HETEROTOPIC AND ORTHOTOPIC LIVER TRANSPLANTATION IN MAN

studies on outcomes and predictive models

S. de Rave

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HETEROTOPE EN ORTHOTOPE LEVERTRANSPLANTATIE BIJ DE MENS

onderzoeken naar uitkomsten en voorspellende modellen

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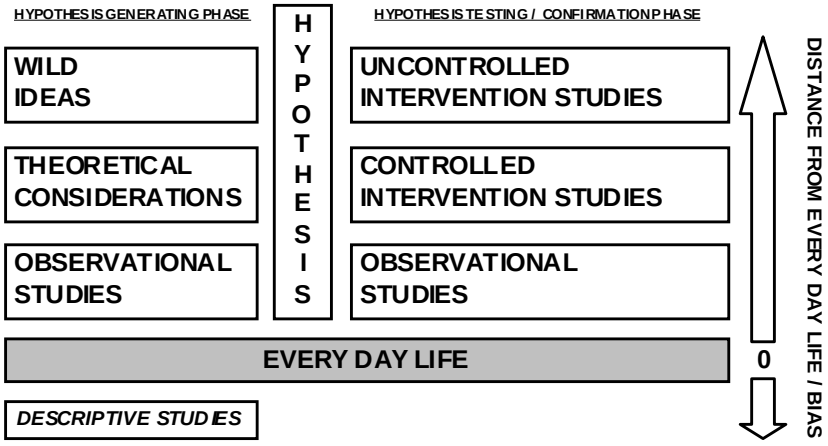
CHAPTER 1

INTRODUCTION

S. de Rave

The foundation of modern basic science is formed by the building of models that mimic the events we can observe in the real world, and can be used to make new and testable predictions. Biomedical research only partly follows this pattern. In clinical studies it usually is impossible to construct models that behave like they should, and here a different route is commonly taken (figure 1). Hypotheses are central in this alternative strategy. They can arise as wild ideas, from theoretical considerations or from the world as we observe it. This hypothesis generating phase is followed by a hypothesis testing phase.

Figure 1: The scientific process in clinical research.



Hypothesis testing studies can take the form of uncontrolled intervention studies, controlled intervention studies or observational studies. These same study types play a role in the final confirmation phase. Many clinical studies are of the hypothesis-testing and hypothesis-generating kind at the same time, although this usually is not explicitly stated. How well these studies reflect what happens in the real world depends on the non-randomness of the sample selected for study and on the objectivity of researchers, reviewers and editors, factors generally referred to as bias.

Various forms of bias operate at the level of the study itself, for instance selection-bias and investigator-bias. Bias can also operate at other levels. One example is publication-bias, caused by the reluctance of authors and journals alike to publish negative results. The bottom line is that no matter how many measures are taken to prevent bias, clinical studies will never reflect what happens in the "real" world with 100% accuracy. Purely

observational studies, if properly conducted, probably come closest to this ideal. Descriptive studies are different in that they are not studies at all, but merely descriptions. They can, however, lead to the generation of hypotheses.

When these ideas are applied to the eight papers in the following five chapters, three fall in the category of descriptive studies, three are mainly hypothesis generating observational studies and two are hypothesis testing observational studies. All papers deal with clinical aspects of liver transplantation. First an outline of the Rotterdam liver transplantation program, that has generated all of the data reported in this thesis is given in chapter 2. The next part concentrates on what happens during the period between enlistment for liver transplantation and the operation itself, and on the survival after transplantation.

In chapter 3a simplified model predicting survival on the waiting list for liver transplantation is proposed. The effect of patient selection on the outcome of transplantation for cholestatic liver disease is described in chapter 3b. Two different techniques for transplantation are compared in chapter 4. Acute liver failure as specific indication for transplantation is the subject of chapter 5. Finally acute rejection of the graft, one of the frequent complications after liver transplantation, is studied in chapter 6. A separate chapter is devoted to a summary of what we can learn from the Rotterdam program and, last but not least, what still needs to be done.

