [45]. Interestingly, two studies show no association between post-operative mortality and steatosis in groups with or without pre-operative chemotherapy and a long term survival benefit for patient with steatosis. However, the LiverMetSurvey, from which this data originated does not categorise severity of steatosis and assessment is heterogeneous amongst centres which contributed to this dataset [5,6].

Steatohepatitis on post-operative histology is associated with poorer post-operative outcomes. In a systematic review comprising 788 patients, steatohepatitis significantly increased the risk of a liver surgery specific complication (OR 2.08; 1.18–3.66; p = 0.012). This composite end-point comprised ascites, post-operative liver failure, bile leak, intra-abdominal abscess, intra-abdominal haemorrhage and operative mortality. Another retrospective analysis of 100 patients undergoing resection for CRLM, steatohepatitis was an independent predictor of post-operative complications on univariate analysis (p = 0.005) alongside requirement of blood transfusion [46]. There was also a non-significant trend towards increased overall morbidity (OR 1.58; 0.99–2.52; p = 0.057) [47]. Steatohepatitis was associated with an increased rate of 90 day mortality (OR = 10.5, CI 2.0–36.4) and death from post-operative liver failure (OR = 7.7, CI 1.24–47.7) in a study of 406 patients undergoing resection for CRLM [26]. Conversely, one study showed no association between steatohepatitis and morbidity [48].

The heterogeneity between published articles on this topic makes comparison of data difficult. In particular, definitions of HS vary between studies, as do categorical levels for severity of HS. The quantity of IHF at which increased risk is conveyed varies between publications. However, this risk appears to increase with greater IHF and is greatest in patients undergoing major resections. Overall, the literature supports an association between steatosis and increased risk of post-operative complications. This risk factor is modifiable pre-operatively and methods to optimise IHF have the potential to improve outcomes.

As mentioned, earlier research in this field implicated elevated IHF with increased morbidity, while latterly steatohepatitis has been highlighted as a risk factor. It is important to note that as these two conditions represent a continuum of the same disease process with the same aetiology, separating these as separate categorical risk factors may not be of use. In fact, approaching this area using NAFLD as a more encompassing risk factor, with features of inflammation, steatosis and fibrosis may be of greater value to the clinician. Furthermore, it is wise to recognise that NAFLD often does not occur in isolation and that unfavourable post-operative outcomes may also be attributable to other components of the metabolic syndrome including hypertension, T2DM and obesity [49–51].

5. Quantification of intra-hepatic fat

The gold standard for classification of steatosis and steatohepatitis is histology. Steatosis is considered present if greater than 5% of a specimen contains triglycerides and steatohepatitis graded based on the degree of steatosis, lobular inflammation, hepatocellular ballooning and fibrosis [52,53]. Table 2 illustrates the NAFLD Activity Score and Table 3 shows SAF score with accompanying diagnostic algorithm depicted in Fig. 3. In the post-operative setting, there is variation in the literature of definitions of steatosis. Some authors use a 5% cut-off, but more frequently, the degree of steatosis is classified into mild (< 30%) moderate (30–60%) or severe (> 60%) [7,8,42]. This makes comparison of studies challenging. Additionally, visual assessment in this semi-quantitative manner is prone to intra- and inter-observer variability [54,55].

Pre-operative histological assessment would require a biopsy, but this method is associated with morbidity and may be inaccurate secondary to heterogeneous fat deposition within the liver. Developments in magnetic resonance (MR) imaging techniques over the past decade

Table 3
Steatosis Activity Fibrosis Score [2].

Activity (hepatocellular ballooning and lobular inflammation)		
Grade	0	None
	1	Mild
	2	Moderate
	3	Severe
Fibrosis		
Grade	0	None
	1	1a or 1b perisinusoidal zone 3 or 1c portal fibrosis
	2	Perisinusoidal and periportal fibrosis without bridging
	3	Bridging fibrosis
	4	Cirrhosis

Steatosis graded as in Table 2.

