Systematic review

Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases

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Background: **Preoperative systemic chemotherapy is increasingly used in patients who undergo hepatic resection for colorectal liver metastases (CLM). Although chemotherapy-related hepatic injury has been reported, the incidence and the effect of such injury on patient outcome remain ill defined.**

Methods: **A systematic review of relevant studies published before May 2006 was performed. Studies that reported on liver injury associated with preoperative chemotherapy for CLM were identified and data on chemotherapy-specific liver injury and patient outcome following hepatic resection were synthesized and tabulated.**

Results: **Hepatic steatosis, a mild manifestation of non-alcoholic fatty liver disease (NAFLD), may occur after treatment with 5-fluorouracil and is associated with increased postoperative morbidity. Non-alcoholic steatohepatitis, a serious complication of NAFLD that includes inflammation and hepatocyte damage, can occur after treatment with irinotecan, especially in obese patients. Irinotecan-associated steatohepatitis can affect hepatic reserve and increase morbidity and mortality after hepatectomy. Hepatic sinusoidal obstruction syndrome can occur in patients treated with oxaliplatin, but does not appear to be associated with an increased risk of perioperative death.**

Conclusion: **Preoperative chemotherapy for CLM induces regimen-specific hepatic changes that can affect patient outcome. Both response rate and toxicity should be considered when selecting preoperative chemotherapy in patients with CLM.**

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Introduction

Surgical resection remains the standard treatment for patients with resectable colorectal liver metastases (CLM) and is the only single-modality therapy associated with cure. Five-year survival rates after resection of CLM have been reported to be as high as 58 per cent[1–4], especially when hepatic resection is combined with chemotherapy. However, only 15–20 per cent of patients with CLM are candidates for surgical resection at the time of diagnosis[5–8].

Many patients with CLM require a multimodal approach. Unfortunately, the response rates achieved with the combination of 5-fluorouracil (5-FU) and leucovorin have changed little over the past 40 years and remain at only about 20 per cent[9]. More recently, however, with the introduction of new regimens that combine fluoropyrimidines with irinotecan or oxaliplatin, the efficacy of chemotherapy as a first-line treatment for CLM has improved dramatically. Combined with 5-FU, irinotecan, a topoisomerase I inhibitor, and oxaliplatin, a platinum derivative with activity against colorectal cancer, have yielded response rates of 54–56 per cent with a median survival of 22 months in patients with stage IV colorectal cancer[10–13]. In addition to these novel cytotoxic agents, new molecular targeted therapies have been developed. Both bevacizumab, a monoclonal antibody to vascular endothelial growth factor, and cetuximab, an anti-epidermal growth factor receptor, have produced

response rates approaching 70 per cent when combined with cytotoxic agents[14,15].

Use of these newer, more effective, regimens has enabled downsizing of CLM, leading to resection in up to 10–13 per cent of the patients who initially presented with irresectable disease[16–19]. In addition, effective treatment for CLM has expanded the use of chemotherapy in initially resectable patients. The rationale for using preoperative chemotherapy in patients with initially resectable disease includes an opportunity to demonstrate regimen-specific efficacy, as well as allowing time to identify those patients who will develop progressive disease and who therefore may not benefit from liver resection. In addition, preoperative chemotherapy may decrease the magnitude of resection needed and also be associated with a lower rate of positive margins compared with immediate resection[20].

Although the use of newer chemotherapeutic agents has a number of theoretical benefits, the effect of these agents on the underlying liver parenchyma remains ill defined. Concern about hepatic resection leaving a damaged liver remnant has led investigators to examine chemotherapy-related hepatic injuries[21]. Specifically, one type of hepatic injury, sinusoidal obstruction syndrome (SOS; previously termed veno-occlusive disease) has been reported to be associated with liver failure and death following intensive systemic chemotherapy and bone marrow transplantation[22–24]. More recently, other reports have suggested an increase in the incidence of several less well understood chemotherapy-associated liver injuries including hepatic steatosis, steatohepatitis and sinusoidal injury[3,20,21,25]. However, the effect of these histopathological changes on outcome after hepatic resection is only beginning to be recognized and investigated.

In this article, data are synthesized from a systematic review of the existing literature to clarify which drugs are implicated in liver injury following preoperative chemotherapy for CLM. In addition, the impact of drug-specific liver injuries on outcome after hepatic resection is assessed. These data provide the framework for discussion of treatment strategies in stage IV colorectal cancer, and provide a foundation for future studies that will contribute to development of the best multimodal care plan for patients with CLM.

Literature search strategy

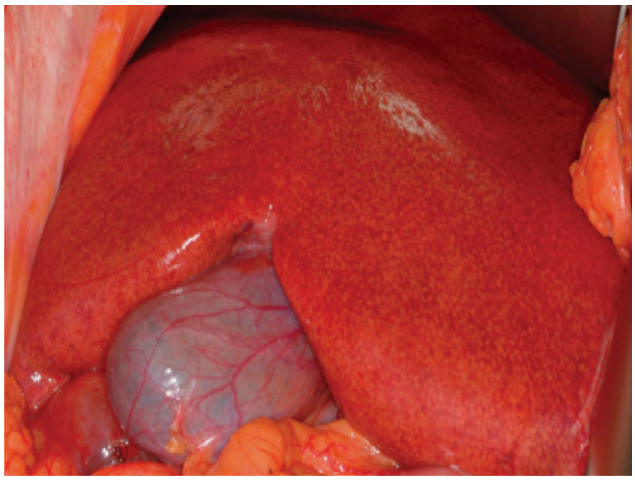
Original published studies were identified by searching the MEDLINE database (January 1966 to May 2006). Articles were selected using keywords 'liver injury', 'hepatic resection', 'chemotherapy', '5-fluorouracil', 'oxaliplatin', and 'irinotecan' to identify all reports that may pertain to liver injury following preoperative chemotherapy for CLM. Manual cross-referencing was performed and relevant references from selected papers were reviewed.

