Clearing steatosis prior to liver surgery for colorectal metastasis: A narrative review and case illustration

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Simple summary
Surgery remains the mainstay of liver tumour management, providing a curative approach to many primary and secondary liver cancers. Non-alcoholic fatty liver disease is becoming a pandemic anomaly in the western world, and is increasingly considered to be a risk factor for resective liver surgery. Here we aim to: [1] highlight the impact of hepatic steatosis on liver surgery for colorectal liver metastases; [2] review the most common on liver pre-habilitation prior liver surgery; [3] report the favourable effect of caloric restriction during a two-stage liver resection for colorectal liver metastases.

Abstract
Over the recent years, non-alcoholic fatty liver disease (NAFLD) has become the most common liver disorder in the developed world, accounting for 20% to 46% of liver abnormalities. Steatosis is the hallmark of NAFLD and is recognized as an important risk factor for complication and death after general surgery, and even more so after liver resection. Similarly, liver steatosis also impacts the safety of live liver donation and transplantation. We aim to review surgical outcomes after liver resection for colorectal-metastases in patients with steatosis, and discuss the most common pre-operative strategies to reduce steatosis. Finally, as illustration, we report the favourable effect of a low-caloric, hyper-protein diet during a two-stage liver resection for colorectal metastases in a patient with severe steatosis.

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Introduction

In the recent years, non-alcoholic fatty liver disease (NAFLD) has become one of the most common forms of liver disease in the Western world, accounting for 20 to 46% of liver abnormalities [1]. Additionally, NAFLD cases will likely continue to increase over the next 20 years, despite already affecting about a quarter of the world's population. It is often associated with metabolic disorders, such as type 2 diabetes, hypertension, obesity, and cardiovascular disease [2]. By being connected with these conditions, NAFLD, defined as the presence of >5% steatosis in the liver, can be identified as an hepatic expression of metabolic syndrome (MetS). In fact, approximately 90% of the patients with NAFLD have more than one feature of metabolic syndrome, and 33% have three or more criteria [3, 4].

Nowadays, neoadjuvant or adjuvant treatments are routinely administered to patients undergoing surgery for colorectal cancer, including 5-fluoruracil, irinotecan, and oxaliplatin. Chemotherapy-associated steatosis (CAS) is therefore increasingly frequent, potentially limiting surgical strategies [5, 6]. Although surgical techniques and patient care have improved in the recent years, hepatic steatosis is still recognized as an important risk factor for short and long-term complications and death after general surgery, and even more so after liver resection [7]. Similarly, steatosis also impacts the safety of living liver donation and transplantation [8]. Furthermore, it has been established that both metabolic syndrome and NAFLD stimulate the development of primary liver cancers [9, 10] and also influence the metastatic potential of CRC [11].

Steatosis is reversible and has been the target of prehabilitation prior to surgery. Indeed, prior to bariatric surgery, a hypo-caloric, hyper-protein diet has become standard practice to clear steatosis and promote liver shrinkage [12]. Living liver donors can also be managed preoperatively with a calorie-controlled diet, exercise, or drugs to improve hepatic parenchymal quality [13].

The aim of this narrative review is to highlight the growing relationship between NAFLD and colorectal cancer. In particular, it assesses the literature on surgical outcomes after liver resection for colorectal metastases in patients with steatosis. It also aims to provide an overview of the most common pre-operative rehabilitation treatments targeting steatosis. Finally, as illustration, we report on the favourable effects of a low-caloric, hyper-protein diet during a two-stage liver resection for colorectal metastases in a patient with severe steatosis.

Metabolic syndrome and non-alcoholic fatty liver disease

Metabolic syndrome describes a cluster of modifiable metabolic abnormalities that are associated with a globally increased risk of developing atherosclerotic cardiovascular disease, type 2 diabetes mellitus [14], neurological complications, and cancer [15, 16]. The definition of metabolic syndrome has undergone considerable changes, but the most recent consensus by the International Diabetes Federation in 2006 [17] defines metabolic syndrome by the presence of an increased waistline measuring > 94 cm for men and >80 cm for women along with the presence of two or more of the following: (1) blood triglycerides >150 mg/dl, (2) high-density lipoprotein (HDL) cholesterol <40 mg/dL in men or <50 mg/dL in women, (3) hypertension (>130/85 mmHg), and (4) elevated fasting glycaemia (>100 mg/dL (5.6 mmol/L) or diagnosed diabetes.