Medical science is a work in progress. There is much we simply don't know, and much of what we do know probably will no longer be relevant or even true at some point in the future. Both the fact that only just over half of the studies in this thesis potentially contribute to our current knowledge and the finite half-life of truth in medicine urge against exaggerated claims based on these studies. On the other hand, purely clinical studies form only a minority of the publications in biomedical journals, even though they are the most important guides for everyday medical treatment decisions. In short, the value of the studies in this thesis should neither be overestimated nor underestimated. Whether there is any real truth in them can only partly be determined at present.

CHAPTER 2

TWO DECADES OF LIVER TRANSPLANTATION IN ROTTERDAM, 1985-2004:

A DESCRIPTIVE STUDY FOCUSSING ON LIVER TRANSPLANTATION CANDIDATES

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SUMMARY

Background The moment of reperfusion is the starting point of most studies on liver transplantation. However, prior to this moment important decisions in patient care have to be made. In order to identify the problems arising at each stage of the liver transplantation process, both before and after the operation, we performed a cohort study on all patients referred to our centre from the start of the liver transplantation program in 1986 through 2002. We focussed on patient selection and treatment outcomes.
Patients and methods During the study period 940 patients were referred for liver transplantation. All data were retrieved from an existing electronic database and from patient files. Referral was for acute liver failure in 143, cirrhosis in 597, hepatocellular carcinoma in 110 and other diseases in 90. Decisions and outcomes were tabulated for different groups. Survival was calculated according to the Kaplan-Meier method. For comparisons logistic regression analysis and Cox regression analysis was used.
Results The yearly number of referred patients has risen from 10 in 1986 to 107 in 2002. No indication for transplantation was present in 29% of the patients and contraindications in 20%. There were 9% deaths without transplantation and 37% of the referred patients were transplanted. The waiting time has increased to a median of 260 days over the same time period, with a concomitant rise in waiting list mortality and in the number of patients removed from the list because of tumour progression or other reasons from 8% in the period 1986-1995 to 25% in 2001 and 27% in 2002. After transplantation for acute liver failure a 5-year survival of 66% was found. In the chronic liver disease group the 5-year survival ranged from 71% for patients with cholestatic liver disease to 31% for patients with hepatocellular carcinoma. The incidence of early acute rejections declined from 40% to 18% after the introduction in 1998 of interleukin-2-receptor blocking agents as part of the primary immunosuppressive regimen.
Conclusions In this descriptive study on a large single-centre cohort of liver transplantation candidates several points emerge. On the positive side are the results in patients with acute liver failure and chronic cholestatic liver diseases. On the other side there are some problems that require more attention. The main one is the waiting list policy.

INTRODUCTION

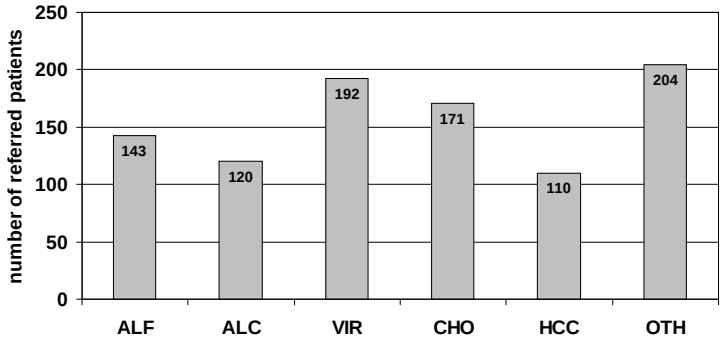
For most studies on liver transplantation the time of enlistment or of the operation is the starting point. However, important decisions on patient management also have to be taken prior to enlistment. Descriptions of transplantation candidate cohorts are available from the Netherlands, from the United States, from France and from the United Kingdom[1-9], but most deal with alcoholic liver disease. After several years of preparation, in 1986

a clinical liver transplantation program was started in Rotterdam. It began as a program of heterotopic liver transplantation, but since 1991 only orthotopic liver transplantations have been done. From the outset, data on all patients referred for liver transplantation have been recorded. Here we describe the patients referred to our centre for liver transplantation between 1986 and 2002, the treatment decisions in this patient group and the outcomes in various subgroups. This study was aimed at identifying problems arising at all stages of the liver transplantation process.