Chemotherapy-associated non-alcoholic fatty liver disease

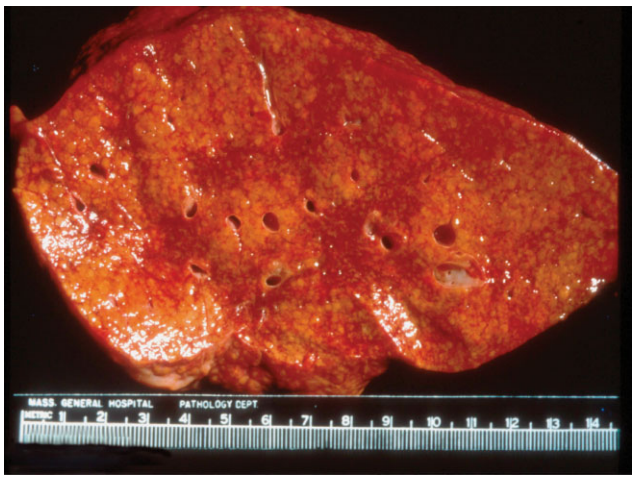
The spectrum of liver changes associated with fat accumulation in hepatocytes is termed non-alcoholic fatty liver disease (NAFLD)[26] (*Fig. 1a,b*). NAFLD is increasingly recognized as the hepatic manifestation of insulin resistance and is part of the systemic complex known as metabolic syndrome[27,28]. Based on the Third National Health and Nutritional Examination Survey, the prevalence of NAFLD in North America and similar regions ranges from 3 to 23 per cent[29,30], and it parallels the 'epidemiology' of obesity[31,32]. The clinical course of NAFLD is indolent in most patients but, in some, a progressive form of NAFLD can lead to fibrosis and cirrhosis in the latter stage of disease[33–36].

Macrovesicular steatosis, which denotes the accumulation of fat in the hepatocytes, represents the mildest manifestation of NAFLD (*Fig. 1c*). In contrast, steatohepatitis is a more serious form of NAFLD characterized by fatty infiltration and inflammation in the liver (*Fig. 1d*). The distinctive features of steatohepatitis include steatosis, monomorphic and neutrophilic portal and lobular inflammation, and perisinusoidal fibrosis in lobular zone 3. Other common morphological features are hepatocellular ballooning, poorly formed Mallory's hyaline, and glycogenated nuclei (*Fig. 1d*). The histopathological spectrum of liver injury associated with non-alcoholic steatohepatitis (NASH) was first described in 1980 by Ludwig and colleagues[37]. Now recognized as a progressive form of NAFLD, NASH can progress to cirrhosis and an increased risk of hepatocellular carcinoma[31,38,39]. Whether severe steatosis can progress to cirrhosis when inflammation is absent is not known.

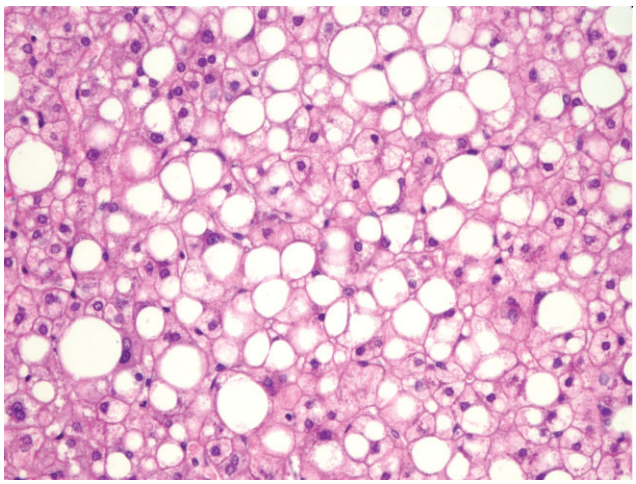
Although abnormal liver function tests and radiographic findings may be suggestive of NAFLD, histological evaluation remains the only way to assess hepatocyte damage accurately and to distinguish NASH from 'simple' steatosis, or steatosis with inflammation[40] (*Fig. 1c,d*). The grading and staging of NAFLD is evolving; the first system was developed by Brunt *et al.*[41] and more recently modified by the Pathology Committee of the National Institute of Health NASH Clinical Research Network[42]. Recently, Kleiner and co-workers[43] proposed a new NAFLD activity score (NAS) based on regression analyses of 14 hepatic histological features. The NAS includes three features (steatosis grade, lobular inflammation and ballooning of hepatocytes) evaluated semiquantitatively. Each of the



