Liver resection for cancer: New developments in prediction, prevention and management of postresectional liver failure

Kim M.C. van Mierlo¹, Frank G. Schaap¹, Cornelis H.C. Dejong¹,², Steven W.M. Olde Damink¹,³,*

Summary

Hepatic failure is a feared complication that accounts for up to 75% of mortality after extensive liver resection. Despite improved perioperative care, the increasing complexity and extensiveness of surgical interventions, in combination with an expanding number of resections in patients with compromised liver function, still results in an incidence of postresectional liver failure (PLF) of 1–9%. Preventive measures aim to enhance future remnant liver size and function. Numerous non-invasive techniques to assess liver function and predict remnant liver volume are being developed, along with introduction of novel surgical strategies that augment growth of the future remnant liver. Detection of PLF is often too late and treatment is primarily symptomatic. Current therapeutic research focuses on ([bio]artificial) liver function support and regenerative medicine. In this review we discuss the current state and new developments in prediction, prevention and management of PLF, in light of novel insights into the aetiology of this complex syndrome.

Lay summary: Liver failure is the main cause of death after partial liver resection for cancer, and is presumably caused by an insufficient quantity and function of the liver remnant. Detection of liver failure is often too late, and current treatment focuses on relieve of symptoms. New research initiatives explore artificial support of liver function and stimulation of regrowth of the remnant liver.

© 2016 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Partial liver resection for hepatobiliary tumours is relatively safe and often the only curative treatment option. The unequalled capacity of the liver to regenerate and restore its functionalities permits the surgical removal of a substantial part of the liver mass. However, postresectional liver failure (PLF) occurs in up to 9% of patients and remains the main cause of postoperative mortality [1,2]. PLF has a subacute course, and an inadequate functional reserve of the remnant liver is central in its aetiology. Insufficient hepatic secretory capacity is reflected by hyperbilirubinemia, whereas decreased synthetic and detoxifying functions can manifest as coagulopathy and hepatic encephalopathy [1].

Hyperbilirubinemia is included in all currently used definitions of PLF. The ‘50–50 criteria’ predict a 59% risk on early postoperative mortality if systemic bilirubin rises above 50 µmol/L and prothrombin time decreases to 50% on postoperative day 5 [3]. The ‘peak bilirubin criterion’ defines PLF as a bilirubin level above 120 µmol/L within 90 days after major hepatectomy, and has a positive predictive value of 33% for liver-related death in non-cirrhotic patients [4]. The definition of PLF developed by the International Study Group of Liver Surgery encompasses bilirubin elevation (according to local criteria) on or after postoperative day 5, and grades PLF based on international normalized ratio (INR) derangement [5]. Postoperative mortality in PLF grade A (INR <1.5), B (INR >1.5 and <2.0) and C (INR >2.0) was 0%, 12%, and 54%, respectively [5]. In order to provide a comprehensive overview of this syndrome, no specific definition was selected for this review.

Keywords: Postresectional liver failure; Liver resection; Hepatic cancer; Liver regeneration; Review.

Received 19 February 2016; received in revised form 3 June 2016; accepted 7 June 2016

¹Department of Surgery, Maastricht University Medical Centre & NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands;
²GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands;
³Department of Surgery, Institute of Liver and Digestive Health, Royal Free Hospital, University College London, London, United Kingdom

Key point

Postresectional liver failure (PLF) is the main cause of postoperative mortality after liver resection for hepatobiliary malignancy.
Liver regeneration after partial liver resection

Liver regeneration following partial hepatectomy is a tightly orchestrated process involving the spatiotemporal interplay between parenchymal and non-parenchymal cells and is driven by multiple signals (see for detailed reviews references [6,7]). First, immediately after partial liver resection, the total hepatic inflow passes through the vascular bed of the smaller remnant liver. Resultant shear stress, a relative increase in supply of signalling molecules from the (portal) circulation, and growth factors released after remodelling of the extracellular matrix, provide the triggers for initiation of liver regeneration. Interleukin 6 and tumour necrosis factor alpha released by activated Kupffer cells are important for cell cycle re-entry of normally quiescent hepatocytes, with further cell cycle progression driven by mitogens such as hepatocyte growth factor. Proliferation of the various non-parenchymal cell types enables re-establishment of the hepatic architecture. Through poorly understood molecular events, liver regeneration terminates when the original liver mass and functional capacity have been restored.

Aetiology of postresectional liver failure

During liver regeneration, a minimum amount of remnant liver is required to maintain vital liver functions and support regrowth. In a seminal study almost half of the patients with a remnant liver volume (RLV) smaller than 26.6% of the pre-resection value, developed severe hepatic dysfunction compared with 1.2% of patients with a larger RLV [2]. Consequently, a RLV of 25–30% is currently used as lower limit in patients with normal liver function, whereas a minimum RLV of about 40% is mandatory in patients with impaired liver function [8]. Five main factors have been recognized in the aetiology of PLF (Fig. 1).