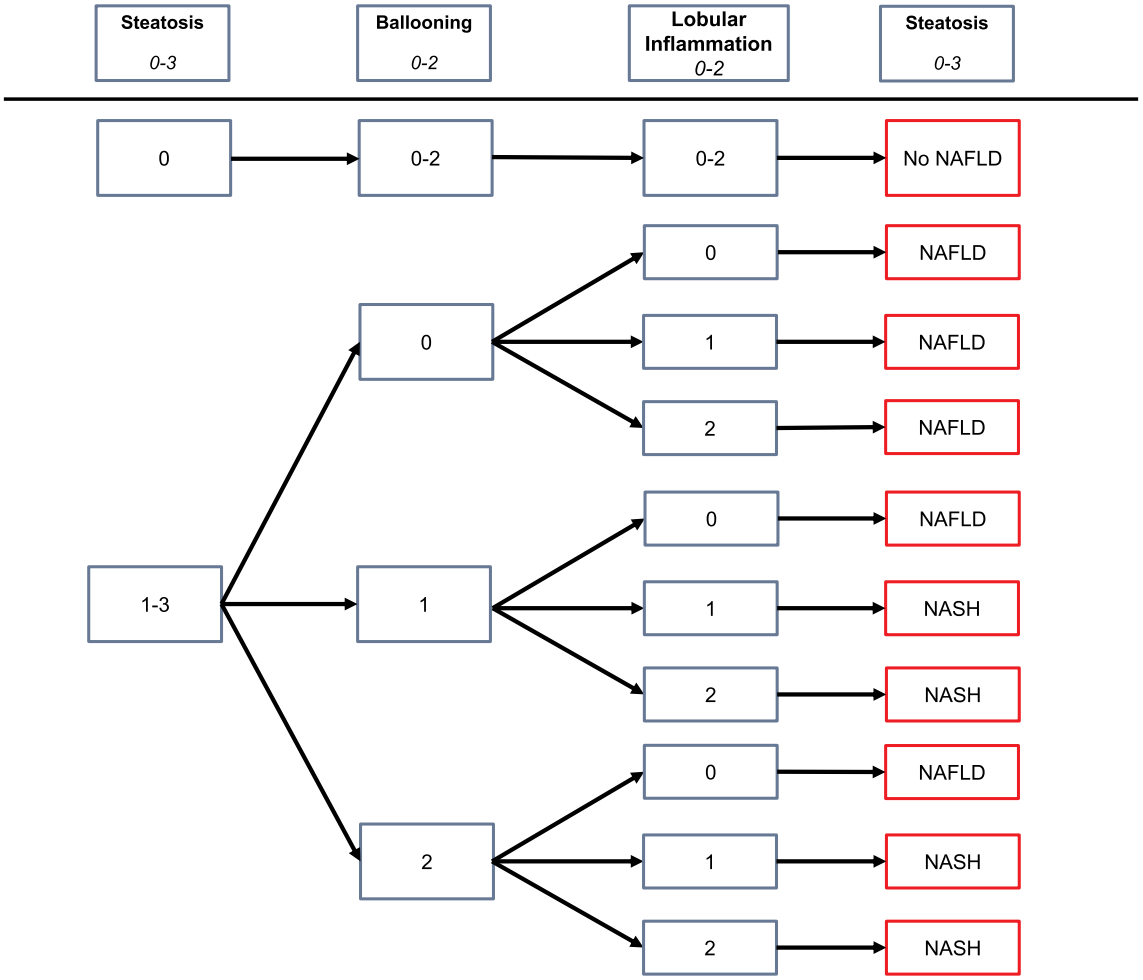

Fig. 3. Diagnostic algorithm for NAFLD and NASH.

has allowed the imaging modalities of MR Spectroscopy (MRS) and Chemical Shift MR (CS-MR) to be used to quantify hepatic fat. MRS is considered the gold standard for radiological assessment of IHF but is largely confined to the research arena. Comparatively, opposed phase CS-MR techniques are widely available, have a strong correlation to MRS when examining phantom controls [56] and have good agreement with MRS in vivo [57]. CS-MR, unlike histology, examines voxels of interest across liver segments, rather than a single sample, making this method less prone to sampling bias [58]. This technique has previously been used to assess the effect of hepatic steatosis on post-operative outcomes following liver resection [10].

We would suggest that CS-MR can be used reliably in clinical practice to assess IHF in patients at risk. Furthermore, patients routinely have pre-operative MR scans to measure tumour size and number so an additional CS-MR sequence adds little extra burden to the patient. This allows the identification of at risk patients to allow pre-operative optimisation.

