Strategies to improve outcome after partial liver resection

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Summary and conclusions
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Although mortality has decreased over the past decade, partial liver resections are still accompanied by substantial post-operative morbidity. Liver failure is an important cause of mortality after partial liver resection. Risk of liver failure increases when the larger part of the liver has to be resected, such as with hemihepatectomy (40-60%) or extended hemihepatectomy (70-75%), especially when liver function is compromised due to cirrhosis, long standing cholestasis or steatosis. It is therefore important to identify patients who are at risk of developing post-operative liver failure and to find methods to decrease this risk.

Another important cause of complications after partial liver resection is massive intra-operative blood loss. Massive intra-operative blood loss increases the risk of infection and transfusion related complications. Vascular inflow occlusion can be applied to reduce blood loss during partial liver resection. It consists of clamping of the portal vein and hepatic artery to the whole liver (Pringle's maneuver) or to part of the liver (segmental clamping). When bleeding is still too much because of hepatic venous backflow or when the tumor is large and situated near the caval vein requiring resection of (part of the) caval vein, total vascular exclusion can be applied. This consists of simultaneous clamping of the portal vein and hepatic artery as well as the supra- and infrahepatic caval vein. The consequence of vascular clamping is, however, a lack of oxygen and energy supply leading to hepatic ischemia and when the clamps are removed, reperfusion injury. This can result in microcirculatory failure, necrosis or apoptosis of hepatocytes, functional loss and the onset of a systemic inflammatory response syndrome.

In this thesis, two important causes of morbidity and mortality after partial liver resections are addressed. The first is inadequate function of the remnant liver, which results in liver insufficiency and liver failure. The second is temporary clamping of the portal vein and hepatic artery, which gives rise to hepatic ischemia and reperfusion injury. Strategies have been developed to recognize and reduce the risk of postoperative liver failure and to prevent and treat hepatic ischemia and reperfusion injury. These strategies were investigated in small and large animal models as well as in a patient series requiring liver resection.

In chapter 2, a series of 99 patients is assessed, who had undergone resection for hilar cholangiocarcinoma (Klatskin tumor) in a 15 year period. These tumors originate at the confluence of the hepatic bile ducts and usually infiltrate proximally into the liver. Especially when the tumor infiltrates into the first segmental branches of the right and/or left hepatic duct (Klatskin type IIIa/b, IV), hilar resection should be combined with partial liver resection in an attempt to obtain negative tumor margins (R0 resection) and to increase survival. As described above however, this is usually accompanied by increased morbidity and mortality. Mainly in the last 5 year period (1998-2003), a more aggressive surgical approach was applied, combining most hilar resections with partial liver resection. This resulted in a higher rate of R0 resections, while morbidity and mortality did not increase. Mean survival increased in the last 5-year period, owing to more R0 resections, better patient selection and improved surgical experience. In univariate analysis, (extended) right hemihepatectomy patients had significantly more postoperative complications as compared to other patients, underlining the relation between resection size and morbidity.
In chapter 3, an overview is given of the current diagnostic and surgical approaches for Klatskin tumor patients as applied in our center. This chapter also focuses on the criteria for resectability and classification systems. Bismuth type IV Klatskin tumors are generally considered unresectable even using extensive liver resections. The anatomy of the biliary ducts at the hepatic duct confluence, however, determines whether in Type IV tumours, tumour free ductal margins can be obtained with preservation of sufficient remnant liver. A group of patients with Klatskin type IV tumors is described who because of special anatomy of the bile ducts draining into the confluence, could undergo curative resection without major morbidity and without mortality.

In chapter 4, the need for concomitant complete excision of the caudate lobe in patients with hilar cholangiocarcinoma is emphasized, along with liver resection. In literature, many authors have promoted this concept to increase the rate of R0 resections and thereby to increase survival. This approach is based on the observation that ductal branches to the caudate lobe are often involved in the tumor. In our study, concomitant complete excision of the caudate lobe resulted in a higher rate of R0 resections without increasing morbidity or mortality.

In chapter 5, hepatobiliary scintigraphy is used as a tool to measure the function of the remnant liver before resection. This future remnant liver function is calculated by measuring liver uptake of technetium-labelled ($^{99m}$Tc-)mebrofenin within different regions of the liver. The liver is visualized by use of a gamma camera. Preoperative future remnant liver uptake function was compared with uptake function of the liver within 3 days after resection. A strong correlation between these two measurements was found, indicating that hepatobiliary scintigraphy of the future remnant liver can be performed preoperatively to accurately estimate the function of the remnant liver after resection.