Metabolic syndrome epidemic represents a major challenge in the Western world, and it is estimated that 12–26% of the global population suffers from this condition [18]. NAFLD is considered as the hepatic manifestation of the metabolic syndrome and it encompasses steatosis and progresses to liver fibrosis and finally to cirrhosis and end-stage liver disease [19]. The prevalence of NAFLD parallels the one of the metabolic syndrome, and the rate of NAFLD is forecasted to double by 2030 [20].

Currently, the correct diagnosis of NAFLD is based on: (1) evidence of intra-hepatic fat accumulation (documented by imaging or histology), (2) the absence of significant alcohol consumption, (3) the absence of concomitant causes of hepatic steatosis, and (4) the absence of co-existing causes of chronic liver disease [21]. Obesity is recognised as a risk factor for both steatosis and the development of colorectal liver metastases (CRLM). Given this, as well as the use of hepatotoxic chemotherapy regimens, steatosis can be found in up to 40% of postoperative surgical specimens derived from patients that have undergone liver resection for CRLM [22]. The histologic features of NAFLD and its developments include

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steatosis, ballooning, hepatocyte degeneration, inflammation, apoptotic bodies, and Mallory-Denk bodies [23]. The level of steatosis severity varies considerably according to lifestyle, diet, duration and type of chemotherapy.

Steatosis can occur in two forms known as macrovesicular and microvesicular steatosis, which have distinct cytoarchitectural phenotypes. Macrovesicular steatosis displays a single large lipid droplet inside the hepatocyte with the nucleus displaced, whereas microvesicular steatosis is characterized by small lipid droplets with the hepatocyte nucleus located centrally. By definition, NAFLD steatosis is predominantly macrovesicular with large droplets storing triglycerides [24], although microvesicular steatosis may also be present. HS is routinely classified in three tiers as mild [5 to 33%], moderate [33 to 66%], or severe [>66%] [23, 25]. With mild steatosis, fat droplets appear to mainly have a zone 3 pericentral pattern, while more severe steatosis presents a panacinar distribution [26, 27]. Steatosis is centered round the central vein, and periportal areas are classically preserved.

Influence of metabolic disease and NAFLD on colorectal cancer

Elements of metabolic syndrome are significant risk factors for the development of colorectal cancer (obesity (BMI>30) [OR:1.54] [28], diabetes [OR:1.831] [29]). In addition, recent epidemiological studies highlight an relationship between NAFLD and the development of colon adenomatous polyps and poor survival of patients with colorectal cancer [30].

Lee *et al.* investigated the colorectal neoplasm incidence in NAFLD patients through a population-based cohort study. In their analysis, after multivariate adjustment, NAFLD patients (n=8,120,674) showed a significantly higher rate of colon cancer (HR:1.16). The data suggests that more active surveillance is needed for NAFLD patients compared to the non-NAFLD population [31]. According to Wu *et al.,* NAFLD is also related to poor survival in patients with colorectal cancer [32]. They demonstrated that NAFLD patients with such cancer have a worse prognosis compared to controls, regardless of BMI or prognostic markers.

Interestingly, NAFLD patients also show a higher rate of colorectal liver metastasis (CRLM). Several clinical studies investigated the role of NAFLD as a potential driver of CRLM [Table 1]. Indeed, in parallel to the intrinsic mechanisms of metastasis (cellular dissemination from the primary tumour and awakening of dormant tumour cells), there is also bidirectional communication between tumour cells and the hepatic microenvironment [33]. Bauer *et al.* attempted to dissect how the liver microenvironment fatty changes impact hepatic metastasis using a choline-deficient high-fat diet with 0.1% methionine (CDAHFD) in mice. They showed that a moderate fatty liver has a protective effect against tumour growth, while more severe liver steatosis could stimulate tumour growth. In more detail, the authors suggested that CRLM proliferation is influenced by hepatic chronic inflammation (driven by increased levels of CD8+, INF-γ, and TGF-β) and hepatic extracellular matrix remodelling [34].