5.1. Non-invasive assessment of NAFLD progression

While the quantification of IHF is useful, it should be considered a component of the assessment of NAFLD alongside markers of inflammation and fibrosis which may assist in the assessment of NAFLD progression along the continuum from steatosis to fibrosis.

A number of biomarkers have been assessed in isolation as predictive tools to differentiate NASH from steatosis without success, likely as a consequence of the complex aetiology of disease progression. Studies have used conventional serum markers of liver function, glycaemic control, demographics and anthropometrics [59]. Composite scoring systems, incorporating multiple biomarkers, have been employed to improve the predictive benefit [60,61]. Several novel biomarkers have been investigated, including Cytokeratin-18 a hepatocytes derived protein, which is elevated in NASH compared to simple steatosis with some predictive benefit [62]. Cytokeratine-18 has also been combined with other biomarkers with improved predictive accuracy [63,64]. These models, however, require further clinical validation before their use becomes commonplace. Imaging advances may also lead to improvements in the assessment of NAFLD progression. A combination of CS-MR and MR-Elastography has demonstrated excellent concordance with NAS in a mouse model with agreement in 80–92% of cases [65]. Such non-invasive assessment tools have not been assessed in the context of chemotherapy induced injury, a field which warrants further investigation.

6. Targeting patients for intervention

There are shared risk factors for NAFLD and CAS that would allow patients to be selected for screening for high IHF. The risk factors proposed to trigger consideration of intervention, taken from examination of the literature, are summarised in Table 4.

Anthropometrics can be easily acquired and provide a simple tool for assessment. Body mass index (BMI) is easily measured and associated with CAS and CASH [26,48]. In patients undergoing chemotherapy for CRLM a BMI > 30 kg/m^2 is associated with severe steatosis (> 30% hepatocytes, as classified by Pilgrim et al.) (OR = 3.14; CI 1.10–8.96; p = 0.05) and each additional kg/m^2 is

Table 4
Triggers for identifying elevated chemotherapy associated steatosis/steatohepatitis risk.

Risk Factor
Elevated BMI (> 27 kg/m^2)
Hepatic Function (Prolonged ICG-PDR > 15%/min)
Metabolic Syndrome (Adiponectin/HOMA-IR)
Neoadjuvant Irinotecan
Increased Susceptibility (reduced DPD expression)
Major Resection (> 3 Segments)

associated with a 4% increased risk in CAS [48]. Patients who develop CASH have a greater average BMI than patients who do not [26,47,48]. This increased risk appears to occur over 27 kg/m^2.

As over 40% of patients receiving treatment with Irinotecan develop CASH and CAS, we believe patients receiving chemotherapy regimens incorporating this agent should be screened [34,35,66]. With elevated IHF having greater implications in major resections, we suggest that patients undergoing more extensive resections are also screened. Although not discussed extensively here, ICG clearance has been shown to reduce after chemotherapy [41] and impaired function measured by ICG (plasma disappearance rate < 17%/min; retention at 15 min > 8%) is associated with increased risk of morbidity and post-operative liver failure [67,68]. Furthermore, peri-operative ICG changes do not match variation in traditional biochemical markers of liver function [68]. Whilst other methods of assessment exist, at present ICG represents a pragmatic tool for functional assessment and we suggest impaired function acts as a trigger to screening.

Other predictors have been demonstrated in the research setting, but are less readily available in clinical practice. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and fasting serum adiponectin predicts IHF in patients with CRLM [58] and metabolic syndrome is associated with an increased risk of CASH (OR = 5.88; CI 1.36–25.00; p = 0.02) [48]. mRNA analysis has shown that reduced dihydropyrimidine dehydrogenase (DPD) expression is associated with an increase in steatosis in those receiving chemotherapy but this remains an investigation for the future [69].

Screening of patients undergoing resection for these predictive factors is simple. Studies of these risk factors and how it might prompt non-invasive assessment of IHF by CS-MR to determine the necessity of pre-operative optimisation might be worthwhile.

7. Interventions to reduce intra-hepatic fat

Published evidence suggests that the 4–6 week window following cessation of chemotherapy is adequate time for a significant reduction in IHF to be achieved with dietary intervention [14,15,70,71]. A smaller volume of evidence suggests that IHF can be reduced over a longer timeframe with pharmacological intervention. This evidence is mostly limited to trials of dietary intervention in the setting of chronic disease of the liver such as NAFLD [11–16] (Table 5). In the pre-operative surgical setting, the effect of dietary intervention on quantity of IHF has primarily been studied in patients undergoing bariatric surgery [72,73]. The sole study to investigate the effect of pre-operative dietary intervention on liver resection did not quantify changes in IHF [74].