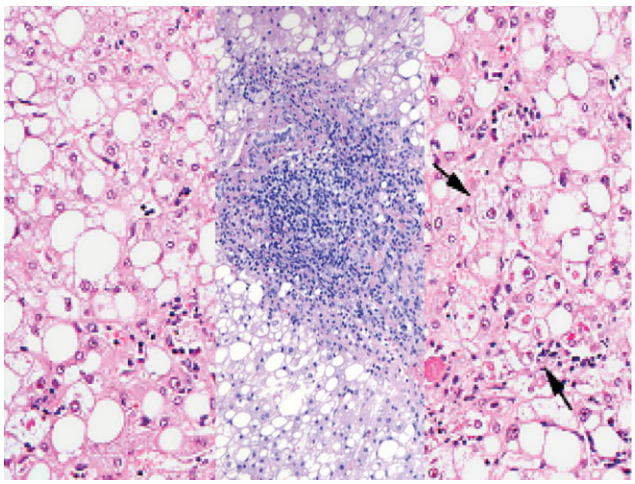
a Intraoperative view of whole fatty liver



b Cut fatty liver



c Simple steatosis



d Steatohepatitis

Fig. 1 Spectrum of non-alcoholic fatty liver disease (NAFLD). **a, b** Macroscopic aspect of fatty ('yellow') liver. The steatotic liver is enlarged, soft and appears yellow in colour because of fatty infiltration. **c** Simple steatosis, the mildest manifestation of NAFLD, denotes the accumulation of large globules of fat in the hepatocytes (macrovesicular steatosis) (haematoxylin and eosin; magnification ×400). **d** Histopathological spectrum of non-alcoholic steatohepatitis. Various degrees of inflammation can be seen scattered throughout the lobule as well as in portal tracts. Hepatocyte damage is demonstrated by scattered ballooned (arrows) and apoptotic cells (haematoxylin and eosin; magnification ×200 for the night and left fields, ×125 for the centre)

three features of the NAS, or 'Kleiner score', independently correlated with a diagnosis of NASH. The NAS was also able to provide a clinically useful scoring of NASH (NAS 5 or more), borderline NASH (NAS 3 and 4) or 'not NASH' (NAS 1 and 2).

Chemotherapy-associated steatosis

Drugs implicated

A number of case reports and studies suggest that chemotherapy for CLM can be associated with steatosis. Zeiss and colleagues[44] reported histologically documented patchy fatty change in a patient with CLM treated with floxuridine via a hepatic artery infusion pump. In this patient drug administration was not equal in all parts of the liver parenchyma, and steatosis occurred in the parts that were overperfused. Peppercorn *et al.*[45] found that 47 per cent of patients with CLM treated with systemic 5-FU and folinic acid had computed tomography (CT) findings consistent with fatty change. No correlation was

observed between liver function test results, chemotherapy dose and the development of steatosis. Reversible steatosis was also reported in 30 per cent of patients with metastatic colorectal cancer treated with a combination of interferon α and 5-FU[46]. One report described CT and biopsy evidence of steatosis in 40 per cent of patients who received adjuvant therapy with 5-FU and levamisole after undergoing surgical resection for stage II or III colonic cancer[47]. Notably, none of these initial studies reported data on the correlation between chemotherapy-induced hepatic steatosis and outcome following hepatic resection in terms of morbidity or mortality.

Impact on outcome following hepatic resection

Based on data from the transplantation literature, it is postulated empirically that each 1 per cent increase in fat content, either microvesicular or macrovesicular, decreases the functional mass of the donor liver by 1 per cent[48]. However, whether steatosis following chemotherapy produces a similar decrease in functional hepatic mass and a subsequent adverse outcome following hepatic resection is unknown. A few studies have explored the association between chemotherapy and steatosis, and have attempted to assess the impact of steatosis on patient outcome following resection (*Tables 1* and *2*). Unfortunately, most

Table 1 Outcome after hepatic surgery correlated with chemotherapy regimen and hepatic injury

		5-FU		IRI		OX						
Reference	Total no. of patients	No. of patients	Postop. complications	No. of patients	Postop. complications	No. of patients	Postop. complications	Simple steatosis	NASH	SOS	BMI correlates with hepatic injury	Chemotherapy dose/duration correlates with hepatic injury
49	135	—	—	—	—	—	—	Yes†	—	—	Yes	—
50	478	—	—	—	—	—	—	Yes†	—	—	—	—
20	108	27	10 (37)	34	10 (29)	0	0	Yes‡	—	—	—	—
51	485	—	—	—	—	—	—	Yes†	—	—	Yes	—
25	153	27	—	17	—	43	—	Yes§	—	Yes¶	—	No
52	37	10	—	10	—	4	—	—	Yes†#	—	Yes	No
53	67	8	3 (38)	37*	14 (38)*	37*	14 (38)*	Yes†	—	Yes†	—	Yes**
21	406	63	17 (27)	94	17 (18)	79	21 (27)	Yes§	Yes††	Yes¶	Yes‡‡	No§§

Values in parentheses are percentages. Hepatic injury includes more than 30 per cent steatosis, steatohepatitis or sinusoidal dilatation. 5-FU, 5-fluorouracil; IRI, irinotecan; OX, oxaliplatin; simple steatosis, mildest form of non-alcoholic liver disease; NASH, non-alcoholic steatohepatitis; SOS, sinusoidal obstruction syndrome; BMI, body mass index. *Thirty-seven patients had IRI or OX therapy, of whom 14 developed postoperative complications. †No stratification of hepatic injury based on specific chemotherapy regimen. ‡Steatosis correlates with IRI regimen. §Steatosis does not correlate with any regimen. ¶Sinusoidal dilatation correlates with OX regimen. #Steatohepatitis, graded according to a NASH score, correlates with IRI–OX regimen. **Number of chemotherapy cycles correlates with postoperative complications. ††Steatohepatitis correlates with IRI regimen. ‡‡BMI correlates with IRI-associated hepatic injury. §§Duration of OX or IRI therapy does not correlate with increased hepatic injury.