PATIENTS AND METHODS

Study population All consecutive patients referred for liver transplantation from 1986 through 2002 were included in this study. Our criteria for transplantation were published in 1998[10] (table 1). These guidelines have also been followed in previous years. Data were collected from our liver transplantation database and from patient files. Follow-up was complete until December 31, 2004. Until the end of 2002, 940 candidates for transplantation have been evaluated (figure 1). The reason for referral was

Figure 1: primary indications in patients referred for liver transplantation



see text for abbreviations

acute liver failure (ALF) in 143 patients (15%). Of the 797 patients referred for transplantation on an elective basis (ELE), 120 (15%) had alcoholic cirrhosis (ALC), 192 (24%) chronic viral hepatitis (VIR), 171 (21%) cholestatic liver disease (CHO), 110 (14%) hepatocellular carcinoma (HCC), and 204 (26%) a variety of other liver diseases (OTH).

Statistics Survival was calculated according to the Kaplan-Meier method. For comparisons between groups Fisher's exact test, logistic regression analysis and Cox regression analysis were used.

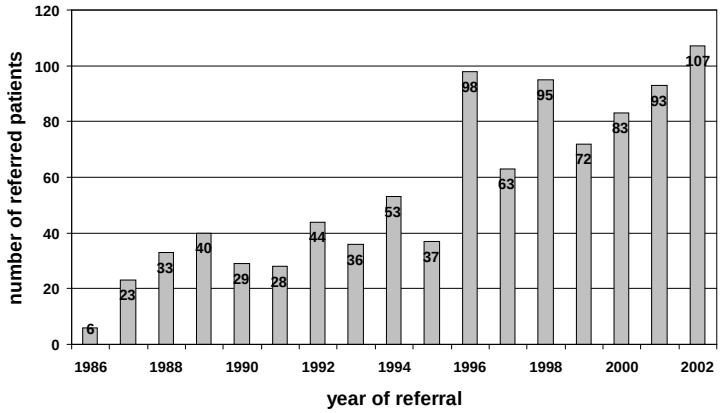
Table 1: Indications and contraindications for liver transplantation according to the Dutch protocol for adult patients, revised version 2002.

INDICATIONS		
Acute liver failure	Hepatitis B	Encephalopathy grade III or IV and Factor 5 < 20% (age ≤ 30 years) Factor 5 < 30% (age > 30 years)
	Paracetamol	Arterial pH < 7.30 or all 3 criteria: Encephalopathy grade III or IV Prothrombin time > 100 sec. / INR > 6.5 Creatinine > 300 μmol/l
	Other causes	Prothrombin time > 100 sec. or 3 of 5: Interval jaundice – encephalopathy > 7 days Age < 10 or > 40 years Prothrombin time > 50 sec. / INR > 3.5 Bilirubin > 300 μmol/l Cause non-viral or unknown
Chronic liver disease	Cirrhosis	Child-Pugh score ≥ 9 or ≥ 7 if Low quality of life or progressive disease
	Metabolic	Life-threatening complications
	Polycystic	Low quality of life
Liver tumors	Hepatocellular Carcinoma	Single tumor ≤ 5 cm or Two tumors ≤ 3 cm
	Other types	Hemangioendothelioma APUDoma
Contraindications		
Absolute	Systemic extrahepatic infections Extrahepatic malignancy (if not definitely cured) Irreversible brain damage Irreversible multi-organ failure Substance abuse (if not abstinent for ≥ 6 months)	
Relative	HIV seropositivity Age ≥ 65 years Mental incapacity Extrahepatic disease limiting the chance of survival Residency outside the Netherlands (unless emergency)	

