Summary
General Conclusions, Discussion
and Future Perspectives
Summary Part 1

The first part of this thesis concerns the impact of blood loss and blood transfusion on short- and long-term outcome in liver resections.

After a general introduction in chapter 1, a review was presented in chapter 2 on studies focusing on blood loss and blood transfusion during liver surgery for the most prevalent malignant tumors of the liver and the relationship with postoperative outcome. In other fields of surgery, perioperative blood loss and transfusion have shown to have a negative impact on outcome. However, it has been debated whether this is due to a real cause-effect relationship or whether this is the result of more complicated surgery. The effect of blood loss and blood transfusion in resection of colorectal metastasis, hepatocellular carcinoma (HCC), and cholangiocarcinoma was separately described. Most studies were retrospective and have demonstrated a significant and clinically relevant association between blood transfusion and postoperative outcome, especially on postoperative infectious complications. Evidence on the effect of blood transfusion on tumor recurrence and long-term mortality is less clear and evidence varies depending on the type of malignancy. For early stages of HCC there is some evidence that blood transfusions may have an impact on tumor recurrence. However, no such effect could be demonstrated for later stages of HCC, colorectal liver metastasis, or cholangiocarcinoma.

In chapter 3 results of a Dutch national survey on the use of topical hemostatic agents in liver surgery were described. Worldwide an increase is seen in partial liver resections for primary or secondary hepatic malignancies. According to this survey among surgeons, topical hemostatic agents are frequently used not only to lower intraoperative blood loss or shorten time to hemostasis, but also with the aim to reduce resection surface-related complications, such as bile leakage, bleeding, and abscess formation. Fibrin sealants were most frequently used.

The subsequent chapter 4 provides a review of the literature on evidence of hemostatic and biliostatic capacities of different fibrin sealants in liver surgery. Fibrin sealants are topical hemostatic agents that are widely used in liver surgery. A systematic literature search was performed. Thirteen comparative fibrin sealant studies were selected. These studies have shown a reduced time to hemostasis when fibrin sealants were used. Only a few studies have been published that have focused on postoperative resection surface-related complications, such as bile leakage, bleeding, or abscess formation. In these studies there is no strong evidence that fibrin sealants reduce the incidence of bile leakage, or resection surface-related complications in general. These data suggest that fibrin sealants can be effective as an adjunct to achieve hemostasis but do not seem effective in avoiding resection surface-related complications during liver resections.

The aim of chapter 5 was to study the effect of prophylactic use of fibrin sealants on the liver resection surface. Results of a multicenter randomized clinical trial on the efficacy of fibrin sealants in reducing resection surface related complications after partial liver resections were described. Bile leakage, bleeding, and abscess formation are major resection surface-related complications after
liver resection. In 310 non-cirrhotic patients undergoing liver resection, we compared prophylactic application of fibrin sealant (156 patients) to the resection surface with no application of fibrin sealant (154 patients). The overall rate of postoperative resection surface-related complications was not different between the two groups. Bile leakage was detected in 14% of patients in the fibrin sealant group and in 14% of controls. The rate of reinterventions for resection surface-related complications and severity of complications did also not differ between the two groups. This randomized multicenter trial showed that prophylactic application of fibrin sealant at the resection surface after liver resections did not lead to a reduction in the incidence or severity of postoperative bile leakage or other resection surface-related complications.

**Summary Part 2**

The second part of this thesis focuses on blood loss and transfusion requirements in liver transplantation and the impact of blood loss and blood transfusion on short- and long-term outcome in liver transplantation.