In chapter 6, a patient series is assessed who had undergone partial liver resection for colorectal metastases, hilar cholangiocarcinoma, hepatocellular carcinoma or other tumors. Preoperative hepatobiliary scintigraphy of the future remnant liver was performed and was correlated with postoperative morbidity, liver failure and mortality. Hepatobiliary scintigraphy was compared to CT-volumetric measurement of the future remnant liver. When a strong correlation was found, optimal cut-off values were calculated and likelihood-ratios as well as sensitivity and specificity rates were obtained. Furthermore, univariate and multivariate analysis were performed to determine other factors that might influence outcome after resection. It was found that in a patient population including patients with chronic liver disease, preoperative measurement of future remnant liver uptake function with $^{99m}$Tc-mebrofenin hepatobiliary scintigraphy is more valuable than CT based measurement of future remnant liver volume during risk assessment of patients requiring extensive liver resection. When future remnant liver uptake function is below the specific cut-off value, the risk of liver failure and mortality is 4 to 5 times increased. In multivariate analysis, operation time was the only factor next to future remnant liver uptake function that was significantly associated with liver failure and mortality.

In chapter 7, portal vein ligation was studied in a rat model. Portal vein ligation in rats simulates portal vein embolization in humans. It can be applied to induce hypertrophy of the future remnant liver, thereby increasing function of the future remnant liver, by ligating/embolizing the contralateral portal vein branch. By increasing future remnant liver function
before resection, liver insufficiency and liver failure can be prevented and resection can be made possible in patients, who would otherwise have insufficient remnant liver function to support life. Portal vein ligation was compared to simultaneous ligation of both the portal vein and hepatic artery. This dual ligation was performed sequentially as well as synchronously. The results showed that portal vein ligation is as effective as sequential dual ligation of portal vein and hepatic artery in inducing regeneration of the contralateral liver segments and that the addition of hepatic artery ligation only lead to both local and systemic inflammatory response affecting liver synthetic function.

In chapter 8, the effect of endogenous as well as exogenous interleukin-10 was examined in a rat model of 60 min hepatic ischemia and reperfusion injury. Interleukin-10 is a potent anti-inflammatory cytokine which inhibits production of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1 and interleukin-6 as well as chemokines such as interleukin-8, produced by monocytes, macrophages and neutrophils. It is also known that tumor necrosis factor-α and interleukin-6 are important factors in the onset of hepatocyte proliferation to overcome loss of functional liver tissue. The aim of this study was to examine the protective effects and the influence on the regenerative response of exogenous recombinant rat interleukin-10 as well as endogenous interleukin-10. Endogenous interleukin-10 was blocked with anti-interleukin-10 neutralizing antibody. The protective effect of endogenous interleukin-10 and even more of exogenous recombinant rat interleukin-10 was clearly demonstrated in this study. This effect can at least in part be attributed to inhibition of the release of pro-inflammatory cytokine interleukin-6, thereby preventing tissue inflammation and necrosis as well as apoptosis. Recombinant rat interleukin-10 administration also sustained a regenerative response after ischemia and reperfusion of the liver. Recombinant rat interleukin-10 administration is therefore useful to prevent ischemia and reperfusion injury and to promote liver regeneration after partial liver resection with temporary inflow occlusion.

In chapter 9, a rat model of hepatic ischemia and reperfusion injury combined with partial heptatectomy was used to study the effect of exogenous administration of bovine intestinal alkaline phosphatase. Exogenous alkaline phosphatase is known to inactivate lipopolysaccharide, a Gram-negative bacteria derived endotoxine. Lipopolysaccharide plays an important role in stimulating inflammatory responses which occur, for example, after hepatic ischemia and reperfusion injury and partial liver resection. The results of the study demonstrated that lipopolysaccharide plays a significant role in ischemia and reperfusion injury in relation with liver resection. Neutralization of endogenous lipopolysaccharide by administration of bovine intestinal alkaline phosphatase appears to be a promising therapeutic tool to attenuate both hepatic and pulmonary injury after liver ischemia/reperfusion and partial liver resection.