Hepatic haemodynamic imbalance

PLF shares features of the small-for-size syndrome that occurs in the setting of (partial) liver transplantation. Portal hyperperfusion of the remnant liver results in adaptive reduction of arterial blood flow through activation of the hepatic arterial buffer response (see reference [9] for a detailed review). While increased perfusion and resultant shear stress are instrumental in initiating the regenerative cascade, portal hyperperfusion and arterial hyperperfusion may have deleterious effects on postoperative recovery of liver function [9]. Increased portal flow and pressure after major hepatectomy increased the risk for PLF in non-cirrhotic patients [10]. In patients undergoing partial liver transplantation, post-reperfusion portal hypertension resulted in sinusoidal damage and reduced levels of nitric oxide, a signal molecule engaged in the initiation of liver regeneration [11].

Unmet hepatic metabolic demand: disturbed bile salt homeostasis

Impaired activity of the canalicular pump(s) involved in bilirubin secretion results in intrahepatic accumulation and systemic release of conjugated bilirubin [12]. While bilirubin is generally not regarded as detrimental to the liver, a more generalized dysfunction of canalicular transporters may result in hepatic accumulation of bile salts. Circulating levels of bile salts rise as early as one minute after partial hepatectomy in rats [13], and this is shortly followed by transient accumulation of bile salts in the liver [14]. An important stimulatory role for bile salts and their membrane-bound and nuclear receptors in liver regeneration is emerging [15]. Being biological detergents, excessive intracellular accumulation of bile salts, however, causes damage to internal membranes (particularly in mitochondria) of the hepatocyte and results in apoptosis [16]. In mice with deranged bile salt homeostasis, otherwise well-tolerated 70% partial hepatectomy results in massive hepatic necrosis and early mortality [17]. Animal studies underscore that tight control of (hepatic) bile salt homeostasis is a prerequisite for unimpeded liver regeneration [17,18].

Impaired liver innate immune defence

Liver regeneration after partial hepatectomy involves activation of the liver’s innate immune system [19]. Innate immune receptors of the Toll-like receptor family that recognize bacterial products, and downstream (adaptor) proteins that relay the signal intracellularly, are engaged in this activation step [20]. Liver-resident macrophages not only play an important role in the regenerative response after liver resection by producing priming factors, they also clear portal endotoxins and eliminate translocated bacteria [21], thus limiting exposure of hepatocytes to (pro-apoptotic) lipopolysaccharide (LPS) and preventing systemic infection [22]. Following resection, adequate numbers of Kupffer cells should remain to preserve these essential functions. The risk of infection increases with the extent of resection, and a majority of patients with hepatic dysfunction also develops infectious complications [2]. Cytokine release by activated Kupffer cells is hampered after major liver resection [22]. Likewise, impaired phagocytic activity of the reticuloendothelial system is observed after major resection [23], and this likely contributes to increased infectious risk [2].

Gut microbiome-gut-liver axis

An emerging concept is that the gut microbiota modulates the regenerative ability of the liver.
This is likely to involve interactions between the gut microbiome and host metabolism, effects of the gut microbiota on bile salt physiology, and effects of bacterial endotoxins [24,25]. Bile salts exert direct antimicrobial activity and shape the composition of the gut flora. Conversely, certain microbial strains can convert the host’s primary bile salts into secondary species, thus affecting the signalling properties of bile salts. This again can impact host metabolism, bile salt homeostasis, and liver regeneration [26–28]. As discussed above, activation of the innate immune response in the liver is important for liver regeneration after partial hepatectomy, and microbial products including LPS are implicated in Kupffer cell activation [29]. Failure of gut-derived endotoxins to reach the liver resulted in impaired DNA synthesis in replicating hepatocytes, likely through reduced production of priming factors [30]. On the other hand, excessive levels of endotoxin can impair liver regeneration and cause mortality after extended hepatectomy.

Impaired background liver function

Impaired liver quality plays a pivotal role in PLF and is frequently present in patients that undergo partial hepatectomy for the three most common indications: colorectal cancer liver metastasis (CRLM), hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). Four types of liver pathology are related to these hepatobiliary tumours, viz. chemotherapy-associated liver injury, fatty degeneration, fibrotic progression, and cholestasis.

Chemotherapy-associated liver injury (CALI)

Neoadjuvant chemotherapy is widely used for downstaging of CRLM. Oxaliplatin is central in most currently used regimens and is considered the main causative agent for development of sinusoidal obstruction syndrome (SOS) and nodular regenerative hyperplasia (NRH), whereas irinotecan has been associated with the development of chemotherapy-associated steatohepatitis.

Sinusoidal obstruction syndrome

SOS is seen in up to 80% of patients undergoing oxaliplatin-based chemotherapy [31], and is characterized by injury of endothelial cells, parenchymal damage, and (fibrotic) venular lesions. Sinusoidal dilatation (SD) is the most common manifestation of SOS in the grading system of Rubbia-Brandt et al. [31].
Although exact mechanisms are unclear, a diminished preoperative functional reserve and longer hospital stay after major hepatectomy was reported in patients with SD [32]. The effect of SD on development of PLF is uncertain. Studies indicate no effect, or an incidence of PLF in up to 21% of patients with moderate to severe SD after major hepatectomy (0–4.2% in patients with absent or mild SD) [33,34]. Rodent models using monocrotaline or oxaliplatin to induce SOS revealed impairment of liver regeneration and induction of liver injury following partial hepatectomy [35]. This was accompanied by less pronounced induction of hepatic mitogens, reduced liver volume recovery, enhanced hepatocellular necrosis and higher serum alanine aminotransferase (ALT) and bilirubin levels [35,36].

Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor A, decreased the incidence of SD in patients that received oxaliplatin-based chemotherapy [37]. Downregulation of matrix metalloproteinase-9, a fibrotic remodelling factor involved in perisinusoidal extracellular matrix breakdown, may be accountable [38].

SD is a histological diagnosis and can be detected by biopsy, however the false-negative classification is high due to the spatial heterogeneity of its manifestation [34]. Surrogate measures are biochemical assessment, functional tests, imaging and spleen size measurement. Increased aspartate aminotransferase (AST) and alkaline phosphatase (ALP) levels can point to SD, but are non-specific. An indocyanine green retention rate after 15 min (ICG-R15) >10% and the preoperative AST-to-platelet-ratio index (APRI) are both independently associated with the presence of SD [32,33]. Patients with SD often have an increased spleen volume [39], with an increase of ≥30% reported to be predictive of SD [40]. Another typical SD-related abnormality seen in imaging is reticular hypointensity that presumably reflects locally impaired Kupffer cell function [41]. Superparamagnetic iron oxide-enhanced MRI can detect moderate to severe SD [41], but gadoxetic acid-enhanced MRI seems superior with a specificity of 96–100% on hepatobiliary phase images [42].

**Nodular regenerative hyperplasia**

A second histological characteristic of SOS is NRH, which is observed in over 24% of patients after oxaliplatin-based chemotherapy [38]. NRH is characterized by diffuse transformation of liver parenchyma into regenerative nodules that compress the surrounding parenchyma, and is graded according to Wanless et al. [43]. NRH probably arises due to changes in intrahepatic sinusoidal or portal blood flow [43].

The incidence of PLF is increased in patients with NRH, even rising to 25% after major hepatectomy in patients with moderate to severe NRH [44]. Furthermore, coexistence of NRH with moderate to severe SD has been noted [44]. Since SD, in contrast to NRH, was no indisputable risk indicator for postoperative outcome, it was suggested that NRH is the true determinant of poor short-term outcome after liver resection. Although the mechanism is not elucidated, hepatic injury, portal hypertension and a lower platelet count may predispose to PLF [45].

A decreased platelet count combined with elevated ALP, gamma-glutamyltransferase (GGT), and total bilirubin levels can be found in NRH [46]. APRI can predict NRH [44]. Percutaneous or transjugular liver biopsy with hepatic venous pressure gradient measurement may be used as a diagnostic tool, but should solely be applied in selected high-risk patients [44]. Reversibility of histological features is uncertain and bevacizumab seems to protect against development of NRH [38].

**Chemotherapy-associated steatohepatitis**

Irinotecan is associated with chemotherapy-induced steatohepatitis with widely ranging incidence reported in literature [47], and steatohepatitis after irinotecan proved to increase the risk of death from PLF [48]. Histopathological findings, prediction and prevention will be discussed below in conjunction with steatosis/steatohepatitis.

**Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis**

The prevalence of non-alcoholic fatty liver disease (NAFLD) in the adult Western population is approximately 20–30% and around 3–5% of adults are estimated to have non-alcoholic steatohepatitis (NASH) [49]. Despite lack of absolute consensus [50,51], steatosis and NAFLD seem to be risk factors for PLF and higher overall postoperative morbidity and mortality [2,52,53].

Rodent models show that vulnerability of the steatotic liver may be due to reduced tolerance against ischemic injury caused by decreased perfusion of the liver [54]. In addition, mitochondrial dysfunction in NAFLD results in impaired ATP synthesis, while Kupffer cell dysfunction increases reactive oxygen production which causes hepatocellular injury [54,55]. In the steatotic liver the ability of hepatocytes to regenerate after major tissue loss is impaired [56]. Multiple pathways contribute to unresponsiveness of fatty hepatocytes to regenerative stimuli, and subsequent cell cycle arrest [57]. Furthermore, cell cycle transition may be negatively affected by disturbed energy homeostasis in the fatty liver [55].

Biopsy remains the most reliable method for assessment of NAFLD but is increasingly replaced by non-invasive alternatives due to a small risk for
complications and sampling errors [58,59]. Non-invasive methods consist of functional liver tests, breath tests, imaging, and biomarkers that assess steatosis and fibrosis. The majority of patients with NAFLD have normal liver function tests, however some have elevated ALT, AST, GGT, and/or serum ferritin. Ultrasonography is still the imaging modality of choice in patients with >33% parenchymal steatosis, but its accuracy decreases in obese patients [60]. Magnetic resonance (MR) imaging (MRI) and MR spectroscopy directly quantify fat and outperform computed tomography (CT) and ultrasonography for prediction of steatosis when the fat content is >5.5% [61].

Transient elastography (TE) and MR elastography (MRE) indicate fibrosis by measuring liver stiffness. TE predominantly detects cirrhosis [62], and MRE can distinguish advanced from mild fibrosis [63]. Especially TE is easily applied in clinic but its use is limited by obesity, although utilization of an XL-probe improves accuracy in obese patients [64].