RESULTS

Indications and contraindications for transplantation The number of patients referred for liver transplantation has gradually risen from six in 1986 to 107 in 2002 (figure 2). The proportion of patients in whom transplantation was not indicated because of the availability of an alternative form of treatment was 29% on average and varied from 15 % in

Figure 2: yearly number of patients referred for liver transplantation



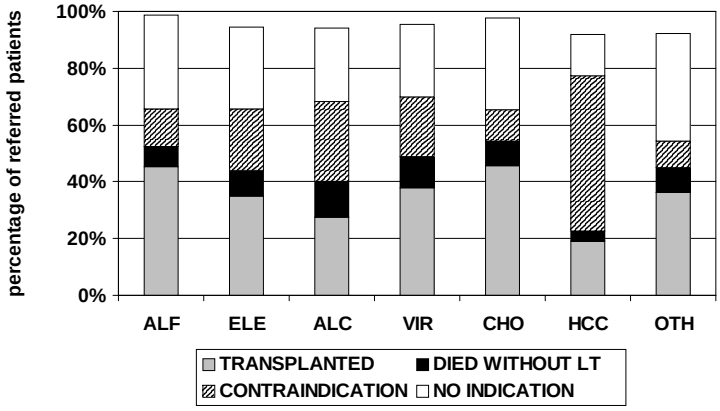
the HCC group to 38% in the group with other liver diseases. Contraindications were found in 20% of patients overall, ranging from 9% in the other liver diseases group to 55% in the HCC group. A treatment decision could not be made prior to death in 4% of patients, and 5% died on the waiting list. The sum of these two figures gives 9% as the overall mortality without transplantation, with a high of 13% in the alcoholic cirrhosis group and a low of 4% in the HCC group. Eventually, 37% of the patients were transplanted, the lowest proportion (19%) in the HCC group and the highest (46%) in the cholestatic liver disease group (table 2).

Table 2: Numbers and proportions of patients with different liver diseases referred for liver transplantation, enlisted and transplanted, 1986-2002

	Referred	**Enlisted**	**Transplanted**
Total	940 (100%)	416 (44%)	344 (37%)
Acute liver failure	143 (100%)	72 (50%)	65 (45%)
Alcoholic cirrhosis	120 (100%)	44 (37%)	33 (28%)
Chronic viral hepatitis	192 (100%)	94 (49%)	73 (38%)
Chronic cholestatic liver disease	171 (100%)	91 (53%)	78 (46%)
Hepatocellular carcinoma	110 (100%)	32 (29%)	21 (19%)
Other liver diseases	204 (100%)	83 (41%)	74 (36%)

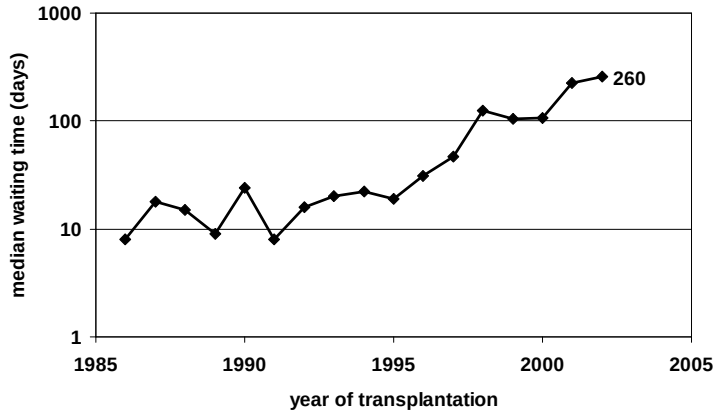
Other outcomes were recorded for 5% of all patients, these either refused transplantation, were referred to other centres or were still waiting on December 31, 2004, the closing date of this study (figure 3).