Of interest, in 2019, Seki *et al.* investigated the role of the hepatic inflammasome (specifically, NOD-like receptor 4 (NLRC4) and IL-1) in colorectal cancer metastasis progression in a high-fat-diet mouse model. They reported that NLRC4 promotes tumour-associated macrophages polarization towards the M2 type, increases IL-1 and VEGF production, and promotes colorectal cancer metastasis proliferation in the fatty liver [35]. Moreover, higher triglyceride levels, serum cholesterol, and saturated fatty acids contribute to a pro-metastatic microenvironment via oxidative stress induced by reactive oxygen species (ROS) (including superoxide, hydroxyl radicals, and H_2O_2) [36, 37]. In summary, steatosis should be considered as an important risk factor for the development and progression of both primary and metastatic colorectal cancer.

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Table 1 - Summary of the studies evaluating the impact of HS on liver surgery complications and outcomes

Author	Year	Type of study	Population enrolled	Main findings	[Ref.]
Berhns et al.	1998	Retrospective	135 patients who had undergone major hepatic resection (≥4 segments)	HS has been associated to longer surgeries, higher rate of blood transfusion, post-operative bilirubine and AST levels.	[49]
Pathak et al.	2010	Retrospective	102 patients undergoing hepatectomy for CRLM	HS does not influences influence post operative long-term survival	[50]
Kooby et al.	2003	Retrospective matched case control	325 patients who had undergone hepatectomy for HCC, biliary cancer or CRLM	HS has been associated to higher rate of wound, hepatobiliary and gastro-intestinal complications. HS does not influence 5 YS survival.	[51]
Fagenson et al.	2020	Retrospective propensity-score matched analysis	2,927 patients undergoing major hepatectomy (≥3 segments)	HS has been associated with significantly higher rate of biliary and pulmonary complications. HS has been conferred an increased risk of postoperative mortality.	[52]
Nishio et al.	2015	Retrospective	518 HCC patients who underwent hepatic resection.	Absence of HS had a significant impact on disease-free survival in non-b non-c HCC patients.	[53]
Gomez et al.	2007	Retrospective	386 patients undergoing hepatic resection for CRLM	HS was associated with increased morbidity following hepatic resection.	[54]
Parkin et al.	2013	Retrospective	1,793 patients who underwent first-time liver resection with background HF	HS was associated with improved 5 YS survival compared with normal background liver	[55]
Ramos et al.	2015	Retrospective	935 patients undergoing hepatic resecgive surgery for CRLM	HS does not predict short-outcome after resection of CRLM and appears to be a favorable prognostic factor for survival	[56]
Sultana et al.	2018	Prospective analysis	949 patients has undergone liver resection for CRLM	When associated to other elements, HS is a factor increasing the risk of post hepatectomy liver failure	[57]
Bhayani et al.	2012	Retrospective analysis of prospectively collected data	3,973 patients who underwent a liver resection	MetS was associated with a greater risk of perioperative complications and with a 2-fold increased risk of death after hepatic resection.	[58]
Reddy et al	2012	Retrospective case control study	174 patients undergoing liver resective surery for CRLM	HS (>33%) does not increases overall and hepatic-related morbidity after liver resection	[59]
Cauchy et al.	2013	Retrospective	560 patients undergoing liver resection for HCC	Abnormal liver had increased rates of major surgeical complications and mortality	[60]
Zarzavdjian Le Bian et al.	2012	Retrospective	151 patients undergoing right hepatectomy and affected by two or more metabolic disorders	MetS toghether with perioperative bleeding (≥1,000 mL), middle hepatic vein resection and primary hepatic malignancy are associated with poor prognosis	[61]
Molla et al.	2017	Retrospective	60 patients who underwent an R0 hepatectomy for crc-lm.	HS has an important potential negative effect on hepatic disease-free survival.	[62]
Belghiti et al.	2000	Retrospective analysis	747 consecutive patients underwent hepatic resection (37 patients with HS)	HS was an independent risk factor for postoperative complications	[63]
Koh et al.	2019	Retrospective analysis	996 patients who underwent liver resection for HCC	NAFLD-related HCC is associated with greater surgical morbidity and post-hepatectomy liver failure. Despite this, long-term survival outcomes are favorable compared with non-NAFLD etiologies.	[64]

Chemotherapy-associated steatosis (CAS)

In current clinical practice, chemotherapy is often offered to patients suffering from colorectal cancer. Many involved hepato-toxic agents induce steatosis, steatohepatitis, and sinusoidal injury [40], and can impair liver function and regeneration [38, 39]. IHF is the first sign derived from the hepatotoxicity of chemotherapeutic regimes.