Simultaneous measurement of steatosis and fibrosis can be accomplished by integration of the controlled attenuation parameter in TE or acoustic radiation force impulse in a conventional ultrasonography machine [65,66]. Serum fibroblast growth factor 21 (Fgf21) and cytokeratin 18 are biomarkers that can discriminate between NASH and NAFLD [67,68], and NAFLD, NASH and fibrosis [67,68]. The Fibrosis-4 score showed a negative predictive value of 98% for detecting patients without advanced fibrosis [69]. Other combined parameters that assess hepatic fibrosis are the APRI, FibroMeter, NAFLD, NAFLD fibrosis score, and BARD score [70–73].

**Fibrosis and cirrhosis**

Hepatic fibrosis is mainly present in patients undergoing partial liver resection for HCC, and is mostly caused by progression of steatosis or related to chronic viral hepatitis [74]. In the past, the decreased regenerative capacity of the fibrotic liver increased the risk of PLF and caused postoperative mortality rates of around 15% [75]. Present mortality rates have declined to 0–5% due to advances in preoperative liver function assessment and strict patient selection [74] (Fig. 2).

Little is known about the influence of fibrosis on PLF. Regeneration of the fibrotic liver is suggested to be a progenitor cell-mediated process, in contrast to replication of existing mature hepatocytes in the non-compromised liver [76]. Animal studies indicate that impaired regeneration and subsequent hepatic dysfunction following partial liver resection are due to inefficient induction of cell cycle transition mediators, hepatocyte necrosis, and a pronounced fibrogenic response [76,77]. Enhanced bacterial translocation and decreased innate and adaptive immune system activity add to vulnerability of the fibrotic liver as shown in animal and human studies [78].

For diagnostic purposes, percutaneous biopsy is increasingly replaced by four-pass transjugular biopsy [79], which provides the advantage of concurrent measurement of the hepatic venous pressure gradient (HVPG). Class I biomarkers (e.g., AST) reflect activity of fibrogenesis, whereas class II biomarkers (e.g., APRI) correlate with fibrosis [80]. TE is the most applied technique, but shows low accuracy in patients with obesity or ascites [81]. Both TE and acoustic radiation force impulse have high accuracy for assessment of cirrhosis [81]. Additionally, multiple combination serum tests, such as the FibroTest, Hepascore, and FibroMeter, are used with or without TE [82]. Gadolinium-enhanced MRI is promising as it showed significant signal intensity differences between patients with and without fibrosis [83].

Two preoperative parameters that directly predict development of PLF in patients with cirrhosis are an RLV-to-body weight ratio <1.4% [84] and the change in portal venous pressure [85]. Furthermore, whereas portal hypertension ought to be a contraindication for hepatic resection in patients with HCC, a recent study on the relationship between the HVPG and the development of PLF found that even in patients with a pressure gradient >10 mmHg, one-quarter of the patients experienced an uneventful postoperative course [86].

**Cholestasis**

Obstructive cholestasis is characterized by retention of biliary constituents and a ductular reaction, and upon longer duration by hepatocyte degeneration, bile salt stasis, and progression of the ductular reaction to biliary fibrosis [87]. Patients with perihilar CCA often present with jaundice, weight loss, and cholangitis, whereas intrahepatic CCA is frequently associated with a silent clinical course and general symptoms such as malaise and loss of appetite resulting in late detection [88].

After extensive resection for perihilar CCA, PLF is seen in up to 30% of patients and mortality occurs in around 8–12% of patients [89,90], possibly due to a combination of cholangitis and a small RLV [91]. A complication rate of up to 38% is reported after surgical removal of intrahepatic CCA, with few patients developing PLF and a mortality rate of approximately 1% [92].

Animal studies suggest that biliary dilatation caused by distal obstruction compresses the portal triad resulting in a decreased portal flow with subsequent compensatory increased arterial flow in combination with portosystemic shunting (reviewed in reference [93]). Additionally, the interrupted enterohepatic circulation, lower expression of proliferative mediators in the priming and early
phase of regeneration, and toxic bile-associated hepatocyte apoptosis, add to defective regeneration after partial resection of the obstructed liver in rodents [93]. A significant suppression of mitotic indices and lower hepatic weight gain after partial hepatectomy is observed in cholestatic rats [94]. Furthermore, animal studies provided evidence for enhanced susceptibility to post-ischemic reperfusion injury in cholestatic rats [95]. The detrimental role of Kupffer cells in cholestatic injury is demonstrated by amelioration of injury in bile duct-ligated mice with prior depletion of Kupffer cells [96]. Moreover, an excessive inflammatory response through pro-inflammatory cytokine production led to deterioration of hepatic function after bile duct ligation, resulting in enhanced susceptibility to infection [97]. Jaundiced patients undergoing laparotomy additionally showed significantly more bacterial translocation [98]. This is in line with the high clinical incidence of postoperative infectious...
complications in cholestatic patients undergoing partial hepatectomy \[90\].