**Chapter 6** provides a review of the literature of clinical and research developments which have contributed to a reduction in blood loss and transfusion requirements in liver transplantation. Blood loss during liver transplantation has long been recognized as an important cause of morbidity and, especially in the early days, also mortality. Blood transfusions are associated with an increased risk of postoperative complications, such as infections, pulmonary complications, delayed recovery, and a higher rate of reoperations. Many studies have been performed to elucidate the mechanisms of increased blood loss in liver transplantation. Several randomized controlled studies have shown effective strategies in reducing blood loss and transfusion requirements during liver transplantation. In addition, improvements in surgical technique, anesthesiological care, and better graft preservation methods have contributed to a steady decrease in blood transfusion requirements in most liver transplant programs. Several centers are reporting liver transplantation without any need for blood transfusion in up to 30% of their patients.

The study in **chapter 7** assessed the impact of transfusion of various blood products on outcome after orthotopic liver transplantation (OLT) in 433 adult patients. The proportion of patients receiving transfusion of any blood component decreased from 100% in the period 1989-1996 to 74% in the period 1997-2004. In uni- and multivariate analyses the indication for transplantation, transfusion of platelets, and RBC were highly dominant in predicting one-year patient survival. These risk factors were independent from well-accepted indices of disease, such as the MELD score and Karnofsky score. The effect on one-year survival was dose-related with a hazard ratio of 1.377 per unit of platelets ($P$ value =0.01) and 1.057 per unit of RBC ($P$ value =0.001). The main finding of this study was that, in addition to RBC, platelet transfusions are an independent risk factor for survival after OLT.

The subsequent **chapter 8** focuses on the specific causes of mortality and graft loss in relation to
platelet transfusions during OLT. In a series of 449 consecutive adult patients undergoing a first OLT we studied the causes of patient death and graft failure in patients who did or did not receive perioperative platelet transfusions. Patient and graft survival were both significantly reduced in patients who did or did not receive platelet transfusions (74% vs. 92%, and 69% vs. 85%, respectively at one year; \( P \) value <0.001). A significant higher early mortality rate due to acute lung injury was seen in patients who received platelet transfusions (4.4% vs 0.4%; \( P \) value =0.004). The main cause of graft loss in patients that received platelet transfusions was patient death with a functioning graft. These findings suggest that platelet transfusions are an important risk factor for mortality after OLT. The current study extends previous described observations by identifying acute lung injury as the main determinant of increased mortality.

In chapter 9 results of a retrospective study on a possible relation between blood transfusion and the incidence of acute rejection after liver transplantation were described. Blood transfusion is generally considered to be harmful, although in kidney transplantation early reports have suggested a protective effect of RBC transfusion on the incidence of rejection after kidney transplantation. Between 1995 and 2004, 292 primary liver transplantations in adults were performed. Specific reason to select this decade is that at that time it was our policy to perform a routine liver biopsy after OLT, if the clinical condition would allow this. All patients who underwent a biopsy within 2 weeks were included. Patients who died or were retransplanted <7 days after OLT were excluded. In total, 197 patients had a biopsy within 2 weeks after OLT. Fifty-nine (30%) patients did not receive any RBC transfusion during OLT. Sixty (31%) patients did not show any signs of acute rejection. Multivariate analysis for reduced risk of acute rejection (any Banff grade) revealed the following independent variables: intraoperative RBC transfusion and induction immunosuppression. This study suggests that there is an increased risk of developing acute rejection after OLT when patients do not receive any RBC transfusion during OLT.

In chapter 10 we studied the impact of extended criteria donor (ECD) liver grafts on intraoperative transfusion requirements during liver transplantation. The use of ECD grafts may reduce waiting list mortality in OLT. ECD livers, however, are associated with increased risk of graft failure and recipient morbidity. A consecutive series of 318 primary adult liver transplant recipients was analyzed. An ECD graft was defined as DRI ≥1.7. ECD livers were used in 115 (36%) recipients. In 95 (30%) of all transplant procedures there was no need for RBC transfusion. After uni- and multivariate analysis the following variables were found to be independently associated with post-reperfusion RBC transfusion requirements: DRI ≥1.7, female recipient, recipient age, and no aprotinin administration. The use of ECD grafts, defined as a DRI ≥1.7, was associated with significantly increased intraoperative RBC transfusion requirements after graft reperfusion.