Table 2 Outcome after hepatic surgery correlated with chemotherapy regimen and hepatic injury

		Postoperative outcome								
		Chemotherapy related				Hepatic injury related				
Reference	No. of patients who had preop. chemotherapy	Complications	Liver failure	Death	No. of patients with hepatic injury	Complications	Liver failure	Death	Hepatic injury	Chemotherapy regimen
49	—	—	—	—	7	– (29)	– (14)	– (14)	Steatosis†	—
50	—	—	—	—	37	8 (22)	—	0 (0)	Steatosis†	—
20	61	20 (33)	2 (3)	0	12	—	1 (8)	0 (0)	Steatosis	5-FU, IRI
51	249	—	—	—	102	27 (26)	3 (3)	6 (6)	Steatosis†	—
25	87	—	—	—	44	—	—	—	Steatosis, SOS	5-FU IRI, OX
52	24*	1 (4)	1 (4)	1 (4)	—	1 (4)	1 (4)	1 (4)	NASH†	5-FU, IRI, OX
53	45	17 (38)	5 (11)	0 (0)	52	—	—	0 (0)	Steatosis, SOS†	5-FU, IRI, OX
21	248	55 (22)	—	—	92	—	3 (3)	6 (7)	Steatosis, NASH, SOS	5-FU, IRI, OX

Values in parentheses are percentages. Hepatic injury includes more than 30 per cent steatosis, steatohepatitis or sinusoidal dilatation. 5-FU, 5-fluorouracil; IRI, irinotecan; OX, oxaliplatin; steatosis, mildest form of non-alcoholic liver disease; NASH, non-alcoholic steatohepatitis; SOS, sinusoidal obstruction syndrome. *Results reported in general for 14 patients treated with either IRI or OX regimen, but no breakdown according to agent. †No stratification of hepatic injury based on specific chemotherapy regimen.

of these studies failed to stratify data by chemotherapy regimen and so were unable to assess whether histopathological liver changes were chemotherapy specific[49–53]. Despite these limitations, a few consistent, important findings can be derived from careful analysis of these reports.

In 1998, Behrns and co-workers[49] reported the first study designed to examine patient outcomes following major hepatectomy in the setting of hepatic steatosis. One hundred and thirty-five patients who underwent major hepatic resection (at least four hepatic segments) for CLM were studied, including 56 with mild (less than 30 per cent) steatosis and seven with marked (moderate to severe) steatosis. The patients with marked steatosis had an increased body mass index (BMI), a longer operating time, a greater likelihood of transfusion, an increased risk of complications and liver failure, as well as a higher postoperative mortality rate (*Table 2*). It was concluded that marked steatosis is associated with increased perioperative morbidity and mortality after major hepatectomy. However, the small number of patients in the study with marked steatosis limits interpretation of these findings.

Belghiti *et al.*[50] subsequently reported on 37 patients with marked steatosis (more than 30 per cent) who underwent hepatic resection. They noted that, although there was an increase in morbidity after hepatic resection (22 per cent *versus* 8 per cent in the control group), there was no difference in postoperative mortality rates based on presence or absence of steatosis (*Table 2*). Furthermore, the increase in morbidity was largely due to an increase in infectious complications.

More recently, a study from Parikh and colleagues[20] showed that preoperative treatment with irinotecan in patients with CLM was associated with steatosis. In this study, mild steatosis (less than 25 per cent) occurred in 15 of 34 patients who received irinotecan. In addition, four patients who received irinotecan were noted to have moderate (25–50 per cent) or severe (more than 50 per cent) steatosis, and one of these developed hepatic insufficiency. The authors confirmed that there were no perioperative deaths in patients with simple steatosis, even when severe (*Table 2*).

Kooby and co-workers[51] examined 325 patients with steatosis, 102 of whom had marked steatosis (more than 30 per cent), who underwent hepatic resection for treatment of a neoplasm. Like Behrns *et al.*[49], they observed a correlation between marked steatosis and high BMI. An association between steatosis and previous exposure to cytotoxic chemotherapy was also noted[51]. The incidence of complications in general, and more specifically infectious complications, correlated with the degree of steatosis. Complication rates were significantly higher in the group with marked steatosis than in the control group (overall complication rate 62 per cent in those with marked steatosis *versus* 35 per cent in controls; infective complication rate 43 *versus* 14 per cent respectively; $P < 0{\cdot}01$). Again, marked steatosis was not significantly associated with an increased mortality rate. The authors concluded that steatosis should not preclude major hepatic resection but that caution should be exercised in patients with marked disease.