Obstructive cholestasis is biochemically characterized by elevated serum bilirubin, ALP and GGT levels \[99\]. Inflammatory parameters are elevated in case of acute cholangitis \[100\]. Imaging of cholestatic parenchyma using ultrasonography, CT or MR cholangiopancreatography is not focused on assessing quality but on detection of dilated intrahepatic bile ducts.

**Assessment of liver volume and function**

Both assessment of liver volume and function is mandatory to predict postoperative functional reserve. Methods for measurement of future RLV range from 2D volumetry on computed tomography, to peroperative 3D modelling. Computational software allows manual or automatic delineation of the liver on all CT or MRI sections, thereby allowing calculation of liver volume \[101,102\].

Liver function can be estimated by preoperative biochemistry, breath tests and imaging. Hepatic secretory (bilirubin), synthetic (INR) and detoxifying (ammonia) functions and liver damage (ALT, AST) are evaluated by clinical chemistry. Metabolic liver function testing can be performed with the LiMAx test and the indocyanine green clearance rate \(\text{ICGR}-15\) \[11,12\]. The LiMAx test measures metabolism of intravenously injected \(^{13\text{C}}\)-labeled methacetin in exhaled breath. Imaging techniques used in the clinic include \(^{99\text{m}}\text{Tc}\)-labeled galactosyl serum albumin (GSA) liver scintigraphy, \(^{99\text{m}}\text{Tc}\)-mebrofenin hepatobiliary scintigraphy with single-photon emission computed tomography (SPECT), and gadolinium-enhanced MRI using gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid \((\text{Gd}-\text{EOB-DTPA})\) \[103–105\]. Impaired enhancement of labeled contrast indicates decreased hepatic uptake and reflects compromised liver quality. Liver enhancement in gadolinium-enhanced MRI shows good correlation with regional liver function, and offers the advantage of simultaneous diagnostic evaluation and functional assessment \[104\].

**Prevention of postresectional liver failure**

Prevention of PLF consists of four principles: optimizing preoperative liver function, enlarging RLV, limiting hepatic haemodynamic disbalance and providing optimal perioperative care.

*(Pre-)*clinical methods of preoperative liver optimization

The liver of patients with SOS is in a prothrombotic state as reflected by upregulation of plasminogen activator inhibitor-1, Von Willebrand factor and factor X \[106\]. The fibrinolytic agent defibrotide is administered in bone marrow transplant recipients for treatment of SOS \[107\], and might be beneficial in chemotherapy-related SOS as well. Anti-platelet therapy such as aspirin seems to protect against oxaliplatin-induced SOS in patients \[108\]. Oxaliplatin is conjugated to glutathione and subsequently excreted from the cell, which is the probable cause of reduced hepatic glutathione levels seen in SOS \[106\]. Supplementation of antioxidant therapy (hydroxyanisole) or flavonoids reduced the severity of sinusoidal injury in rodents \[106,109\]. This effect has not yet been confirmed in humans. Chemotherapy-free interval prior to liver resection may reverse SOS, as suggested by a longer period since the last cycle of chemotherapy in patients without histological evidence of SD at the time of liver resection \[32\]. On the other hand, hepatic sinusoidal lesions and even progression of fibrosis are reported up to several months after cessation of chemotherapy \[31\]. Portal hypertension can be diminished by perioperative splenic artery ligation in patients with severe NRH and portal hypertension, and might decrease postoperative morbidity \[110\].

Liver steatosis can be reduced by a preoperative very-low calorie diet, as has been shown in potential liver transplant donors \[111\]. Less steatosis and steatohepatitis was observed in patients with one week of calorie restriction prior to resection for benign or malignant liver disease, compared to ad lib fed patients \[112\]. However, despite less intraoperative blood loss in the diet group, no effect was seen on postoperative complications in this patient group.

Optimization of liver function in patients with cirrhosis has not yet been attempted, however, platelet infusion may be an option. Thrombocytopenia in cirrhosis may be caused by a decrease in (hepatic) thrombopoetin production and systemic removal of platelets in the spleen \[113\]. Platelets have a stimulatory effect on liver regeneration \[114\], and platelet infusion might provide an option for preoperative optimization.

The preventive role of preoperative biliary drainage in obstructive cholestasis is uncertain. Internal (stenting via endoscopic retrograde cholangiopancreatography, ERCP) or external (percutaneous transhepatic biliary drainage, PTBD) drainage in pancreatic head cancer patients has been shown to have no benefits on surgical outcome and induced drainage-related complications \[115\], whereas its role in proximal malignant bile duct obstruction is inconclusive. Preoperative improved secretory liver function, improved postoperative liver regeneration, and a reduction of mortality after right hemihepatectomy were reported \[116\], but this could not be reproduced by others \[117,118\]. Drainage-related complications such as cholangitis and haemorrhage are seen in up to 33% of patients \[116\]. Especially infectious complications are more...
Review

Disease progression after PVE occurs in up to 66% of patients, and is likely due to increased arterial flow to the embolized lobe and or waiting period to surgery [124]. The interval between PVE and surgery should therefore be as short as possible but not less than 2–3 weeks [124]. Post-PVE chemotherapy before resection may halt disease progression without affecting subsequent liver regeneration [125].

