Transplantation of extended criteria donor livers

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Chapter I

General Introduction and Aims of this Thesis

Orthotopic liver transplantation is the only available life-saving treatment for patients with end-stage liver disease. Unfortunately, the number of organs required for transplantation greatly outnumbers the available donors, leading to strict selection criteria for transplant candidates and long waiting lists for those patients that reach candidate status. As a result of this shortage about 40 patients die yearly in the Netherlands while they are on the liver waiting list[1] However, the magnitude of the shortage of donor livers is underestimated when only waiting list mortality is considered. For example, in the United States about 60,000 people annually die of liver disease according to death certificates of whom many (theoretically) could have been treated with a liver transplant.[2] In fact, only about 1.5% of liver disease-related mortality is accounted for by waitlisted patients.[3]

The transplant community is forced to push the boundaries for transplantation to increase the number of donor organs available. Criteria for donor liver selection have been continuously extended, which has resulted in a steady increase in the use of suboptimal or compromised grafts. Livers from donors that fall outside of standard criteria are known as 'extended criteria donors' (ECD) and are increasingly considered for transplantation during the past decades.[4] For instance, 30% of transplanted livers in the Netherlands are now procured from donation after circulatory death (DCD) donors.[1] In the United Kingdom this percentage is even higher with 42% DCD liver transplantation.[5] Other important criteria of which the limits have been stretched in the past include donor age, steatosis, blood type ABO incompatibility, and infectious diseases in the donor.[6,7] The number of transplantable donor organs has significantly increased in the past two decades along with the increased transplantation of livers from ECD.[8,9]

Currently, the survival rate after transplantation of DCD liver grafts is similar to that of transplantation of donation after brain death (DBD) liver grafts.[8,10-12] However, transplantation of DCD liver grafts is associated with an approximately 10% lower 1-year graft survival rate compared to DBD livers and an evidently higher incidence of biliary complications such as non-anastomotic biliary strictures (NAS).[13-16] NAS are also known as ischemic-type biliary lesions or ischemic cholangiopathy. In general, these three names refer to the same clinical entity characterized by narrowing and dilatations of the larger intra- and extrahepatic donor bile ducts (or even intraparenchymal bile leakage), in the presence of a patent hepatic artery, either with or without intraluminal sludge and cast formation. The incidence of NAS can be as high as 30-50% after transplantation of DCD liver grafts, but varies between 4% and 15% after transplantation of DBD livers.[16,17] The severity and location of NAS along the biliary tree may differ considerably between patients and clinical symptoms vary from no symptoms to jaundice, life-threatening cholangitis, biliary cirrhosis, or need for retransplantation.[18] The occurrence of NAS significantly impacts the patient's long-term survival rate, incidence of retransplantation, quality of life and costs of health care.[19,20]

However, it is not the question whether or not to transplant ECD livers as these grafts are immediately needed at present to increase the pool of potential donor livers. The aim of this thesis is to assess strategies to further improve the outcome of liver transplantation with ECD grafts. The aim of the first two chapters of this thesis is to assess whether specific subgroups of ECD liver grafts

can be identified with acceptable outcome and cost-effectiveness.

The ECD liver grafts with an increased risk of NAS would benefit from protective methods against the development of NAS. Machine perfusion is a promising technique that has gained renewed interest in the past decade as a tool to optimize livers for transplantation. The aim of the chapters 4 through 8 is to assess the role of machine perfusion as a strategy to improve transplantation of ECD liver grafts by reducing the risk of NAS.

As mentioned before, adult DCD liver grafts are an accepted important source of liver grafts, despite less favorable outcome compared to adult DBD liver grafts.[8,10-16] The implementation of DCD programs in adults has substantially increased the total number of available livers and thereby reduced waiting list mortality.[21-23] Similar to the adult DCD program, a pediatric DCD program may be able to increase the number of donated pediatric livers with 13% to 80%.[24] However, in contrast to adult grafts the outcome of liver transplantation with pediatric DCD grafts has only been scarcely studied. Only three single center reports are available on a total number of ten cases of pediatric DCD liver grafts.[25-28] The aim of the study described in **chapter 2** is to assess the long-term outcome of liver transplantation with pediatric DCD liver grafts in a large retrospective cohort study and to compare the outcome with that of pediatric DBD liver grafts in the same time period, including graft survival, patient survival and incidence of NAS.