Vauthey *et al.*[21] recently reported a systematic analysis of the association between chemotherapy type, histopathological liver injury and postoperative outcome. In this study, each of the 406 resected liver specimens from patients who underwent resection for CLM underwent a full pathological review. Liver injury was classified according to established standards using the NAS[43]. Importantly, in this study steatohepatitis was differentiated from steatosis as a separate pathological entity for the purposes of outcome analyses. The authors noted that no specific chemotherapy regimen was associated with steatosis when steatohepatitis was excluded (*Table 1*). Similar to previously published data, there was no increase in mortality after hepatic resection in patients with steatosis. However, unlike steatosis, the pathological finding of steatohepatitis had important implications for outcome from resection (see below).

Chemotherapy-associated non-alcoholic steatohepatitis

Several mechanisms have been identified that can lead to the progression of steatosis to NASH[54]. Among them, oxidative stress and the production of reactive oxygen species due to mitochondrial dysfunction appear to play central roles[55]. Recently, Laurent *et al.*[56,57] showed that several chemotherapy drugs (for example 5-FU, platinum derivatives and taxanes) induce oxidative stress in both cancer cells and normal cells exposed to chemotherapy. This chemotherapy-induced oxidative stress in the presence of steatosis can lead to NASH. This is consistent with the proposed 'two-hit theory' of NASH pathogenesis[54], in which the first hit is steatosis and the second hit is production of reactive oxygen species.

Drugs implicated

Two recent studies[21,52] have demonstrated an increased incidence of NASH in patients treated with preoperative chemotherapy for CLM. Fernandez *et al.*[52] were the first to report an increased incidence of NASH in patients treated with hepatic resection after preoperative chemotherapy for CLM. The NASH score, according to the Brunt system[41],

was noted to be significantly higher in patients who had received mainly irinotecan (only four patients received oxaliplatin) than in those who had been treated with 5-FU or who had no chemotherapy. The total dose and the duration of administration of chemotherapy did not affect the risk of NASH in this small cohort, but high BMI was significantly correlated with a high NASH score (*Table 1*). The authors concluded that obese individuals were more likely than lean individuals to develop steatohepatitis following treatment with modern chemotherapeutic agents. Moreover, they proposed that chemotherapy-associated NASH could affect hepatic reserve and may have implications with regard to the percentage of liver volume that can be safely resected. In the multicentre study by Vauthey *et al.*[21], the association between chemotherapy type, liver injury and the impact of liver injury on outcome following hepatic resection for CLM was examined. On final pathological analysis, 23 per cent of the patients had liver injuries, and 8 per cent of patients had steatohepatitis as defined by the NAS[43]. No chemotherapy regimen was associated with steatosis when steatohepatitis was considered as a separate entity. Only irinotecan was associated with steatohepatitis ($P < 0{\cdot}001$) (*Table 1*). Furthermore, irinotecan was associated with an increased risk of steatohepatitis independent of BMI, although the risk was higher in patients with a BMI greater than 25 kg/m^2. Given these findings, the authors recommended caution when irinotecan is being considered for patients with a BMI over 25 kg/m^2, especially in individuals who are potential candidates for major hepatic resection.

Impact on outcome after hepatic resection

Fernandez *et al.*[52] reported on an index patient who developed severe steatohepatitis following oxaliplatin chemotherapy. This patient subsequently developed liver failure and died 88 days after hepatic resection (*Table 2*). Vauthey *et al.*[21] similarly reported an increased 90-day postoperative mortality rate in a larger cohort of patients with steatohepatitis. Specifically, patients with steatohepatitis had a 90-day mortality rate of 15 per cent compared with 2 per cent for patients who did not have steatohepatitis (odds ratio (OR) 10·5, $P = 0{\cdot}001$). In particular, patients with steatohepatitis had a higher risk of death from postoperative liver failure compared with all other patients (6 *versus* 1 per cent; OR 7·7, $P = 0{\cdot}01$) (*Table 2*). These findings suggest that steatohepatitis may result in failure of the remnant liver to regenerate following major hepatectomy, which can lead to progressive liver failure. Given these data, caution is advised when using irinotecan-based therapies in patients with known steatosis or steatohepatitis, and in patients at known risk for steatosis (for example with a high BMI, diabetes mellitus, predisposing metabolic syndrome).

Chemotherapy-associated hepatic sinusoidal obstruction syndrome

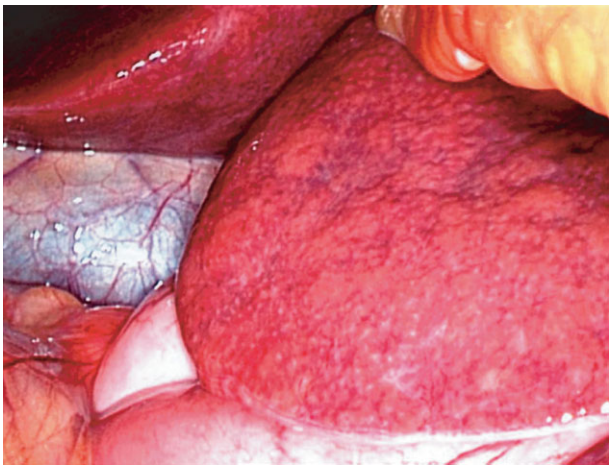
SOS (veno-occlusive disease) was initially described in 1920 following a lethal intoxication by pyrrolizidine alkaloids (present in some plants)[58]. For many years after that initial report, SOS was observed only rarely. However, with the introduction of bone marrow transplantation and treatments involving combinations of several cytotoxic drugs, the syndrome has become more prevalent[22–24]. SOS following chemotherapy in a clinical context other than bone marrow transplantation is rare[59,60]. The use of oxaliplatin, however, has recently been implicated in the development of hepatic SOS (*Fig. 2*).