In chapter 11, 3 appendices are added: appendix 1 contains the questionnaire used in chapter 3. In appendix 2 correspondence related to chapter 5 is described. In appendix 3 correspondence related to chapter 7 is described.

In chapter 12, the current chapter, the results of this thesis are summarized and discussed.
GENERAL CONCLUSIONS, DISCUSSION AND FUTURE PERSPECTIVES

PART 1 Blood transfusion in liver resection and the effect on short- and long-term outcome

1) Blood transfusions are an independent risk factor for postoperative morbidity and mortality in liver resections. There is limited evidence on the effect of intraoperative blood transfusion on oncological outcome in liver resections for hepatobiliary malignancies. (Chapter 2)

Improvements in surgical techniques used for hepatic resection and optimization of perioperative patient management have led to significant improvement in short- and long-term outcome. Despite these improvements blood loss during liver resection remains a problem that is usually treated with allogeneic red blood cell (RBC) transfusion. RBC transfusions have been identified as independent risk factor for postoperative morbidity and mortality after liver resections. In several cancers, like gastric, colon, lung, and soft tissue carcinomas, an adverse effect of RBC transfusion on tumor recurrence has been reported. In this review a similar adverse effect was described in liver resection studies in early hepatocellular carcinoma (HCC), but there was no such evidence in late stages of HCC, colorectal liver metastasis, or cholangiocarcinoma. Apart from the fact that there may not be an effect of RBC transfusion on long-term outcome in hepatobiliary malignancies, this lack of evidence may also be explained by several other factors like the retrospective design of studies, low patients numbers, high transfusion rates in previous studies, contradicting results between studies, the fact that long-term outcome is influenced by (stronger) tumor-related factors, and also heterogeneity of patient groups.

A more recent retrospective HCC study by Sugita et al. describes a significant worse cancer related survival and disease free survival in patients with tumors >5 cm who received intraoperative RBC transfusion, compared to patients who did not receive RBC transfusion (5-year cancer related survival 25.4% vs 68.5% and 5-year disease free survival 30.6% vs 0%). Furthermore, they describe a significant lower lymphocyte count 1 day after liver resection in patients who received RBC transfusions compared to the patients who did not (881/mm3 vs 1081/mm3). This effect was not seen on day 3 and 7. They suggest that the immunosuppressive effect of RBC transfusion influences residual HCC cells in the liver and does not so much influence multicentric cancer development. It's generally accepted that blood transfusions have an immunosuppressive effect. Although the exact underlying mechanism is unknown, several studies have suggested suppression of host immunity via a reduction in natural killer cells, cytotoxic T-cells, IL2 receptor-positive cells and helper T-cell function, and an increase in suppressor T cells. Many of these effects are thought to be related to the residual amounts of donor leukocytes within the stored blood as well as preservation-related changes in erythrocytes.

Nowadays blood transfusions in most developed countries are leukocyte depleted, posing the question whether part of the immunosuppressive effect of a blood transfusion is eliminated.

A few randomized studies in colorectal cancer have been performed that compare the long-term outcome and cancer recurrence after leukocyte containing (buffy coat depleted) RBC transfusions
with leukocyte depleted RBC transfusions. They found no difference in cancer recurrence at short-term and five-year follow-up.\textsuperscript{6-8} No such trials have been performed in hepatobiliary malignances. Other strategies to reduce risks of allogeneic transfusions are reducing storage time of blood and the use autologous blood transfusion. Methods for autologous blood transfusion include preoperative blood donation, intraoperative blood salvage using cell-saver techniques, or intraoperative normovolemic hemodilution. Although these methods seem promising, a matched pair analysis by Park et al. between allogeneic and autologous transfused patients in hepatectomy, did not show any benefit for autologous transfusions considering perioperative complications.\textsuperscript{9}

Intraoperative blood salvage autotransfusion (IBSA) during liver resection theoretically increases the risk of tumor cell dissemination. Based on this theoretical risk and one case report published in 1975,\textsuperscript{10} the American Medical Association Council of Scientific Affairs in 1986 recommended against the use of IBSA.\textsuperscript{11} In practice, a few studies have now shown that there may not be a risk but there may even be a benefit in the use of IBSA compared to allogeneic RBC transfusion.\textsuperscript{12-14} In this discussion the balance should be weighed between the risk of tumor recurrence by allogeneic transfusion by immunosuppressive effects and the risk of tumor cell spread by IBSA.