PVE is commonly performed after the administration of chemotherapy [108]. Evidence for the influence of CALI on post-PVE hypertrophy is conflicting. Whereas SD seems to have a clear inhibitory effect on hypertrophy [126], chemotherapy has no effect on liver regrowth [121,127]. Moreover, patients with NASH show a trend towards less post-PVE liver volume gain compared to patients with normal liver function [126]. Although robust evidence is lacking [121], cholestasis appears to have no negative impact on hypertrophy after PVE. After right hepatectomy in patients with chronic liver disease, PLF developed in 50% of patients without PVE vs. 7.1% in patients with PVE [128]. Impaired hypertrophy after technically successful PVE in patients with chronic liver disease is a contraindication for major resection [128].

The two-staged hepatectomy is an excellent method to increase RLV and consequently achieve curative opportunity for initially non-resectable patients. Although ALPPS is currently performed in all stages of hepatectomy, albeit that during the first stage in ALPPS the liver is split in situ combined with portal vein ligation, and the second stage consists of removal of the ligated lobe 7–14 days later [129]. An astonishing average hypertrophy rate of 35–40% and improves eligibility for hepatectomy by 20% [1]. In less than 5% of patients the hypertrophic response following PVE is inadequate [121]. Major PVE-related complications occur in approximately 2.5% of patients and include intra-abdominal abscess, liver hematoma, and backflow of embolization material [121]. A recent meta-analysis comparing PVE with ligation of the portal vein (PVL) showed comparable preoperative hypertrophic responses and postoperative morbidity [122]. New developments exist of polyvinyl alcohol particles with plugs or coils as embolizing materials, and have resulted in lower recanalization rates, enhanced hypertrophy, and a decreased occurrence of PLF [123].

Enlarging of future remnant liver volume

Hypertrophy-inducing procedures and surgical adaptations should be performed if the RLV is expected to be <25% in patients without liver disease and <35–40% in patients with impaired liver function [8]. In general, portal vein embolization (PVE, Fig. 3) enlarges the RLV with approximately 35–40% and improves eligibility for hepatectomy by 20% [1]. In less than 5% of patients the hypertrophic response following PVE is inadequate [121]. Major PVE-related complications occur in approximately 2.5% of patients and include intra-abdominal abscess, liver hematoma, and backflow of embolization material [121]. A recent meta-analysis comparing PVE with ligation of the portal vein (PVL) showed comparable preoperative hypertrophic responses and postoperative morbidity [122]. New developments exist of polyvinyl alcohol particles with plugs or coils as embolizing materials, and have resulted in lower recanalization rates, enhanced hypertrophy, and a decreased occurrence of PLF [123].

Enlarging of future remnant liver volume

Hypertrophy-inducing procedures and surgical adaptations should be performed if the RLV is expected to be <25% in patients without liver disease and <35–40% in patients with impaired liver function [8]. In general, portal vein embolization (PVE, Fig. 3) enlarges the RLV with approximately 35–40% and improves eligibility for hepatectomy by 20% [1]. In less than 5% of patients the hypertrophic response following PVE is inadequate [121]. Major PVE-related complications occur in approximately 2.5% of patients and include intra-abdominal abscess, liver hematoma, and backflow of embolization material [121]. A recent meta-analysis comparing PVE with ligation of the portal vein (PVL) showed comparable preoperative hypertrophic responses and postoperative morbidity [122]. New developments exist of polyvinyl alcohol particles with plugs or coils as embolizing materials, and have resulted in lower recanalization rates, enhanced hypertrophy, and a decreased occurrence of PLF [123].

Enlarging of future remnant liver volume

Hypertrophy-inducing procedures and surgical adaptations should be performed if the RLV is expected to be <25% in patients without liver disease and <35–40% in patients with impaired liver function [8]. In general, portal vein embolization (PVE, Fig. 3) enlarges the RLV with approximately 35–40% and improves eligibility for hepatectomy by 20% [1]. In less than 5% of patients the hypertrophic response following PVE is inadequate [121]. Major PVE-related complications occur in approximately 2.5% of patients and include intra-abdominal abscess, liver hematoma, and backflow of embolization material [121]. A recent meta-analysis comparing PVE with ligation of the portal vein (PVL) showed comparable preoperative hypertrophic responses and postoperative morbidity [122]. New developments exist of polyvinyl alcohol particles with plugs or coils as embolizing materials, and have resulted in lower recanalization rates, enhanced hypertrophy, and a decreased occurrence of PLF [123].

Key point

Treatments to enhance liver regeneration may enlarge the number of patients eligible for curative intent surgery.

Fig. 3. Visualization of pre- or perioperative interventions and their effect on liver remnant volume. (A) Malignant liver disease (B) Embolization/ligation of the right portal branch (1) results in atrophy of the right hemi-liver and compensatory growth of the left hemi-liver, which can be removed when appropriate hypertrophy has been achieved (2). (C) Removal of tumours from the left hemi-liver and occlusion of the right portal branch (1). After 4–6 weeks, the volume of the left hemi-liver is increased and the right hemi-liver can be removed (2). (D) Removal of tumours from the left hemi-liver, in situ splitting of the hemi-livers, and simultaneous ligation of the right portal vein branch (1). After one week, augmented hypertrophy of the left hemi-liver permits removal of the right hemi-liver (2).
applied in HCC patients with low-grade fibrosis. ALPPS should not, or with great caution, be applied in patients with perihilar and intrahepatic CCA due to the (already) high postoperative mortality rate in this patient category [130,133]. Modifications such as monosegment ALPPS, in which only one instead of two or more Couinaud segments remain, showed promising results in a small cohort of 12 patients, with a PLF rate of 33% but without mortality [134].