Figure 3: outcomes in liver transplantation candidates according to primary indication



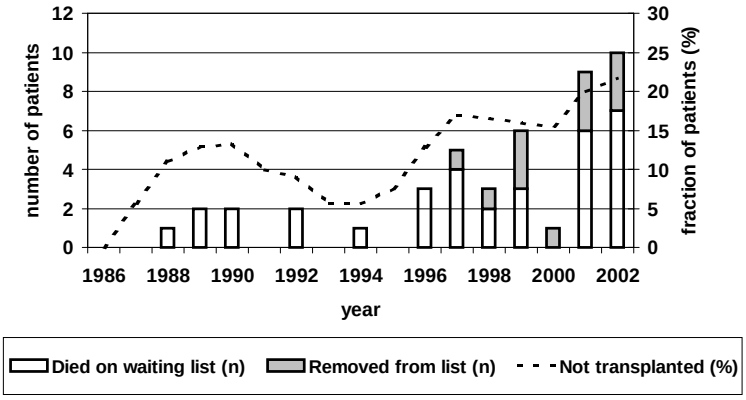
Waiting time and waiting list events The overall median waiting time for elective transplantations has risen exponentially since the early nineties,

Figure 4: median waiting times according to year of transplantation



reaching 260 days in 2002 (figure 4). This was due to a rise in the yearly number of patients enlisted from 2 in 1986 to 63 in 2002, without a concomitant increase in the number of donor organs. There are differences between blood groups, but the trend remains the same. Deaths on the waiting list were infrequent until 1995, with a mean of 0.8 per year. From 1996 onwards the incidence has risen to 6 in 2001and 7 in 2002. In the same period an increasing number of HCC patients had to be removed from the waiting list because of tumour progression. The proportion of patients from all diagnostic categories enlisted for elective liver transplantation that could not be transplanted was 8.2% between 1986 and 1995, and rose to 25.0% in 2001 and 26.3% in 2002 (figure 5).

Figure 5: dropouts from the liver transplantation waiting list

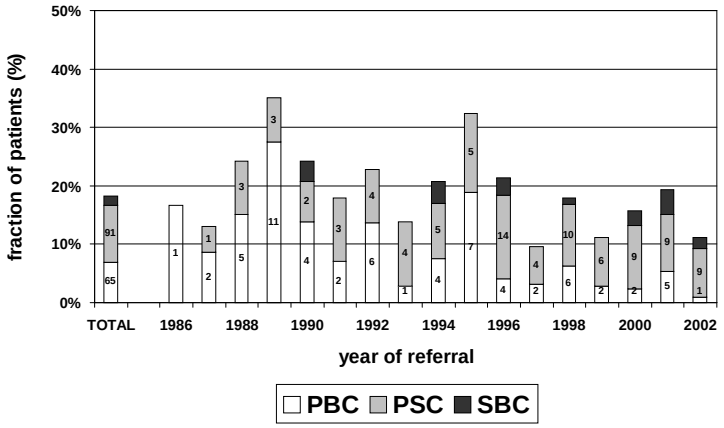


Heterotopic liver transplantation Between 1986 and 1990 23 heterotopic liver transplantations were performed in 21 patients. The survival at 1, 2 and 5 years after heterotopic transplantation for chronic liver disease was 71% (95% CI 43% to 87%), 53% (95% CI 28% to 73%) and 24% (95% CI 7% to 45%), respectively[11]. There were three patients in this category who survived for more than 10 years[12]. Four patients underwent heterotopic transplantation for acute liver failure, including one with acute on chronic liver failure. In this group there was one long-term survivor whose own liver regenerated so she could be taken of immunosuppressive drugs[13]. The other three patients all died in the early postoperative period.