Normovolemic hemodilution is not common practice in our institution partly because of required training of the operating team but probably more important the lack of necessity with a transfusion incidence of around 10% in liver. For the future it might be interesting to develop a model that predicts the necessity of blood donation, like was described by Tomimaru et al. in liver resections for HCC.\textsuperscript{15}

Hemostatic agents

2) Topical hemostatic agents are used on a large scale in liver surgery. The most frequently used agents are fibrin sealants. These agents are not only used for hemostasis, but are also used with the aim to reduce resection surface-related complications. (Chapter 3) Several studies have shown a reduced time to hemostasis when fibrin sealants are used. There is no clear evidence in literature that fibrin sealants reduce resection surface-related complications. (Chapter 4) In a Dutch multicenter randomized controlled trial fibrin sealants did not reduce resection surface-related complications. (Chapter 5)

In liver surgery hemostatic agents can never replace meticulous surgical hemostasis, but can be used as an adjunct to achieve hemostasis. It seems a logical method to apply fibrin sealants (hemostatic agents that contain active components that mimic endogenous coagulation) as a fixing layer to the resection plane to reduce the risk of resection surface-related complications, like bile leakage, bleeding, or abscess formation. Studies show conflicting results when looked at the effect on resection surface-related complications. Most of the studies that show a positive effect of fibrin sealants on resection surface-related complications are not powered for this endpoint. With our study, now two large randomized controlled trials both do not show an effect of fibrin sealants on the incidence of resection surface-related complications.\textsuperscript{16,17} The answer to the question why fibrin sealants are not effective in reducing bile leakage may be derived from an in vitro study in
which the effect of bile on stability of fibrin clots was examined.\textsuperscript{18} Basically, this study shows that bile contains fibrinolytic activity (mediated by tissue-type plasminogen activator and plasminogen in bile) leading to premature lysis of fibrin clots. With this evidence we think we can state that there is no place for prophylactic use of fibrin sealants in liver resections.

Limitation of our randomized study is that we only investigated one fibrin sealant. These results cannot automatically be translated to other sealants. Although, based on minor differences in composition of commercially available fibrin sealants, we do not believe that the outcome would have been different with other fibrin sealants. Nevertheless, we did not compare fibrin sealants with newer, so-called carrier-bound fibrin sealants that consist of a solid matrix (e.g. collagen fleece) with an active hemostatic layer containing thrombin and fibrinogen. Again, a fibrin clot is formed on this matrix, which may be affected by the fibrinolytic capacity of bile, but we cannot draw these conclusions without new \textit{in vitro} and clinical evidence. So far only small series have been published on the efficacy of the carrier-bound fibrin sealants in liver surgery.\textsuperscript{19-21} Primary endpoint of two of these comparative studies (carrier-bound FS vs Argon and carrier-bound FS vs no treatment) focused on hemorrhage and not on bile leakage.\textsuperscript{19,20} In both studies bile leakage incidence did not differ between groups. The third study was a small comparative retrospective study on the incidence of bile leakage after split liver transplantation comparing a carrier-bound fibrin sealant with a fibrin sealant. This study describes a bile leak incidence of 6.3\% vs 43.7\%, but the groups were small containing only 16 patients per arm.\textsuperscript{21} Another combination of fibrin sealant with a matrix product called PGA (Polyglycolic Acid) felt shows promising results in the reduction of bile leakage.\textsuperscript{22,23} But again these studies were underpowered and not randomized.