The outcome and complication rates in ECD liver transplantation have been extensively studied, while the financial impact of ECD liver transplantation have only been investigated for one type of ECD liver: the DCD liver.[29-30] The costs were found to be about 110 to 126% higher for DCD liver transplantation compared to DBD liver transplantation.[31-34] However, the quality of a DBD grafts can vary substantially and DBD grafts may also belong to the group of ECD grafts. The aim of study presented in **chapter 3** is to assess the financial impact and clinical outcome of transplantation of high risk DBD liver grafts in a prospective, observational, multicenter study.

Machine perfusion is a dynamic preservation method aiming to assess and improve organ viability. Especially organs from ECD can benefit as they suffer increased ischemic injury after revascularization[35-37], resulting in an increased risk of graft dysfunction and graft failure.[30,38] Machine perfusion has been used increasingly in the clinical setting in the past decade and has been shown to decrease post-transplant dysfunction and complications.[39-44] However, the impact of machine perfusion on ischemic injury of the bile ducts and biliary complications has been underexplored. **Chapter 4** provides an overview of the current and emerging insight into the pathogenesis of NAS and the effect of machine perfusion on bile duct injury and incidence of NAS. Moreover, different modalities of machine perfusion and various endpoints for assessment of the biliary tree in the setting of machine perfusion are presented.

There is a wide variety of machine perfusion modalities with different settings including timing, temperature, pressure, and fluid type. Experimental studies have suggested that end-ischemic hypothermic machine perfusion may reduce ischemia-reperfusion injury and restore hepatocellular energy status.[45-51] Guarrera *et al* and Dutkowski *et al* have successfully transplanted ECD liver

grafts after end-ischemic hypothermic machine perfusion.[39-42] While Guarrera *et al* did not apply active oxygenation, Dutkowski *et al* only perfused via the portal vein. However, it is well known that oxygenation has beneficial effects[50-52] and blood supply to the bile ducts is largely dependent on the hepatic artery.[53] Dual hypothermic oxygenated machine perfusion (DHOPE) combines the advantages of the two techniques mentioned above: active oxygenation and perfusion via both the portal vein and hepatic artery. In experimental and preclinical studies, DHOPE has demonstrated its promising effects.[48,54] The aim of the phase-1 prospective case-control clinical study described in **chapter 5** is to assess the safety and feasibility of DHOPE in DCD liver transplantation.

A known risk factor for NAS is the ischemic period during transplantation leading to a cascade of effects known as ischemia-reperfusion injury.[37,55-57] Such injury to the bile ducts at the time of transplantation has been associated with the development of NAS after transplantation.[58-60] The aim of the study presented in **chapter 6** is to assess whether DHOPE reduces the degree of ischemia-reperfusion injury of the bile ducts in the phase-1 study described in chapter 5.

The excellent results in experimental studies of end-ischemic hypothermic machine perfusion have led to its application in clinical setting of liver transplantation in hospitals in New York, Zurich, Torino, and Groningen (see chapter 5).[39-42,61-62] These first clinical experiences have shown that the preservation method is safe, feasible, and attenuates ischemia-reperfusion injury as reflected by a reduction of postoperative serum markers of liver injury and a reduced degree of bile duct injury (chapter 5 and 6). Furthermore, fewer complications such as NAS and shorter hospital stay were observed compared to a retrospective control group of patients receiving a liver preserved with SCS alone.[39-42,62] Although the results of these studies are promising, they were studies with relatively small cohorts and without a randomized control group. **Chapter 7** describes the study protocol of an ongoing randomized controlled trial which aims to determine the efficacy of DHOPE in DCD liver transplantation in reducing the incidence of NAS.

Along with the increasing number of ECD organs used for transplantation, the clinical application of machine perfusion has come to play a central role in organ transplantation.[63] In **chapter 8** the technical development and construction of an organ preservation and resuscitation (OPR) unit is described which aims to facilitate machine perfusion of lungs, livers, and kidneys at a clinical level.

In **chapter 9** the results of this thesis are summarized and discussed, followed by future perspectives. Finally, this thesis is concluded with **chapter 10** by means of a Dutch summary.

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