Cholestatic liver disease Primary Biliary Cirrhosis (PBC), Primary Sclerosing Cholangitis (PSC) and a small number of other cholestatic liver diseases formed the third largest category in our series, and accounted for

171 (18%) of the 940 referrals for liver transplantation. This fraction has declined somewhat over time (figure 6), due to a lower number of patients

Figure 6: yearly number and fraction of patients with cholestatic liver diseases referred for liver transplantation



with PBC referred after 1995. From 1986 through 1995 patients with PBC contributed 13% to the total of referred patients against 4% in later years, while the contribution of patients with PSC remained constant at around 10%. There were 55 patients in this group that did not meet our minimum criteria for enlistment. Contraindications were found in 17 patients, 3 were referred to other centres and 5 died during the work-up for transplantation. We enlisted 91 patients, 10 of these died, 2 were removed from the waiting list because new contraindications emerged, 1 was still waiting at the closing date of the study, and 78 were transplanted. The survival at 1, 2 and 5 years after transplantation in this patient category was 78% (95% CI 67% to 86%), 74% (95% CI 63% to 82%) and 71% (95% CI 59% to 80%), respectively.

Hepatocellular carcinoma The proportion of patients with hepatocellular carcinoma among those referred for liver transplantation was 13% overall, with a peak at around 25% in the early nineties, and a decline to around 10% later on. The tumours were considered to be inoperable in 52 (47%) of the 110 patients referred for hepatocellular carcinoma, 16 (15%) were offered partial hepatectomy and 32 (29%) were enlisted for transplantation. Of the remaining 10 patients 5 refused transplantation, 4 were referred to other centres and 1 died during the work-up for transplantation. Of the 32 enlisted patients, 3 died while on the waiting list, 7 had to be removed from the list because of tumour progression and 1 emigrated before she could

be transplanted. Eventually, liver transplantation was performed in 21 (19%) of the patients. The 1-year survival in the transplanted group was 81% (95% CI 57% to 92%), the 5-year survival was 31% (95% CI 13% to 51%). When we assume that the nine patients removed from the waiting list because of tumour progression died within six months, the 5-year survival calculated on an intention-to-treat basis was 22% (95% CI 9% to 38%). There were 10 deaths at more than 1 year after transplantation, all caused by tumour recurrence. Hepatocellular carcinoma presumably was the cause of death in 20 of the 32 patients enlisted for liver transplantation because of this tumour. In contrast, 17 previously undetected tumours were found during the waiting time or in explanted livers of patients with other indications, and only one of these 17 patients died of tumour recurrence.

Acute liver failure Between 0% and 30% of the yearly total number of patients in the period from 1986 to 2002 was referred for acute liver failure, with a mean of 15%. Of the 143 patients, 3 died before the indication for transplantation could be established and 47 did not meet the criteria for transplantation. Transplantation was refused in one case, and one patient was referred to another centre. Absolute contraindications were present in 19 patients. Of the 72 patients that were enlisted 7 died and 65 were transplanted. The 1-year survival after transplantation was 69% (95% CI 56% to 79%). Survival at 2 years was 68% (95% CI 55% to 78%) and at 5 years 66% (95% CI 53% to 76%). When calculated on an intention-to-treat basis the 1-year survival was 63% (95% CI 50% to 73%). Transplantation improved the survival of enlisted patients, but significance was not reached (relative risk of death after transplantation 0.50, 95% CI 0.13 to 1.99, P=0.33, Cox analysis with transplantation as time-dependent factor).

Acute rejection The overall incidence of acute rejection during the first 3 months after liver transplantation in our patients was 31% (95% CI 26% to 36%), with a peak at day 7. In the 155 patients treated with Interleukin-2 Receptor Blocker's (IL2RB's) it was 18% (95% CI 13% to 26%), versus 40% (95% CI 33% to 47%) in the 212 others (hazard ratio 0.37, 95% CI 0.24 to 0.57, P<0.001, Cox regression analysis). In a preliminary univariate Cox analysis with acute rejection as time-dependent factor there was no effect on overall mortality (HR 1.15, 95% CI 0.76 to 1.72, P=0.509). Deaths between 10 and 182 days after transplantation were due to infections in 36 (84%) out of 43 patients, contrary to earlier (9%) and later (23%) periods. When only these 32 intermediate-term deaths were analysed the effect of acute rejection was significant (HR 1.87, 95% CI 1.02 to 3.44, P=0.043). For earlier deaths the hazard ratio was 2.25 (95% CI 0.55 to 9.28, P=0.260) and for later ones 0.82 (95% CI 0.39 to 1.74, P=0.614).