So where do we go from here? The incidence of bile leakage should be reduced to the minimum. Bile leakage in liver resections is described in 1-14\% of the cases, leading to additional interventions, prolonged hospital stay, mortality and higher costs. Recently, a large retrospective study describing a consecutive cohort of 1001 liver resections without biliary reconstruction was published.\textsuperscript{24} The incidence of clinically relevant bile leakage was 8\%. Bile leakage was proved to have a significant negative impact on hospital stay (16 vs 9 days, \textit{P} value <0.001) and one-year mortality (11 vs 5\%, \textit{P} value =0.03). The incidence of bile leakage may be reduced by applying a bile leakage test,\textsuperscript{24-26} although this preventive effect is debated by Ijichi et al, who performed a randomized controlled trial on the effect of biliary leakage test on the incidence of bile leakage.\textsuperscript{25} They showed no difference in bile leakage in the group who had a bile leakage test compared to the group that did not get a bile leakage test during liver resection. Several authors describe independent risk factors for bile leakage mainly in large retrospective cohorts: advanced age,\textsuperscript{27} wide resection surface area,\textsuperscript{27} exposure Glisson’s sheath/ central resection/ S4 or S8 subsegmentectomy,\textsuperscript{27-29} bilioenteric anastomosis, preoperative chemotherapy,\textsuperscript{24} major hepatectomy,\textsuperscript{24} two stage hepatectomy,\textsuperscript{24} selective clamping technique,\textsuperscript{24} R1/R2 resection,\textsuperscript{24} and the absence of a bile leakage test\textsuperscript{24,26}.

In the future prevention of bile leakage requires a tailor made surgical strategy and research should
focus on the group of patients with increased risk of bile leakage. New large randomized studies powered for resection surface-related complications, or bile leakage only, are necessary in the field of carrier-bound sealants (whether they are ready-made or home-made). However, considering the fact that bile contains fibrinolytic capacities, a possible solution to the problem of bile leakage after liver resection may lie in the development of safe and ready to use synthetic sealants instead of fibrin sealants.

PART 2 Blood loss and transfusion requirements in liver transplantation and the impact of blood loss and blood transfusion on short- and long-term outcome in liver transplantation.

3) Surgical, pharmacological, and anesthesiological factors have led to a steady decrease in blood transfusion requirements in most liver transplant programs over the years. Several centers are now reporting liver transplantation without any need for blood transfusion in up to 30% of their patients. (Chapter 6) RBC and platelet transfusions are both independent risk factors for survival after OLT. (Chapter 7) Lower survival rates in patients who received platelets were attributed to a significantly higher rate of early mortality because of a higher incidence of acute lung injury. (Chapter 8)

In liver transplantation, extensive clinical and experimental research has led to the identification of independent risk factors and mechanisms of increased blood loss in patients undergoing OLT. Blood loss in OLT is influenced by multiple factors, such as preoperative condition, surgical technique, organ preservation, hemostatic disorders occurring during OLT, and anesthesiological care. Progress in these fields has led to a remarkable reduction in blood loss and thus transfusion requirements in OLT. Median intraoperative RBC transfusion requirement in adult patients who received a first liver transplant in our center declined steadily from around 20 units in the late 1980s to 2 units in the year 2003.

Our studies have shown that both intraoperative RBC and platelet transfusion are independent risk factors for survival after OLT. As previously described, blood transfusions have an immunosuppressive effect. Platelets seem to play a complicated role, not just being important in hemostasis but they also contain many cytokines and vasoactive and inflammatory mediators, which are rapidly released on activation, and which make platelet transfusions theoretically proinflammatory. Patients who received platelet transfusions suffered more from acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The adverse effect of platelet transfusion is due to a systemic response. Passive transfer of antileukocyte antibodies in plasma-rich blood products (like platelets) and accumulation of inflammatory mediators in stored platelets may lead to ALI or ARDS. It is not known whether leukocyte reduction techniques and reducing storage duration will eliminate the negative effects of RBC and platelet transfusion. Whether a potential negative effect of platelet transfusion can be attributed to the harvesting technique, a ‘one-donor’ pheresis technique versus ‘pooled-donor’ whole-blood technique (platelet-rich plasma or buffycoat based) remains to be debated.