Limiting hepatic haemodynamic imbalance

Splenectomy and splenic artery ligation can be effective strategies that limit the postresectional increase in portal blood flow and pressure, by activating the hepatic arterial buffer response. These procedures resulted in increased arterial inflow, and enhanced liver regeneration and liver function after (extended) partial hepatectomy in rodent models [135]. Furthermore, in animal models of partial hepatectomy and small-for-size liver grafts, the administration of terlipressin and somatostatin seemed to reduce postresectional portal hyperperfusion and increase regenerative parameters [136–138].

Providing optimal perioperative care

Excessive perioperative blood loss, blood transfusion, ischemia-reperfusion injury, and hepatic manipulation predispose to PLF. Blood transfusion enhances postoperative morbidity and tumour recurrence presumably via a transfusion-related inflammatory response [139]. A recent meta-analysis confirmed that hepatic preconditioning (i.e., intermittent vascular inflow occlusion) results in less intraoperative blood loss and a shorter operating time in comparison to hepatectomy alone, but without improved postoperative outcome [140]. Prolonged clamping should nonetheless be avoided since ischemia-reperfusion injury has been shown to induce severe hepatic damage [141]. Hepatic manipulation per se elicits an inflammatory response [142]. Methods to minimize mobilisation of the liver include laparoscopic surgery and the hanging method [143]. Laparoscopic resection of HCCs reduced the incidence of PLF compared to open surgery [144].

Since infectious complications such as bile leakage or abdominal collections may contribute to the development of PLF and negatively affect the postresectional course, several preventive measures have been explored. Postresectional primary placement of abdominal drains proved not to be beneficial after major liver resection and is even associated with increased rates of complications such as bile leakage and PLF [145,146]. Multiple human studies focused on either pre- or postresectional antibiotic prophylaxis, without evidence for a significant effect on the rate of infectious complications [147,148]. Preoperative selective bowel contamination has been explored in rodent models, showing amelioration of parenchymal injury and increased liver regeneration after partial liver resection [149]. A meta-analysis of human transplant studies however showed no benefits on infectious complications [150].

Regenerative interventions

Augmentation of the regenerative response after liver resection may be an option for prevention and treatment of PLF. The nuclear bile salt receptor FXR (farnesoid X receptor, Fig. 4) may be an attractive therapeutic candidate, through effects on hepatic haemodynamics, bile salt and lipid homeostasis, hepatic inflammation, and hepatocellular proliferation [18,151–153]. Being the key regulator of hepatic bile salt homeostasis, genetic disruption of Fxr in mice resulted in mortality and delayed liver regeneration after partial hepatectomy. Conversely, activation of Fxr by its endogenous ligands (i.e., bile salts) or synthetic agonists enhanced liver regeneration in hepatectomized mice. Furthermore, the FXR-regulated enterokine FGF19 reduced mortality after (extended) partial hepatectomy in rodent procedures resulted in increased arterial inflow, vating the hepatic arterial buffer response. These increase in portal blood flow and pressure, by acti- effective strategies that limit the postresectional

Controlling bile salt homeostasis ensures proper progression of postresectional liver regeneration. Bile salt receptor FXR in small intestine and liver exerts homeostatic control by regulating import, synthesis, conjugation (i.e., N-amidation) and export of bile salts. Moreover, bile salt signaling via FXR results in induction of genes engaged in cell cycle control (e.g., Foxm1b). On the other hand, hepatic bile salt overload gives rise to liver injury. Bile salt toxicity may be reduced by stimulation of phase I/II metabolism and phase III efflux via agonistic activation of nuclear receptors PXR and CAR. An excessive inflammatory response of Kupffer cells may be dampened by TGR5 agonism. OCA, obeticholic acid (FXR agonist); PB, phenobarbital (CAR activator); FGFR4, fibroblast growth factor receptor 4.

Fig. 4. Targeting of bile salt receptors may improve liver regeneration after partial hepatectomy through direct trophic and bile salt homeostatic effects. Control of bile salt homeostasis ensures proper progression of postresectional liver regeneration. Bile salt receptor FXR in small intestine and liver exerts homeostatic control by regulating import, synthesis, conjugation (i.e., N-amidation) and export of bile salts. Moreover, bile salt signaling via FXR results in induction of genes engaged in cell cycle control (e.g., Foxm1b). On the other hand, hepatic bile salt overload gives rise to liver injury. Bile salt toxicity may be reduced by stimulation of phase I/II metabolism and phase III efflux via agonistic activation of nuclear receptors PXR and CAR. An excessive inflammatory response of Kupffer cells may be dampened by TGR5 agonism. OCA, obeticholic acid (FXR agonist); PB, phenobarbital (CAR activator); FGFR4, fibroblast growth factor receptor 4.
Management of PLF consists of goal-directed therapy and functional support.