This non-randomised study investigated the effect of a pre-operative 900 kCal (30–40% carbohydrate, 20–40% fat) per day restriction diet for one week in 51 patients undergoing liver resection [74]. This group were compared to a historical control of 60 similar patients. Forty-two percent of patients received pre-operative chemotherapy within three months prior to resection and there was no significant difference in the frequency of major resection between groups. The study assessed histology of operative liver specimens and found that the intervention group was associated with a significantly lower amount of intra-operative blood loss, decreased IHF and reduced frequency of steatohepatitis. Although the lack of quantification of IHF pre- and post-dietary intervention and non-randomised nature of the study makes it difficult to draw conclusions from. However, the study demonstrated that dietary intervention is feasible in this patient group.

In patients undergoing bariatric surgery a four week diet can reduce IHF by 40%. These patients routinely undergo pre-operative calorie restriction to reduce liver volume and facilitate laparoscopic gastric bypass. A 800–1100 kCal restriction for four weeks pre-operatively has demonstrated a reduction of 40% in IHF and 12% in liver volume [72].

Dietary intervention trials in non-surgical cohorts demonstrate that significant reductions in IHF can be achieved in a short timeframe. Notably,10 days of carbohydrate restriction in 10 healthy volunteers with a median BMI of 28 (range 23–32) and median IHF of 9% showed a reduction of between 11% and 43% IHF [12]. In obese adults (BMI > 30) significant reductions in IHF can be achieved. A 55% reduction in IHF can be achieved with a 2 week carbohydrate restricted diet and 28% reduction on a calorie restricted diet [11]. Elsewhere, a low calorie and low carbohydrate diet as well as low calorie high carbohydrate diet significantly reduced levels of intrahepatic triglycerides after 48 h and showed that a 38% and 45% reduction in IHF was achievable after 11 weeks of dietary intervention respectively [75]. Independent of calorie restriction, dietary composition influences IHF. One randomised crossover study demonstrated a reduction in levels of IHF with a Mediterranean diet compared to a low fat high carbohydrate diet in patients with biopsy proven NAFLD, even when there is no associated weight loss (39% v 7%; p = 0.012) [14]. Very applicable to the pre-operative scenario, isocaloric carbohydrate restriction with a high protein component has been shown to reduce IHF by 48.3% within 2 weeks in obese patients with NAFLD [70].

Several studies have also demonstrated IHF reduction with pharmaceutical intervention. Liraglutide, a glucagon-like peptide-1 analogue, has resolved histological changes associated with NASH in a multicentre randomised, double blinded, controlled trial of 52 patients [76]. Other drugs conventionally used in insulin resistance have shown benefits as 21 T2DM patients over a 12 month period showed a significant reduction in IHF with daily pioglitazone (11.0 ± 3.1% to 6.5 ± 1.9%) and more so when used in combination with exenatide (12.1 ± 1.7 to 4.7 ± 1.3%) [77]. These changes were detected over 48 weeks and 12 months making the results less applicable within a shorter pre-operative window before resection of CRLM. Lastly, in a double blinded randomised crossover study of patients with polycystic ovarian syndrome, a daily dose of 4 g of omega-3 fatty acids for 8 weeks compared to placebo has demonstrated a reduction in IHF [78]. Mean IHF measured by MRS was 8.4 ± 0.9% in the treatment arm compared to 10.2 ± 1.1% after an olive oil based placebo. However, IHF was only measured after these interventions, which weakens this evidence. Taken together, current evidence suggests that dietary interventions may yield significant reductions in IHF within the window available pre-operatively whilst pharmacological intervention is untested in this shorter timeframe. As mentioned, the single study assessing pre-operative dietary intervention prior to resection of CRLM [74] suggests that such a tool may be tolerated in patients undergoing hepatic resections but no study has quantified IHF changes with dietary intervention in this patient group. The ideal intervention and timeframe are unknown.