Whether we can extrapolate the reduction in transfusion rate described in the previous decade to
the current situation remains a subject for research. The use of the antifibrinolytic agent aprotinin was stopped in 2007, because of market withdrawal after the publication of a large prospective observational study in cardiothoracic surgery by Mangano et al, and the BART study, which described an association between aprotinin and serious end-organ damage.\textsuperscript{33,34} The use of the antifibrinolytic drug aprotinin was first described by Neuhaus et al. in 1989.\textsuperscript{35} From then on aprotinin was almost routinely used in our institution. The efficacy of aprotinin in reducing RBC transfusion requirements by around 30\% during OLT has been proven by randomized placebo controlled studies.\textsuperscript{36,37} A retrospective study from our center shows that the proportion of patients without RBC transfusion decreased from 39\% in the aprotinin era (2000-2007) to 21 \% in the post-aprotinin era (2007-2013, $P$ value $<$0.001). The median amount of RBC transfusion increased from 2 (interquartile range $=$0-6) in the aprotinin era, to 4 units (interquartile range $=$1-9) in the post-aprotinin era ($P$ value $<$0.001). (Unpublished data F. Arshad) Since the withdrawal of aprotinin we have not routinely changed to the administration of tranexamic acid, another effective antifibrinolytic agent, even though previous studies have shown that tranexamic acid is comparable to aprotinin in terms of reducing blood loss and in terms of side effects.\textsuperscript{38,39} This may explain the difference with another recent retrospective cohort study, showing no difference in RBC transfusion after the withdrawal of aprotinin.\textsuperscript{40} In this study tranexamic acid was used after aprotinin withdrawal in 62\% of cases.

The reason not to change to routine use of another antifibrinolytic drug such as tranexamic acid in our institution can be explained by a growing awareness of the concept of ‘rebalanced hemostasis’ in cirrhotic patients. The average cirrhotic patient appears to be in a hemostatic balance with adequate hemostatic function despite abnormal coagulation tests.\textsuperscript{41,42} During OLT the balance may be turned to either hypocoagulation or hypercoagulation, making patients with cirrhosis both prone to bleeding as well as thromboembolic complications.\textsuperscript{42}

Although we have not found a clear relation between antifibrinolytic drugs and thromboembolic complications,\textsuperscript{43} it seems logical to only administer antifibrinolytic drugs when there are signs of hyperfibrinolysis during OLT. The best way to avoid blood loss and hemostatic imbalance during OLT is probably to obtain a fluid restrictive policy, because administration of fluids results in a further increase in portal and central venous pressure, which promotes bleeding during surgical exploration.\textsuperscript{41,44-46}

Furthermore, there is a growing sense that as transfusion requirements for liver transplantation continue to drop, and the number of patients transplanted without RBC transfusion increases, the balance between risks and benefits of antifibrinolytic therapy in OLT is changing. At many institutions there is a move away from routine use of antifibrinolytic agents to a more select prophylaxis or treatment only.

In a current multicenter randomized study we aim to investigate whether the preoperative administration of prothrombin complex concentrate, a low volume pro-hemostatic product, in cirrhotic patients undergoing liver transplantation, is a safe and effective method to reduce perioperative blood loss and transfusion requirements.\textsuperscript{47} Prothrombin complex concentrate (PCC)
Chapter 12

does not only contain procoagulant factor such as factor II, VII, IX, and X, but also contains protein C and S, which are critical anticoagulant proteins. This gives the theoretical advantage that PCC 'adds weight to both sides of the hemostatic balance'.