The pathophysiology of SOS involves the depolymerization of F-actin in sinusoidal endothelial cells, the activation of metalloproteases[61], and the consequent induction of oxidative stress[62]. As noted previously, several chemotherapeutic agents (5-FU, platinum derivatives and taxanes) can induce oxidative stress[56,57].

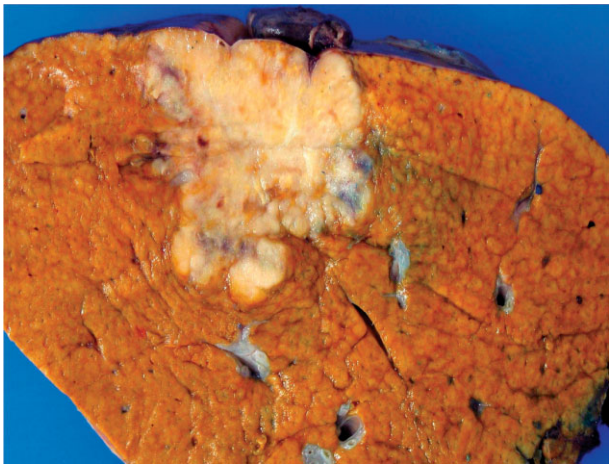
Oxaliplatin-associated sinusoidal obstruction syndrome

Rubbia-Brandt *et al.*[25] were the first to report oxaliplatin-associated SOS in the non-tumorous liver specimens of patients undergoing hepatic resection following treatment with oxaliplatin (*Table 1*). Perisinusoidal injuries, including dilatation and congestion with fibrosis and venous occlusion, were present in 78 per cent of patients treated with oxaliplatin. There was no correlation between the cumulative dose of oxaliplatin and the presence or severity of the sinusoidal injury (*Table 1*). Whether oxaliplatin is solely responsible for sinusoidal injuries or whether such injuries are linked to the combination of oxaliplatin with other chemotherapeutic agents (such as 5-FU) has not been fully investigated. Rubbia-Brandt and colleagues[25] did not address the clinical impact of sinusoidal injuries on outcome from hepatic resection.

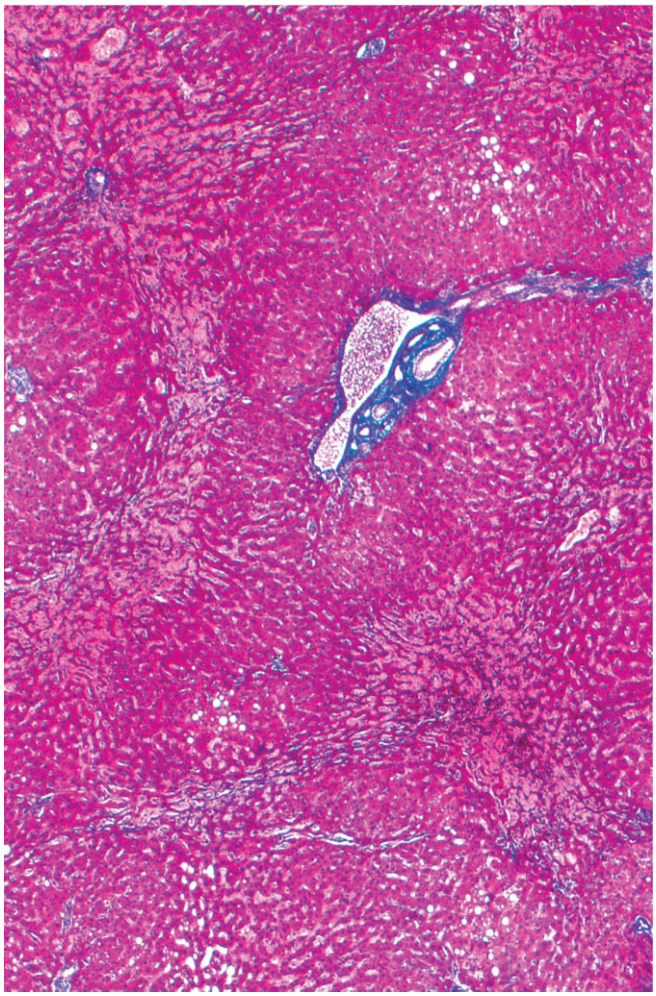
Karoui *et al.*[53] recently reported that systemic chemotherapy was significantly associated with microvascular changes, such as sinusoidal dilatation and hepatocyte necrosis, but it was not associated with fatty degeneration. Liver injury was not stratified by chemotherapy regimen type (although two-thirds of patients received oxaliplatin), and all patients had undergone total vascular exclusion, so meaningful conclusions regarding regimen-specific liver injuries



a Whole liver with SOS



b Cut liver with SOS



c Sinusoidal dilatation

Fig. 2 Spectrum of oxaliplatin-associated sinusoidal obstruction syndrome (SOS). **a, b** Macroscopic aspect of liver with oxaliplatin-associated injury ('blue' liver). The distended sinusoids lead to entrapment of erythrocytes that in turn makes the liver blue in colour (**b** courtesy of Dr 1. Brown, Brisbane, Queensland, Australia). **c** Microscopic demonstration of centrilobular sinusoidal dilatation with only scattered macrovesicular steatosis (trichrome; magnification x100)

cannot be made. These authors did, however, demonstrate that preoperative chemotherapy was associated with increased postoperative morbidity (38 per cent in the chemotherapy group *versus* 14 per cent in the control group). The increased morbidity was mainly due to a higher incidence of postoperative liver failure in the chemotherapy group (11 per cent *versus* 0 per cent) (*Table 2*). Furthermore, an increased risk of surgical complications as the number of chemotherapy cycles increased was reported (*Table 1*). Perioperative mortality, however, was not associated with the number of chemotherapy cycles.