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Three different pathways have been confirmed for explaining the presence of steatosis: excessive import of free fatty acids (FFAs), diminished hepatic excretion of FFAs, and impaired FFAs oxidation [41]. All of these mechanisms can be exacerbated by colorectal cancer-directed chemotherapy agents. Irinotecan, 5-fluorouracil (5-FU), and leucovirin are currently considered as the most common agents for colorectal cancer treatment [42]. Irinotecan is strongly associated with liver steatosis by affecting mitochondrial membranes and increasing toxic ROS species intermediates [43].

In 2017, Sommer *et al*. developed *in vitro* and *in vivo* models for 5-FU-induced steatohepatitis with the aim of identifying the underlying mechanisms for the induction of steatosis and its progression to inflammation. They reported that mitochondrial dysfunction is one of the major causes of steatosis and is driven by an increased expression of fatty acid acyl-CoA oxidase 1 (ACOX1), which catalyses the initial step for peroxisomal β-oxidation [44]. Furthermore, 5-FU combined with leucovirin leads to steatosis [45], which significantly increases if irinotecan is added [46].

Chemotherapy duration impacts the manifestation of steatosis, and it is routinely considered that 6 cycles of chemotherapy are sufficient for its emergence [47]. To date, the benefits of chemotherapy clearly outweigh the risk of hepatotoxicity. Nevertheless, a comprehensive awareness of downstream complications is fundamental to the global management of these patients.

Impact of hepatic steatosis in liver surgery

Besides jeopardizing patients' oncological outcomes for primary and metastatic colorectal cancer, there are growing data confirming the major role of hepatic steatosis on surgical outcomes. Additionally, for liver surgery, steatosis is a serious precondition in terms of perioperative outcomes [48] and has been comprehensively explored, as illustrated in Table 1 [49-64]. Berhns et al. [49] reported as early as 1997 that patients with steatosis (n=135) had longer surgery times, higher rates of blood transfusion, and higher post-operative bilirubin and AST levels. At the same time, larger studies established that HS is associated with higher rates of wound, hepatobiliary, and gastro-intestinal complications in cases of hepatic resection for colorectal cancer metastasis [50, 52].

Later, Kooby et al. [51] published results of a retrospective matched analysis comparing surgical outcomes of patients with mild (n=122), moderate (n=60), and severe HF (n=12). All steatosis forms were associated with higher rates of hepatobiliary complications (such as cholangitis and ascites of hepatic abscess). In 2018, Sultana et al. recognized that when associated with other metabolic syndrome components, steatosis increases the risk of liver failure after hepatectomy [57]. More recently, Fagenson et al. reported similar findings [52]. Their retrospective propensity-score-matched analysis investigated 2,927 patients with steatosis and normal livers undergoing major hepatectomy (≥3 segments). The data not only confirmed steatosis as a risk factor for biliary complications, but also highlighted its role on pulmonary complications.

Thus, to address the risk of morbidity and mortality in patients with steatosis, de Meijer et al. conducted a meta-analysis grouping 1000 patients from six different observational studies [65]. Compared to normal liver parenchyma, steatosis < 30% led to a significantly increased risk of postoperative complication with RR of 1.53 (1.27-1.85). Starting from 30% steatosis, the RR increased to 2.01 (1.66-2.44). Additionally, HS ≥ 30% was associated with higher mortality with RR of 2.79 (1.19-6.51).

In light of the above, steatosis of all forms of severity is an important factor in patient outcomes after surgery. Over the last 20 years, tremendous medical and technological progress has enabled increasingly aggressive liver surgery. However, these strategies remain strongly linked to the quality of the remaining liver parenchyma, which may lead to surgical planning to deviate from the standard guidelines. Indeed, steatosis accompanied by impaired lipid metabolism hinders liver regeneration ability [66, 67]. This can be explained in part by the detrimental effects of steatosis on liver microcirculation and resistance to ischemic damage after significant parenchymal resection.

Clearing steatosis prior liver surgery

Based on the studies mentioned, metabolic syndrome and steatosis negatively impact the short- and long-term outcomes after liver resection. Because the number of patients with steatosis is likely to increase in

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the coming years, it is of paramount importance to define measures to improve outcomes. While published evidence suggests that a 4 to 6-week interval is enough to clear part of the chemotherapy-induced liver toxicity [68], several studies have aimed to demonstrate the utility of other types of intervention to reduce steatosis content [69-71].

