General introduction and outline of this thesis
Chapter 1

The liver and its role in hemostasis

The liver is a multifunctional, complex organ, playing a key role in metabolism of the human body. The liver plays a central role in hemostasis, being the producer of the majority of coagulation factors. In patients with liver disease the production of these coagulation factors can be reduced, which can lead to disturbed clot formation. On the other hand, the liver produces also many anticoagulant proteins such as antithrombin (AT), protein C and protein S, leading to a fragile, yet rebalanced hemostatic system in patients with severe liver disease. Operating a patient with end-stage liver disease is a challenge, because clotting disturbances and portal hypertension can lead to major blood loss. (Figure 1)

Figure 1: Example of severe blood loss during liver transplantation.

Liver resection in patients with a normal liver function can be complicated by major blood loss because the densely vascularized, soft structured parenchyma needs to be transected during resection. Nowadays both liver resection and liver transplantation are generally accepted methods to treat patients with liver tumors or patients with end-stage liver disease. Although Wendell described the first resection of the right side of the liver for a primary tumor in 1911, true anatomical right hemihepatectomy was first described in 1952 by Lortat-Jacob and Robert. The first liver transplantation was performed by Starzl in 1963. Unfortunately, this first patient died of hemorrhage, illustrating that blood loss during liver transplantation was one of the hurdles to take in improving outcome in liver transplantation in those early days. As in liver transplantation, hemorrhage was an important risk factor for mortality in the early days of liver resection. Ongoing improvements in surgical and anesthesiological techniques and postoperative patient management in liver resection and transplantation have led to a significant improvement in short- and long-term outcome. Despite
these improvements, even nowadays blood loss and blood transfusions remain independent risk factors for morbidity and mortality after liver resection\textsuperscript{7-10} and liver transplantation.\textsuperscript{11-13}

**Use of hemostatic agents in liver surgery**

Although topical hemostatic agents can never replace meticulous surgical hemostasis, they can be helpful when bleeding problems persist. Hemostatic agents can roughly be divided in matrix products, only providing a matrix to stimulate clot formation, and in active hemostatic agents. Active hemostatic agents consist of human or bovine derived coagulation factors, when locally applied they mimic clot formation or can help to stimulate clot formation.

**Outline of this thesis**

This thesis focuses on intraoperative blood loss and blood transfusion in liver surgery, and is subdivided in two parts. Part 1 evaluates the impact of blood loss and blood transfusion on short- and long-term outcome in liver resections. In this part the use and efficacy of hemostatic agents in liver surgery is also evaluated. Part 2 focuses on blood loss and transfusion requirements in liver transplantation and its impact on short- and long-term outcome after liver transplantation.

**PART 1 Studies on liver resection**

Since the first publication of a true anatomical right hemihepatectomy in 1952, the subsequent early experience in hepatic resections has been discouraging. In major hepatectomy mortality was reported to be over 20\% in a retrospective series of 621 liver resections.\textsuperscript{5} Death was attributed to hemorrhage in 20\% of these cases. Over the years outcome has improved by evolution in surgical and anesthesiological techniques and better understanding of segmental liver anatomy. Nowadays major liver resections can be performed with a mortality rate below 5\% in specialized centers, even though the indications have been extended also to high-risk patients.\textsuperscript{6} Liver resection has now been accepted as the standard treatment for most liver tumors. In 2004, Poon et al have described a gradual reduction in the percentage of transfused patients from around 90\% in 1989 to 5\% in 2003 in a series of 1,222 consecutive liver resections.\textsuperscript{6} Despite these improvements blood loss remains an important predictor of both perioperative morbidity and mortality after liver resection.\textsuperscript{9,10} Chapter 2 provides a review of the literature on the impact of blood loss and blood transfusion on postoperative and oncological outcome in liver resections for hepatobiliary malignancies. Blood loss in liver resection is mainly related to the technical difficulty to transect the liver parenchyma, which makes blood transfusion sometimes inevitable. Several techniques can be applied to reduce blood loss: reduction of the central venous pressure (CVP), vascular occlusion techniques, and the choice of the device to transect the parenchyma. Besides these techniques several topical agents have been developed to improve hemostasis on the resection surface. The purpose of Chapter 3 is to describe the use of topical hemostatic agents during liver resections in the Netherlands and to describe when and for which purpose these agents are used.
Topical hemostatic agents are not only used to achieve hemostasis but are also used with the aim to reduce postoperative resection surface-related complications, such as bile leakage. In **Chapter 4** a study is described in which the evidence for hemostatic and biliostatic capacities of different fibrin sealants in liver surgery is assessed through a review of the literature. In **Chapter 5** the effect of prophylactic use of fibrin sealants on the liver resection surface is described in a prospective randomized controlled study including 310 patients.