4) **There is an increased risk of developing acute rejection after OLT when patients do not receive any RBC transfusion during OLT. (Chapter 9)**

Anesthesiological and surgical improvements in liver transplantation have made it possible to perform liver transplantation without transfusion of blood products. Early reports in kidney transplantation have suggested a protective effect of RBC transfusion on the incidence of rejection. In our study we demonstrated after multivariate analysis that absence of intraoperative RBC transfusion was associated with an almost 3-fold increased risk for rejection at 2 weeks. We could not show any protective effect of preoperative RBC transfusion on the incidence of acute rejection as has been shown in kidney transplantation. The beneficial effect of RBC transfusion during OLT is offset by significant undesired side effects of RBC (and other blood product) transfusion. We and others have previously demonstrated that blood product transfusion during OLT is dose-dependently associated with morbidity and mortality. Since management of rejection after OLT is relatively easy, and as early clinical or subclinical rejection has no long-term adverse effects, we remain in favor of a restrictive transfusion policy during OLT as the benefits of RBC transfusion do not outweigh its detrimental effects. Nevertheless, it is important for clinicians to be aware of the elevated risk of rejection in those patients that do not receive intraoperative RBC transfusion. Those patients may require more intensive monitoring or a more aggressive initial immunosuppressive therapy.

5) **The use of extended criteria donor (ECD) grafts is associated with significantly increased intraoperative RBC transfusion requirements after graft reperfusion. (Chapter 10)**

In an era of increasing organ shortage, accepting ECD grafts seems a necessary way to reduce mortality on the waiting list in liver transplantation. In general, ECD grafts are considered to be organs with a higher risk of initial poor function or non-function and are associated with an increased risk of postoperative recipient morbidity and mortality. The results of our study indicate that the poor quality of the donor liver, as reflected by the donor risk index (DRI), has an impact on RBC transfusion requirements after graft reperfusion. There is no clear definition of the features of an ECD liver, but in general high donor age, high grade of steatosis, DCD (donation after circulatory death) grafts, partial grafts, or cerebrovascular cause of death are considered ECD criteria. Donor risk scores, such as the DRI, have been developed to quantify the risk associated with donor variables. In this study a DRI cut-off point of 1.7 was used to identify an ECD graft, as was previously done in a study by Maluf et al. Whether this is a right assumption may be a subject of debate.

Potential mechanisms for increased blood loss after graft reperfusion may be related increased ischemia-reperfusion injury in ECD grafts. Increased reperfusion injury is accompanied by a high
release of fibrinolytic proteins from the donor graft, which may contribute to excessive blood loss in the last phase of the operation.62,63

Focus of future research should lie in organ optimization and reduction of preservation-reperfusion injury. New strategies are the use of extracorporeal membrane oxygenation (ECMO) and normothermic regional perfusion in DCD donors.64,65 Ex-vivo pharmacological conditioning of the liver,66,67 or pharmacological conditioning in the recipient,68,69 have demonstrated efficacy in reducing ischemia reperfusion injury. But most exciting seems the regained interest in ex-situ machine perfusion (MP) techniques the last couple of years, which has now recently moved to the clinical setting. Advantages of MP over standard cold storage include continuous supply of metabolites and oxygen, washout of waste products, assessment of viability,70 and intraoperative therapeutic interventions. Only few clinical trials have been published on the use of MP in liver transplantation,71,72 but the first results are promising. No clinical trials on normothermic machine perfusion are published yet, but technically it is feasible.73 So far it is not clear what the optimal temperature is for MP, and there is a pressing need for multicenter clinical trials that can verify the early clinical experience with these new ex-situ MP techniques.
REFERENCES


Summary. General Conclusions, Discussion and Future Perspectives


52. Higgins RM, Raymond NT, Krishnan NS, et al. Acute rejection after renal transplantation is reduced by approximately 50% by prior therapeutic blood transfusions, even in tacrolimus-treated patients. Transplantation 2004;77:469-471.


Summary. General Conclusions, Discussion and Future Perspectives

193

Transplant Proc 2009;41:975-979.