The recent series from Vauthey *et al.*[21] helped to clarify that sinusoidal injury was more common with oxaliplatin than with other chemotherapeutic regimens. Oxaliplatin therapy was associated with sinusoidal dilatation nearly five times more often than therapy with irinotecan (19 *versus* 4 per cent). The risk of SOS did not seem to increase with increasing duration of chemotherapy, but most patients in the study had received relatively short-course therapy (3–4 months of preoperative chemotherapy). Importantly, the same study[21] confirmed the findings of others[63] that short-course oxaliplatin therapy was not associated with increased morbidity or mortality following hepatic resection. Specifically, no deaths occurred among the 22 patients with moderate to severe sinusoidal injury.

Floxuridine-associated liver injury

In 1985, Kemeny and co-workers[64] first described hepatic artery infusion chemotherapy as adjuvant treatment after resection of CLM. This requires implantation of an intra-arterial catheter via a port or pump, which allows the infusion of high-dose cytotoxic agents directly into the liver via the hepatic artery. Floxuridine has an extraction rate of 94–99 per cent in the liver during the first pass, making it a particularly good candidate for use in this context. Although hepatic artery infusion was designed to optimize delivery of chemotherapy to the liver directly, few studies have reported benefits[65–67]. Despite the suggestion of good locoregional response rates, a systematic review of seven randomized trials of such therapy including 592 patients failed to find a significant improvement in long-term survival with this approach[68].

The hepatotoxicity of floxuridine is reported to be dependent on both the dose and duration of treatment[69]. Damage to the intrahepatic and extrahepatic bile ducts has also been reported in up to 25 per cent of patients[69]. The classical bile duct sclerosis associated with hepatic artery infusion principally involves the extrahepatic biliary tract and often spares the distal common bile duct. Bile duct sclerosis is probably a result of ischaemia secondary to small vessel arteritis[70]. Another recent study reported biliary sclerosis in six of 17 patients (35 per cent) who received such treatment; two of the affected patients died from sepsis and liver failure[71]. Overall, reported rates of biliary injury after hepatic artery infusion chemotherapy range from 20 to 35 per cent[65,71–74].

Hepatic parenchymal changes may include mild to moderate triaditis, portal fibrosis with bridging, ductular proliferation, cholestasis and central vein fibrosis[75]. In a study of 168 patients, Link *et al.*[72] showed that sclerosing cholangitis or liver cirrhosis developed in 38–41 per cent of those who had received floxuridine by hepatic artery infusion; in contrast, no patient developed sclerosing cholangitis or cirrhosis after treatment with 5-FU. Of particular note, sclerosing cholangitis prevented potential hepatic resection in the floxuridine group. These changes can be responsible for an increased risk of bleeding during surgery as the parenchyma tends to be more congested and friable[76,77]. In one series, hepatic artery infusion chemotherapy before hepatic resection was associated with increased postoperative morbidity (57 per cent in the treated group *versus* 18 per cent in the no-chemotherapy group)[76].

Support for use of hepatic artery infusion chemotherapy before surgery is lacking. The reported rate of resectability after such chemotherapy is less than 1 per cent[78] compared with 10–13 per cent following oxaliplatin-based chronomodulated systemic chemotherapy[16]. The evolution of systemic chemotherapy, with its increased response rate and decreased risk of hepatotoxicity compared with hepatic artery infusion, has reduced the theoretical advantages of the latter. Furthermore, because stage IV colorectal cancer is considered a systemic, not locoregional, disease, the advantages of systemic chemotherapy that complements liver resection outweigh the potential benefit of intra-arterial therapy that is directed at the liver alone.

Implications for clinical practice

New chemotherapy treatments are associated with improved overall survival in patients with stage IV colorectal cancer[79]. A proportion of patients with irresectable CLM may undergo downsizing of liver disease after systemic chemotherapy to enable potentially curative resection[16]. In addition, some patients with resectable CLM may benefit from chemotherapy. The rationale for treating resectable tumours with systemic therapy includes assessment of the efficacy of the chosen regimen in the individual patient (evaluation of tumour response), observation of tumour biological behaviour in order to spare non-responders non-therapeutic surgery, and potential downsizing of the tumour(s) to increase the chance of complete resection and/or to spare normal hepatic parenchyma.

The association between chemotherapy and steatosis is not clear. Some studies suggest that patients who receive chemotherapy develop steatosis[45,49–51], whereas others show no correlation between any chemotherapy regimen and severe steatosis, when stratified for steatosis and steatohepatitis[21]. Whether other variables, such as weight gain during chemotherapy, steroids administered to manage nausea during chemotherapy, or other factors, modulate risk for steatosis remains to be clarified. Analysis of existing data shows that major resection in patients with severe steatosis is more difficult, with an increased risk primarily of bleeding and infectious complications. There is no definite increase in postoperative mortality in patients with simple steatosis, perhaps because liver regeneration is not sufficiently impaired to interfere with liver functional recovery.