8. Pre-operative modification of intra-hepatic fat and liver function

8.1. Improvements in hepatic function

Modification of IHF may reduce post-operative morbidity by improving liver function, decreasing systemic inflammation and insulin resistance. There is evidence from the metabolic literature that reductions in IHF directly affect liver function as weight loss improves insulin resistance [14]. After liver resection, synthetic liver function is a key

Table 5
Summary of dietary intervention studies and changes in IHF content measured by CS-MR or MRS.

Author	Study size	Baseline Characteristics	Intervention	Imaging Modality and method of HFF Quantification	Outcomes: Change in weight and hepatic fat fraction
Browning et al., 2011 [11]	18 (5 male, 13 female)	NAFLD BMI 35 ± 7 HFF: 20 ± 10%	Carbohydrate restriction (< 20 g/d) or low calorie (1200 kcal/d women, 1500 kcal/d men) For 2 weeks	MRS	Weight loss: Carb restriction: −4.0 ± 1.5 kg Low calorie: −4.6 ± 1.5 kg HFF change: Carb restriction: −55 ± 14% Low calorie: −28 ± 23%
Lim et al., 2011 [69]	11 (9 male, 2 female) +control (group of 8)	T2DM BMI 33.6 ± 1.2 HFF: Diabetic pts: 12.8 ± 2.4% Control: 8.5 ± 1.9%	8 weeks on a 600 kcal/day diet	CS-MR Three point Dixon method	Weight loss: 13.1 kg HFF change: −9.1%
Kirk et al., 2009 [64]	22	Obese BMI 36.5 ± 0.8 HFF: a. 11.2 ± 2.9% b. 12.4 ± 2.9%	a High carbohydrate (> 180 g/d) b Low carbohydrate (< 60 g/d) energy deficient diet 11 weeks	MRS	Weight loss: a −7.3 ± 0.6% b −7.6 ± 0.5% HFF: no figures given, graphical estimates: a −45% b −38%
Ramon-Krauel et al., 2013 [70]	17 16 completed study	Obese children age 8-17 HFF: a 23.8 ± 12.2% b 29.3 ± 14.1%	(a) Low glycaemic-load versus (b) low-fat diet 6 months	MRS	HFF change: a −8.8 ± 4.1% b −10.5 ± 3.7%
Hollingsworth et al., 2006 [12]	10 (3 male, 7 female)	Healthy BMI 28 (range 23–32) Mean HFF: 9%	Low carbohydrate (< 20 g per day for 10 days) No other food restriction	CS-MR	Weight change: 1.7 kg at day 3 3.0 kg at day 10 HFF change: 11–43% reduction at day 10
Westerbacka et al., 2005 [13]	10 female	BMI: 33 ± 4 HFF: 10 ± 7%	2 weeks of isocaloric periods of either: a 16% of total energy as fat b 56% of total energy as fat	MRS	Body weight unchanged. HFF change: a −20 ± 9% b +35 ± 21%
Bozzetto et al., 2012 [71]	45 (37 male, 8 female(	BMI Group: a 30 ± 2 b 28 ± 3 c 31 ± 3 d 30 ± 4 HFF: a 17.7 ± 9.7 b 7.4 ± 2.8 c 8.8 ± 4.9 d 11.6 ± 8.0	Isoenergetic diet 8 week diet. a High-carbohydrate/high-fibre/ low–glycaemic index diet(CHO/fibre group) b High-MUFA diet (MUFA group) c High-carbohydrate/high-fibre/ low–glycaemic index diet plus physical activity program (CHO/fibre + Ex group) d High-MUFA diet plus physical activity program (MUFA + Ex group).	MRS	Weight change: Stable across all 4 groups HFF change: a −9.6% (non-sig) b +1.1% (non sig) c −29% (p = 0.01) d −21.5% (p = 0.02)
Ryan 2013 [14]	12 in a cross-over design	BMI 32 ± 4.2	6 weeks, wash out, then cross over and 6 weeks a Mediterranean diet b Low fat high carb	MRS	a 39 ± 4% reduction b 7 ± 3% reduction
Rietman et al., 2013 [72]	27 individuals	'Lean'	2 week cross over trial a (n = 10) balanced diet- (28 energy% fat; 17 energy% Protein; 55 energy% CHO) for 4 weeks b (n = 17) hypercaloric high-fat diet (HD-group; + 2 MJ per day, 40 energy% fat) in a 2-week cross-over design, with a high protein content (High Protein; 26 energy% protein) or a normal protein content (NP; 15 energy % from Protein) and vice versa.	MRS	HFF changes: 0.13% difference between HFF between groups (p = 0.06) Group (b)- trend for lower HFF on High Protein compared with Normal Protein (0.2% p = 0.08)
Utzschneider et al., 2013 [15]	35	BMI 26.9 ± 0.8	4 week RCT a (n = 20) low-fat/low-saturated fat/low GI (23% fat/7% sat fat/GI < 55) b (n = 15) High fat/high sat fat/high GI (43% fat, 24% sat fat, GI > 70)	MRS	a 0.44 reduction in HFF b 0.001 increase in HFF
Marina et al., 2014 [16]	13	BMI 33.6 ± 1.3 NAFLD	6 week cross over trial a Control (35% fat/12% sat fat) b Low fat (20% fat/8% sat fat) c High fat (55% fat/25% sat fat)	MRS	b . 13.9 ± 10.2% relative reduction. Absolute reduction −2.13% (significant) c . absolute reduction −1.25% (not significant)
Volynets et al., 2013 [73]	10	BMI 31.1 (25.6–40.6) NAFLD	6 months a 50% reduction in fructose – through counselling advice	MRS	a . HFF change −36 ± 24% (significant) Many confounders such as total calories ingested
	21		12 months	MRS	