DISCUSSION

Indications and contraindications for transplantation The indications for liver transplantation fall within 7 broad categories. In the Netherlands there has been a large shift from the other liver diseases to acute liver failure, alcoholic liver disease and chronic viral hepatitis, with no changes for cholestatic liver diseases and HCC (table 3).

Table 3: Composition of two Dutch groups of patients referred for liver transplantation in different periods.

Center	**Groningen**	**Rotterdam**
Period	**1977-1985**	**1986-2002**
Acute liver failure	6 (2%)	143 (15%)
Alcoholic liver disease	10 (3%)	120 (13%)
Chronic viral hepatitis	0 (0%)	192 (20%)
Cholestatic liver disease	67 (18%)	171 (18%)
Hepatocellular carcinoma	56 (15%)	110 (12%)
Other liver diseases	224 (62%)	204 (22%)

Half of the patients referred to our centre for liver transplantation between 1986 and 2002 had either no indication or various contraindications. This proportion has remained constant over time, in spite of more awareness of the possibility of liver transplantation as treatment of severe liver disease and the growing numbers of referrals. Apparently the greater awareness is not matched by an increase in the knowledge of the criteria for this form of treatment. It is up to the liver transplantation centres to put more effort into educating the referring physicians and the general public on the indications and contraindications of liver transplantation. This kind of knowledge transfer certainly would be worthwhile if the number of referrals based on unrealistic expectations could be reduced.

Waiting time and waiting list events One of the major problems, in our centre as well as in many others, is the growing discrepancy between the number of patients on the liver transplantation waiting list and the number of available donor organs. As a consequence the waiting time for elective transplantations has increased to a median of 260 days in 2002, and the waiting list mortality has also risen. Changes in the allocation system were made to improve the situation, but these have not been very successful. Expanding the donor pool by accepting marginal donors and non-heart-beating donors has become unavoidable[14,15]. The shortage of donors has also led to the expansion of living related donor transplantation[16].

These measures cannot, however, be regarded as the most appropriate solutions of the problem, since they increase the risks of transplantation. Of the factors defining marginal donors, steatosis and prolonged ischemia have a negative influence on graft survival, especially when both are present[14]. In the case of living donor transplantation a second person, the donor, faces morbidity and even death[17,18]. We are, therefore, in urgent need of other measures aimed at optimising the use of the donor potential. In the mean time, the allocation system has to be improved in order to minimise the waiting list mortality and to optimise chances of a successful outcome of transplantation. One of the tools that has proven its value in this respect is the MELD-score[19]. It might, however, be possible to further enhance the efficiency of the liver graft allocation system by using a modified version of the MELD-score[20].

Heterotopic liver transplantation Our short-term experience with the heterotopic technique did seem to support the hypothesis that avoidance of the anhepatic phase during liver transplantation for chronic liver disease leads to better outcomes[21]. In practice heterotopic liver transplantation has not withstood the test of time, even though this hypothesis has not been tested in a formal study until recently. A definite answer could have been given by a comparison with orthotopic liver transplantation in a randomised controlled trial, but such a trial has never been done. Therefore, we have to rely on less direct evidence based on a case-control study[11]. Some patients in the heterotopic group have survived for at least 10 years[12], but overall the results of orthotopic liver transplantation appeared to be better. The number of patients with acute liver failure in our heterotopic group is too small for a meaningful analysis. A larger number, including our patients, was reported in a multicentre study[13] that unfortunately did not use a case-control design. Heterotopic transplantation for acute liver failure also failed to find general acceptance.

Cholestatic liver disease Whereas the proportion of patients referred for PSC has remained constant over time, that of patients with PBC dropped by 75%. European Liver Transplant Registry data on the yearly numbers of transplantations for PBC also show a decline. One of the possible explanations is that the more widespread use of Ursodeoxycholic acid in the treatment of PBC has led to a better prognosis and a reduced need for transplantation[22]. In this category the proportion of referred patients that went on to transplantation was larger than in any of the other diagnostic groups, but a considerable number of patients either died on or had to be removed from the waiting list. As far as survival after transplantation is concerned, patients with cholestatic liver disease do better than most others. Still, there appears to be room for improvement by transplanting patients earlier in the course of their disease[23].