Steatosis is also considered one of the major causes of donor exclusion in living-donor liver transplantation programs [72]. Thus, several protocols have been proposed to reverse steatosis to enlarge the pool of liver living donors [73]. To reverse steatosis and thus make 16 patients eligible for donation, Choudhray et al. suggested a 1200-kcal/day and at least 60 min/day of moderate cardio training for at least 18 days [74]. This diet led to significant weight lost (7 ± 4.3 kg) in 15/16 patients, while 14/16 underwent living donation according to a second biopsy confirming hepatic steatosis reversal. Moreover, a complete normalization of liver parenchyma was observed in 7/16 candidates.

The decrease in steatosis following a preoperative diet has gained attention for being able to reduce bleeding during liver surgery. In a landmark retrospective study, Reeves et al. (2013) reported that a one-week hypocaloric diet (900 kcal/day; 20-40% fat and 30-50% carbohydrate) reduced steatosis compared to control patients (15.7% versus 25.5%, p-value=0.05). However, they reported no significant differences in mortality, overall complication rates, infectious complication rates, and mean hospital stay. Following these findings, the same group explored the impact of a low-fat diet on intraoperative blood loss and outcomes after liver resection in a bi-institutional, surgeon-blinded, randomized prospective trial [75]. 60 patients (BMI ≥25 kg/m^2) were randomly assigned to an 800-kcal/day diet (20 g fat, 70 g protein) or normo-caloric diet one week prior liver surgery. In the diet group, intraoperative blood loss was reduced (452 versus 863 mL; p-value >0.005), and the liver was judged as more easy to manipulate. Interestingly, no difference was detected in the level of steatosis, although there was significant reduction in glycogen content in the liver parenchyma (PAS stain score 1.61 versus 2.46; p-value <0.0001).

Besides life-style interventions, a plethora of pharmaceutical molecules have been tested to decrease steatosis, including liraglutide [76], pioglitazone [77], and ω-3 fatty acids [78]. One of the main drawbacks of drug-based management of steatosis is the longer window to obtain significantly results. Depending on the molecule used, this period ranges from 4 months to 1 year. Therefore, it is difficult to apply them in a short pre-operative timeframe. Combined, these data identify lifestyle interventions and dietary modification as important tools for decreasing steatosis in the available window of preoperative time.

Illustrative case

Herein we report the favorable effect of a low-caloric, hyper-protein diet during a two-stage liver resection for colorectal metastases in a patient with severe steatosis

A 59-year-old male (American Society of Anaesthesia score 2; Weight 94 kg; Body Mass Index 32.5 kg/m^2; casual drinker) was diagnosed with a sigmoid colon adenocarcinoma at 18 cm from the anal verge, accompanied by multiple synchronous and bilobar liver metastases. Thanks to an excellent response to neo-adjuvant chemotherapy including 12 cycles of folinic acid/5-fluoruracil, oxaliplatin, and irinotecan (FolfoxIri), followed by a steady line of 5-fluoruracil, a liver-first strategy with a two-stage liver resection was planned. Considering criteria for steatosis on MRI (Figure 1a), a transjugular biopsy was performed and demonstrated severe macrovacuolar steatosis (up to 80%), and a hepatic venous pressure gradient of 6 mmHg. The first resection, a left parenchymal-sparing procedure, removed 5 metastases, all R0 also with severe (90%) parenchymal macrovacuolar steatosis (Figure 1b). A right portal vein embolization was then completed (future remnant liver: 670 ml). Because of the severe steatosis, a hypocaloric (850 Kcal), hyper-protein diet (120 g of protein, 60 g of carbohydrates, and 8 g of fat) (Scitec Nutrition®) was given during 3 weeks prior to the second liver resection. The patient lost 7 kg (-7.44%; BMI 29.8 kg/m^2), and a new MRI demonstrated a sharp decrease in the fat liver content (Figure 1c). A R0 right liver lobectomy was then performed. On histology, macrovacuolar steatosis had decreased to mild steatosis (30%) (Figure 1d). The patient recovered without complication, and ultimately underwent a laparoscopic sigma resection three months later. During follow-up, a recurrence of colorectal liver metastases was found and a new line of

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chemotherapy was then introduced (trifluridine and tipiracil) leading to stable disease. The patient remains alive 24 months after the sigma procedure.