(*continued on next page*)

Table 5 (*continued*)

Author	Study size	Baseline Characteristics	Intervention	Imaging Modality and method of HFF Quantification	Outcomes: Change in weight and hepatic fat fraction
Sathyanarayana et al., 2011 [67]		T2DM, Metformin and diet control	a (n = 10) 45 mg/day pioglitazone b (n = 11) 45 mg/day pioglitazone and exenatide (10 μg/day SC)		a HFF change 11.0 ± 3.1% to 6.5 ± 1.9% b HFF change 12.1 ± 1.7 to 4.7 ± 1.3%
Lewis et al., 2006 [74]	18	Bariatric surgery recipients	6 week very low calorie diet meal replacement sachets supplemented with low calorie foods (450-800kCal/day)	MR-S	Mean 72.5% IHF reduction in patients with steatosis
Cussons et al., 2009 [68]	25	PCOS, women, BMI 34.8	8 weeks, double blind randomised crossover a Placebo b 4 g/d omega-3 fatty acids	MRS	a HFF 10.2 (1.1) b HFF 8.4 (0.9)% (p = 0.002)
Bjermo et al., 2012 [75]	60	BMI a 30.2 ± 3.7 b 31.3 ± 3.9	10 week RCT a (n = 28) PUFA b (n = 29) SFA	MRI and MRS	a −0.5 (−2.3-0.2) % MRI; −0.9 (1.7–0.0) % MRS b 0.7 (−0.2- 2.1) % MRI; 0.3% (−0.6 to 1.8) % MRS
Jin et al., 2014 [65]	24	Overweight Hispanic adolescents a HFF 14.5 (± 1.79)%; BMI 2.25 (± 0.19) b HFF 14.0 (± 1.77)%; BMI 2.15 (± 0.09)	4 week RCT, double blinded, beverage intervention a 3 Fructose drinks/day b 3 glucose drinks/day	MRS	a 14.5% to 13.6 (1.83)% p = 0.314 b 14.0% to 13.8 (1.92)% p = 0.814
Mardinoglu et al., 2018 [59]	10	Obesity & NAFLD (Mean IHF 16.0% ± 2.3%)	14 day isocaloric low carbohydrate high protein diet (< 30 g carbohydrate, mean 3115 kCal/day)	MR-S	Mean 43.7% reduction in IHFF
Markova et al., 2017 [60]	44	NAFLD & T2DM	6 week high protein diet, no calorie restriction (30% protein, 40% carbohydrate, 30% fat) a Animal protein (n = 19) b Plant protein (n = 19)	MR-S	a 48.0% mean IHF reduction b 35.7% mean IHF reduction

BMI body mass index; CHO carbohydrate; CS-MR chemical shift magnetic resonance; HFF hepatic fat fraction; GI glycaemic index; MJ mega Joule; MRS magnetic resonance spectroscopy; MUFA mono-unsaturated fatty acids; MRI magnetic resonance imaging; NAFLD non-alcoholic fatty liver disease; PCOS polycystic ovary syndrome; PUFA polyunsaturated fatty acids; RCT randomised control trial; SFA saturated fatty acids; T2DM type 2 diabetes mellitus.

determinant of post-operative outcomes and it is therefore of interest if reductions in IHF can lead to improvements with the potential to reduce intra-operative blood loss and post-operative liver failure [74].