Steatohepatitis appears to be a much more dangerous entity. Steatohepatitis can progress to fibrosis, cirrhosis and liver failure[34–36], and appears to impair the functional reserve and regenerative capacity of the liver significantly. Data suggest that irinotecan chemotherapy is associated with the development of steatohepatitis in some patients[21,52]. The recent finding that resection in patients with steatohepatitis is associated with significant

mortality may affect decision making regarding selection of chemotherapy in resectable or potentially resectable situations. To date, information concerning the potential impact of bevacizumab and cetuximab on the development of liver injury is limited, but hepatic resection after treatment with these agents requires further study.

Finally, it is evident that liver injuries are not mutually exclusive. Patients with steatosis can develop steatohepatitis, SOS and other injuries. Assessment of the underlying liver is critical in selection of the type of surgical resection. An extensive resection (up to 80 per cent of the functional parenchyma) can be tolerated with virtually no risk of death when the underlying liver is normal[80]. In contrast, even a minor hepatectomy can be dangerous in patients with a severely compromised liver. Where steatosis, steatohepatitis and SOS fall on the continuum of liver disease is not clearly defined. There is no prospective study to validate a systematic approach to patients with chemotherapy-induced hepatic injury. Percutaneous biopsy may be helpful in some patients to assess the underlying liver before planning treatment. Liver injuries, however, can be characterized by a patchy distribution in the liver, and sampling error may not permit accurate estimation of the overall severity of liver disease. In patients with suspicion of hepatic injury or at high risk for hepatic injury, laparoscopy combining direct inspection and core biopsy of the liver may be a useful method for evaluation of chemotherapy-induced hepatic injury.

Portal vein embolization may provide an important functional test of liver reserve in patients with marginal remnants. Patients with liver remnants that are inadequate based on systematic liver volumetry are candidates for such embolization[18,80–83]. In addition to absolute liver volume, hypertrophy of the future liver remnant (FLR) in response to embolization predicts outcome from hepatectomy[84]. Portal vein embolization may provide information about functional hepatic reserve to help determine whether major resection will be safe. If adequate hypertrophy occurs, hepatectomy may be safe. Continuing chemotherapy while embolization is performed does not impair hepatic hypertrophy in response to portal vein embolization[85]. The minimum FLR that must remain after resection in patients with various types of chemotherapy-related liver injury remains unknown. However, after analysis of currently available data on the safe limits of liver resection based on liver remnant volume, a general consensus has been reached[86]. Portal vein embolization is indicated when the FLR volume is 20 per cent or less of the total liver volume (TLV) in patients with normal liver, 30 per cent or less of the TLV in patients who have had extensive chemotherapy, and 40 per cent or less of the TLV in patients with well compensated cirrhosis (*Fig. 3*).

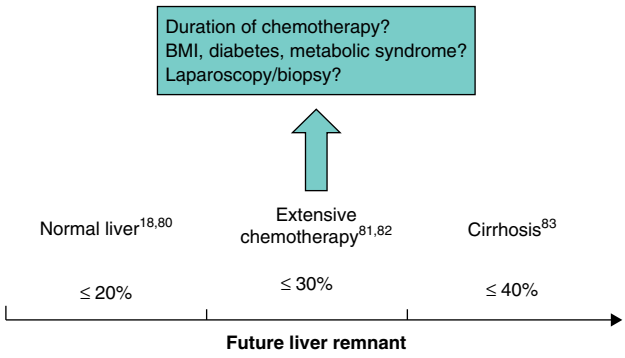


Fig. 3 Indications for portal vein embolization. There is consensus that, in patients treated with aggressive preoperative chemotherapy, the remnant liver volume should be at least 30 per cent of the total liver volume to avoid a high risk of complications following hepatic resection. BMI, body mass index

Advances in chemotherapy and hepatic surgery have expanded the pool of candidates for potentially curative hepatic resection for CLM. Recognition of chemotherapy-related liver injuries further emphasizes the need for patient-by-patient, multidisciplinary planning to optimize care. This implies that patients should be evaluated by experienced hepatic surgeons and medical oncologists before starting therapy to avoid extensive and unnecessary treatment. Similar response rates between 5-FU plus oxaliplatin (FOLFOX) and 5-FU plus irinotecan (FOLFIRI) balanced against the unique liver injuries associated with each – SOS for FOLFOX and steatohepatitis for FOLFIRI – must be considered when designing first-line *versus* second-line treatments for patients likely to have hepatic resection for CLM. The finding that steatohepatitis is associated with the risk of progressive hepatic failure and death after resection, whereas SOS is not, should further influence treatment planning.

Consideration must be given to patients with CLM who may proceed to surgery, particularly those with the currently known risk factors for steatohepatitis, including a BMI exceeding 25 kg/m^2, diabetes mellitus and pre-existing steatosis. Future challenges include the refinement of liver function assessment, the establishment of better methods for evaluation and diagnosis of liver injury, and the discovery of means to protect the liver parenchyma from chemotherapy-induced injuries. Response to treatment should no longer be the only consideration when selecting treatment for patients with CLM.

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