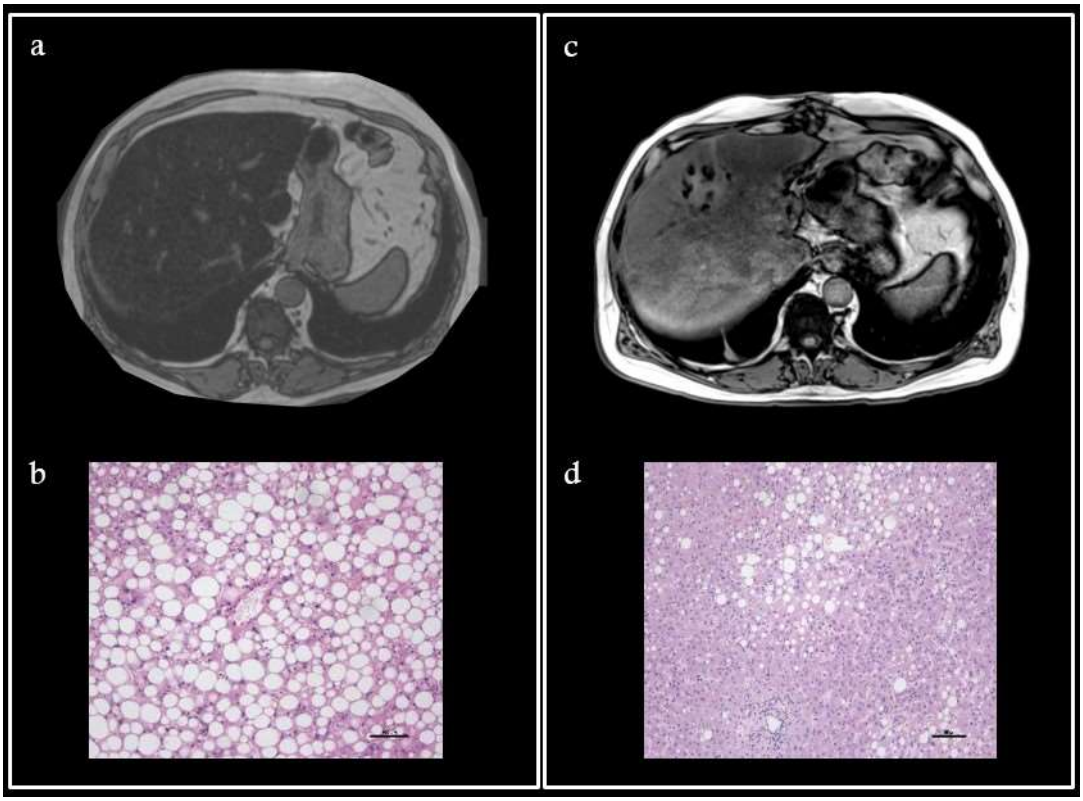

Figure 1 - Preoperative MRI (T1-weighted) showed important steatosis (a). Liver biopsy confirmed 90% macrovacuolar steatosis (b - H&E). New MRI (T1-weighted) performed 3-week after hypocaloric hyper-protein diet demonstrated a decrease in the fat liver content (c) with vacuolar steatosis decreased to 30% on histology (d - H&E).

Conclusion

Pre-operative liver optimization through nutritional therapy is increasingly important due to the epidemic of NAFLD and chemotherapy-induced liver injury. Severe steatosis represents one of the most significant risk factor for complications after major surgery. Ischemic/reperfusion injury and post-operative complications occur more often in livers with steatosis [4]. Prior to bariatric surgery, a hypo-caloric, hyper-protein diet has become standard practice to clear steatosis and promote liver shrinkage. Live liver donors can also be managed preoperatively with a calorie-controlled diet, exercise, and/or drugs to improve hepatic parenchymal quality [3]. We herein document the benefits of a low-calorie diet in a two-stage liver resection process. Furthermore, a study including two-stage liver resection combined with chemotherapy shows that chemotherapy produces steatosis but that it does not disappear much more than 3 weeks after stopping treatment [5]. Overall the available literature together with the present observation, support that the described 3-week hypocaloric hyper-protein diet can be used safely and efficiently in patients at risk of steatosis or with documented steatosis, and especially before surgery. It could be indirectly linked to a decreased surgical risk profile.

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