In light of the above, future studies assessing pre-operative interventions should measure hepatic function. Traditional serum markers of liver function are unlikely to be of benefit, but there are other modalities that do exist to assess hepatic enzyme function. As mentioned, ICG has been used previously to detect functional changes with CAS/CASH and to assess improvement following cessation of chemotherapy [41,79]. The LiMAX test which measures the breakdown of ^{13}C-methacin has also been used to assess changes in function related to chemotherapy [41,80,81]. ICG PDR and LiMAX are both simple, safe and can conveniently be performed in the clinic or at the bedside. Limitations of ICG clearance testing, including dependence on adequate hepatic perfusion, decreased accuracy in hyper-bilirubinaemia and greater ability to detect mild chemotherapy induced injuries, mean LiMAX is often regarded as a superior method of assessment but as yet its use is not widespread [41,80].

Contrast Enhanced Magnetic Resonance (CE-MR) using gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid (Gd-EOB-DTPA) represents another method which can assess regional and global liver function as uptake is greatly affected by liver function [82,83]. This method has previously been used on one and three Tesla scanners and has been shown to be useful in differentiating NASH from HS in rats [84]. At present we are not aware of this method being used for longitudinal perioperative assessment in humans, and therefore, presents another method which could be incorporated into clinical practice. To help answer these questions, future studies looking to assess the impact of prehabilitation in patients undergoing liver surgery should use quantification of liver fat as well as novel markers of liver function as outcomes.

8.2. Improvements in systemic health

Interventions to reduce IHF are likely to have a beneficial effect on other obesity related risk factors for post-operative morbidity. Improvements in insulin sensitivity, reduction in blood pressure and resting heart rate are among the many established improvements in cardiovascular risk that occur following dietary intervention and weight loss [14,77,78,85]. Patients undergoing liver resection with metabolic syndrome are at increased risk of surgical site infection, post-operative myocardial infarction, re-intubation and longer ventilation requirements and overall major cardiorespiratory complication [49–51]. Therefore, interventions to reduce IHF in the pre-operative setting have systemic as well as liver specific effects that may reduce morbidity. The presence of metabolic syndrome in this patient cohort is a confounding variable which cannot be separated from IHF as a risk factor alone.

8.3. Oncological outcomes

The majority of the literature does not suggest a long term effect on survival from excess IHF at the time of surgery [86,87]. One study has associated higher levels of IHF in resection specimens with increase rates of local recurrence following resection of CRLM [88]. However, an important confounding factor is the use of neoadjuvant chemotherapy in patients with more advanced disease and the consequent increase in IHF [89].

Interestingly, metformin has been associated with improved response rates from pre-operative chemotherapy in diabetics taking the drug in breast and rectal cancer [90] and a survival advantage has been noted in other malignancies [91–94]. Results are awaited of work conducted to formally assess if this is as a result of indirect or direct

action [95]. Metabolic alterations may also impact tumour biology as many tumour cells are obligate glucose metabolisers and creating a low glucose environment has potential benefits to cancer outcomes in mouse models and initial studies in man [96–99]. Such interventions may serve as an adjunct to neoadjuvant chemotherapy therapy in CRLM.

9. Conclusion

Elevated IHF is an independent risk factor for post-operative morbidity following hepatic resection of CRLM. Elevated IHF may be associated with obesity, metabolic syndrome, T2DM and insulin resistance or induced or exacerbated by neoadjuvant chemotherapy in this patient group. Dietary interventions can reduce IHF in the timeframe available pre-operatively, however, this has only been examined in NAFLD. Such interventions have not been assessed adequately in the context of malignancy and chemotherapy. Advances in non-invasive methods of quantifying IHF have the potential to facilitate longitudinal studies of such interventions. The natural progression of CAS and CASH after the cessation of neoadjuvant chemotherapy should also be evaluated.

10. Declarations of interest

None.

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Appendix A. Supplementary data

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