In chapter 10, hypothermic perfusion is applied in a pig model of 60 min hepatic ischemia and reperfusion injury. Hypothermic perfusion is a technique by which the liver is cooled in situ by perfusion of the portal vein or hepatic artery with a cold solution, such as Ringer-lactate solution. By cooling the liver, oxygen and energy demand is reduced while metabolism is slowed down, thereby reducing damage from ischemia and reperfusion injury. Hypothermic perfusion can only be applied during total vascular exclusion when the liver is totally isolated from the systemic blood circulation, because perfusion solution may not
be spilled into the rest of the circulation. It is known that under hypothermic conditions, although hepatocytes are protected, sinusoidal endothelial cells are more prone to damage. In earlier studies performed in our laboratory (Bob Heijnen, 2003), it was found that cooling the liver to 28°C by hypothermic perfusion, results in adequate protection of hepatocytes while sinusoidal endothelial cell function remained intact. The aim of our present study was to further cool the liver to 20°C and examine hepatocyte and sinusoidal endothelial cell damage and function. It was found that hypothermic perfusion at 20°C equally preserves sinusoidal endothelial cells as well as hepatocyte function and equally prevents the occurrence of microvascular perfusion failure compared to hypothermic perfusion at 28°C. Also, to cool the liver for 1 hour to an average core temperature of 20°C without isolation, an impractically large volume of perfusion fluid is required. Although interleukin-6 release was decreased with hypothermic perfusion at 20°C, it was concluded that a mean core liver temperature of 28°C is both sufficient and practical when applying hypothermic perfusion.

In chapter 11, a relatively new organ preservation solution, called Celsior, was tested in a pig model of carotid artery preservation. In this model, Celsior solution was compared to the more established preservation solutions as University of Wisconsin solution and Histidine-tryptophane-ketoglutarate solution. The benefit of organ preservation solutions over mineral based infusion solutions such as Ringer-lactate is, that the former have ability to prevent tissue acidosis, cell swelling, free radical damage and energy depletion, phenomena which occur during and after ischemia. The aim of this study was to evaluate Celsior for future use as hypothermic perfusion solution. Carotid artery segments were stored up to 14 days in Sodium-chloride 0.9%, University of Wisconsin, Histidine-tryptophane-ketoglutarate and Celsior solution. Celsior solution was found to be equally effective as University of Wisconsin solution and Histidine-tryptophane-ketoglutarate solution in preserving vascular smooth muscle and endothelial cell function for up to 3 days of hypothermic storage. During long-term preservation (7-14 days) University of Wisconsin solution was found to be superior than Histidine-tryptophane-ketoglutarate solution and Celsior solution.

In chapter 12, hypothermic perfusion was performed in the same model as described in chapter 9. Celsior solution was used as hypothermic perfusion solution and was compared to Ringer-lactate solution. University of Wisconsin solution was not used, because it has important disadvantages as a solution for in situ hypothermic perfusion. These disadvantages are high viscosity and high potassium concentration. In this study, the protective effect of in situ hypothermic perfusion during total vascular exclusion was confirmed. Furthermore, whereas no differences in parenchymal damage or microcirculatory disturbances were found, hypothermic perfusion with Celsior solution was more effective in reducing metabolic acidosis, restoring radical scavenging capacity and bile production and in maintaining coagulation capacity as compared to hypothermic perfusion with Ringer-lactate. Therefore, when applying in situ hypothermic perfusion in humans, Celsior solution is considered the preferred perfusion solution.
Future directions

While local ablative techniques such as radiofrequency ablation (RFA) or cryoablation are coming up as treatment options for selected patients with liver tumors, partial liver resection still remains the gold standard of therapy. As the indications for performing more extensive liver resections have increased, it is crucial to study methods to reduce the risk of postoperative morbidity and mortality, especially for patients with compromised liver function. Research is now continued to combine hepatobiliary scintigraphy with single photon emission computerized tomography. Using this combination, the future remnant liver can be more precisely characterized, measuring volume and function of the future remnant liver at the same time. This technique may prove especially useful in selecting patients who will benefit from portal vein embolization and in determining the time after portal vein embolization at which resection may be undertaken.

Exogenous alkaline phosphatase as well as other pharmacological interventions directed towards decreasing activation of coagulation and stimulating fibrinolysis, require further experimental studies. Animal models of hepatic ischemia and reperfusion as well as liver resection will be combined with bile duct ligation, to mimic the cholestatic patient with a proximal bile duct tumor requiring extensive liver resection.

Application of in situ hypothermic perfusion using Celsior solution in patients requiring prolonged vascular inflow occlusion is now ready for clinical assessment in extensive liver resections. Also a new organ preservation solution was developed in our laboratory, called Polysol. Experimental results in rat liver preservation studies are promising. Polysol may be especially valuable to apply as in situ hypothermic perfusion solution as it contains many nutrients and vitamins, while viscosity is low and Na and K concentrations are similar to plasma values.