Review

JOURNAL OF HEPATOLOGY

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

Kim M.C. van Mierlo[1], Frank G. Schaap[1], Cornelis H.C. Dejong[1,2], Steven W.M. Olde Damink[1,3,*]

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.

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

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.

[1]*Department of Surgery, Maastricht University Medical Centre & NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands*;
[2]*GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands*;
[3]*Department 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.

Abbreviations: PLF, postresectional liver failure; INR, international normalized ratio; RLV, remnant liver volume; CALI, chemotherapy-associated liver injury; CRLM, colorectal cancer liver metastasis; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; SOS, sinusoidal obstruction syndrome; NRH, nodular regenerative hyperplasia; SD, sinusoidal dilatation; ALP, alkaline phosphatase; ICG-R15, indocyanine green retention rate after 15 min; APRI, AST-to-platelet-ratio index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MR, magnetic resonance; CT, computed tomography; TE, transient elastography; MRE, magnetic resonance elastography; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage; PVE, portal vein embolization; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; FXR, Farnesoid X Receptor.

Key point

Insufficient remnant liver volume and function are central in the aetiology of PLF, and detailed assessment of preoperative liver function is pivotal in surgical management of hepatobiliary tumours.

* Corresponding author. Address: Universiteitssingel 50, H5.485, 6229 ER Maastricht, The Netherlands. Tel.: +31 43 3881497.
E-mail address: steven.oldedamink@maastrichtuniversity.nl (S.W.M. Olde Damink).

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 hypoperfusion 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 hepatocyte 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 livers' 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