**PART 2 Studies on liver transplantation**

After reporting the first successful liver transplantations with prolonged survival in 1968 by Starzl et al., liver transplantation was considered a possible, but hazardous treatment for end stage chronic liver failure. Many hurdles towards successful liver transplantation have been overcome over the last decades. The introduction of cyclosporine in the early 1980s and development of the University of Wisconsin preservation solution in the late 1980s were important steps in improving outcome after liver transplantation. However, high morbidity and mortality rates kept being reported, frequently related to high intraoperative blood loss and transfusion requirements. In **Chapter 6** techniques and developments are described which have contributed to an impressive reduction in blood loss and transfusion requirements in liver transplantation over the years.

It is well known that blood transfusions have an immunosuppressive effect, which may play a role in the negative correlation between the amount of intraoperative blood transfusion and postoperative outcome in liver transplantation. In **Chapter 7** the impact of transfusion of different blood products on graft and patient survival after liver transplantation was assessed retrospectively. **Chapter 8** focuses on the influence of platelet transfusion on short term outcome after liver transplantation. Nowadays several centers describe liver transplantation without the need for blood transfusion in 26 up to 80% of cases. Given the immunosuppressive effects of blood transfusion, this raises the question whether patients who did not require any blood transfusion have an increased risk of developing acute rejection. In **Chapter 9** the relation between blood transfusion and the incidence of acute rejection after liver transplantation is evaluated.

In an era of organ shortage expanding the donor pool by accepting extended criteria donor (ECD) grafts is a way to reduce waiting list mortality. Aim of **Chapter 10** is to determine the impact of implantation of ECD grafts on intraoperative blood transfusion requirements during liver transplantation.

**Chapter 11** consists of 3 appendixes. Appendix 1 is the dutch questionnaire used for the analysis in Chapter 3; Appendix 2 are letters to the editor and reply, related to Chapter 5; Appendix 3 is a letter to the editor and reply, related to Chapter 7.

In **Chapter 12** the previous chapters are summarized and discussed in a broader perspective. Finally, this chapter provides directions for future research.
The aims of this thesis were to study:

1. The impact of blood loss and blood transfusion on postoperative and oncological outcome in liver resections for hepatobiliary malignancies.
2. The use of topical hemostatic agents during liver resections in the Netherlands and describe when and for which purpose these agents are used.
3. The evidence for hemostatic and biliostatic capacities of different fibrin sealants in liver surgery.
4. The effect of prophylactic use of fibrin sealants on the liver resection surface in a multicenter prospective randomized controlled study.
5. Techniques and developments which have contributed to an impressive reduction in blood loss and transfusion requirements in liver transplantation over the years.
6. The impact of transfusion of different blood products on graft and patient survival after liver transplantation.
7. The influence of platelet transfusion on short term outcome after liver transplantation.
8. The relation between blood transfusion and the incidence of acute rejection after liver transplantation.
9. The impact of implantation of ECD liver grafts on intraoperative blood transfusion requirements during liver transplantation.
REFERENCES


Part I. Studies in liver resection