**Management of postoperative liver failure**

Due to the lack of randomized controlled trials with PLF as primary outcome measure, almost no treatments for acute and acute-on-chronic liver failure have been validated for PLF. When PLF is detected after resection in (non-)compromised liver, goal-directed therapy and functional support can be offered (Fig. 2).

**Goal-directed therapy**

PLF is frequently accompanied by multi-organ dysfunction, requiring a systemic treatment approach [169]. Goal-directed therapy focuses on support of circulatory, ventilatory, and renal function in combination with treatment of hepatic encephalopathy, coagulopathy and malnutrition as reviewed elsewhere [1].

**Functional support**

Molecular absorbent recirculation system, an extracorporeal artificial liver support device that reduces liver failure-induced toxicity by facilitating exchange of albumin-bound and water-soluble toxins from plasma, is applicable as treatment for PLF [170]. In addition, extracorporeal bio-artificial liver devices fulfill functions of the liver (including synthetic and immunological) by separation and passage of blood plasma through a reactor containing layers of animal or human hepatocytes [171]. The recently developed University College London-Liver Dialysis Device extracts albumin by hemofiltration and removes certain endotoxins by haemoperfusion, in combination with human albumin infusion [172]. Unfortunately, although the latter two devices show survival benefits, they have thus far been tested only in a pre-clinical setting. Furthermore, promising treatment modalities that focus on extracorporeal high-flux haemodialysis in combination with albumin dialysis (Prometheus®), and patient plasma replacement with fresh frozen plasma (high-volume plasmapheresis), have been tested almost exclusively as treatment for acute and acute-on-chronic liver failure with sparse (underpowered) data on its use in the context of liver failure after hepatic resection [173,174].

**Rescue and elective liver transplantation**

The limited data on rescue liver transplantation in patients with PLF showed a 5-year overall survival of 40% [175], however appropriate criteria for patient selection are lacking. Hence, rescue liver transplantation is barely applied nowadays. Moreover, rescue liver transplantation should not be performed if the patient was not eligible for transplantation before partial hepatectomy.

**Conclusion**

The incidence of liver failure after surgical resection is relatively low. This is accomplished to a large
extent by (I) better insight into the aetiology of PLF and liver regeneration, (II) new imaging techniques and biochemical tests for preoperative assessment of liver quality, (III) highly effective preventive measures, and (IV) improved perioperative care. Due to the low event rate, prospective studies with PLF as primary endpoint are nearly unachievable [176], and most evidence is based on retrospective cohort studies. Furthermore, a uniform definition and outcome set are lacking, but imperative to compare different cohorts [177]. In view of the current increase of extensive resections in a compromised liver background, the development of universal prediction models, more advanced surgical techniques, and efficient preventive measures become particularly important to obtain curability in these challenging patients. Global collaborations and registrations such as seen in the EASL-CLIF consortium (acute-on-chronic liver failure) [130] or the ALPPS-registry [178] seem the only manner to obtain the required number of events for robust evidence on risk factors, prediction models and interventions.

Conflict of interest
The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors’ contributions
Study concept and design: KvM, FS, CD, SOD; Drafting of the manuscript: KvM, Critical revision of the manuscript: FS, CD, SOD; Acquisition of data/Analysis and interpretation of data/Statistical analysis/administrative support/study supervision: n/a. All authors approve of and take responsibility for the final version of this manuscript.

References

Author names in bold designate shared co-first authorship


Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–676.


1. The most common liver histologic finding in oxaliplatin-associated SOS is:
   a. Centrizonal liver cell necrosis
   b. Sinusoidal dilatation
   c. Plugging of central veins with cellular debris
   d. Central to portal fibrosis

True or False

2. Cholestatic patients undergoing partial hepatic resection have a higher incidence of post surgical infection compared to those without cholestasis

3. Bevacizumab, when used in conjunction with oxaliplatin, enhances the liver toxicity of oxaliplatin

4. Irinotecan is associated with the development of non-alcoholic steatohepatitis

5. Fatty liver without NASH on biopsy has no impact on the incidence of post resection liver failure

6. A bilirubin level >7.0 mg/ml (120 umol/L) within 90 days after liver resection defines postresectional liver failure and carries a ~33% mortality rate in non-cirrhotic patients.

7. Intervention to increase the residual liver volume after resection include pre-resection portal vein embolization and two stage hepatectomy

8. Post resection liver failure is more common after resecting intrahepatic cholangiocarcinoma vs. perihilar cholangiocarcinoma

9. Post resection, arterial hyperperfusion and portal hypoperfusion as a result of the smaller liver remnant can lead to liver dysfunction

10. Patients with oxaliplatin-induced sinusoidal dilation have a decreased ability to regenerate liver tissue after partial resection

11. ERCP is clearly indicated in patients with obstructive jaundice prior to hepatic resection to minimize post-surgical complications

12. Features that suggest development of oxaliplatin-associated NRH include thrombocytopenia, increased alkaline phosphatase and increased APRI.

13. Aspirin therapy during oxaliplatin chemotherapy may reduce the incidence of SOS