Hepatocellular carcinoma Patients with HCC form a special category in several respects. First, because of the availability of an alternative form of treatment and the presence of contraindications in most of the referred patients, transplantation was considered to be possible in only 29% of the patients. Second, a third of those accepted for transplantation either died on the waiting list or had to be removed from the list because of tumour progression. Although we have applied the Milan criteria[24] ever since they were first published, our drop-out rate from the waiting list exceeds that reported by others[25-27] (table 4). Finally, it is generally accepted that survival after liver transplantation for HCC is lower than that after transplantation for other indications[28], and the Rotterdam program is no exception to this rule. There clearly is a need to improve selection criteria and preoperative measures to control tumour progression[29].

Table 4: Rates of dropout from the waiting list and of transplantation for patients with hepatocellular carcinoma in different centers.

Reference	Year	Enlisted	Dropout	Transplanted
Llovet[25]	1999	87	8 (9%)	79 (91%)
Yao[26]	2002	46	13 (28%)	21 (46%)
Maddala[27]	2004	54	8 (15%)	46 (85%)
Total		187	29 (16%)	146 (78%)
Present study		32	11 (34%)	21 (66%)

Acute liver failure First of all, there is little doubt that the dismal prognosis of patients with acute liver failure can be improved considerably by emergency liver transplantation, although it is hard to find statistical proof of this idea because an appropriate control group is lacking. Our updated figures are very similar to those we published in 2002[30]. The 1-year survival is lower than that for elective transplantations, but the number of life-years gained probably is higher. In our series, one-year survival is above the European average, there were only few late deaths and most long-term survivors have been doing well, even though they develop a growing number of complications over time[31].

Acute rejection Even though acute rejection had no effect on overall mortality, it might be associated with a higher medium-term mortality. This discrepancy suggests that factors that protect against acute rejection lead to a higher late mortality. One obvious candidate is immunosuppression, but a more detailed analysis will have to be done to find support for this hypothesis. Meanwhile, there is every reason to aim at the lowest level of immunosuppression possible for every individual patient. To reach this goal a model to estimate the risk of acute rejection for transplanted

patients is needed, preferably based on a limited number of characteristics that are known immediately after transplantation. A model that might be used for such an estimate has been developed[32], but the score based on this model requires external validation before it can be applied in practice.

General conclusion Our study is one of the few describing the fate of patients referred for liver transplantation in some detail. Taken together, patients with acute liver failure and with chronic cholestatic liver diseases form one third of the total group. In these subgroups, the proportion moving on to enlistment and transplantation is higher than in any of the other categories, and the long-term results are at least comparable to the European average. However, some problems requiring more attention or further study were identified. Apparently more efforts are required to develop referral guidelines in co-operation with referring physicians. Development and testing of models that can be used to design a more efficient waiting list strategy is urgently needed. The incidence of early acute rejections has dropped since the introduction of potent new immunosuppressive agents, but this might well come at the cost of over-immunosuppression and its negative effects. A more rational approach to the potentially harmful primary immunosuppressive regimen after liver transplantation could also serve to improve the results.

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CHAPTER 3a

MELD AND SURVIVAL OF PATIENTS AWAITING LIVER TRANSPLANTATION: DEVELOPMENT AND EXTERNAL VALIDATION OF A SIMPLIFIED SCORE

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SUMMARY

Background The Model for End-stage Liver Disease is used to establish priority on liver transplantation waiting lists. We analysed the predictive value of the model's components in our chronic liver disease patients awaiting transplantation, since their independent contribution has not been proven in this setting.
Methods We studied 359 chronic liver disease patients enlisted for transplantation in Rotterdam between 1986 and 2003. The model's components were tested by logistic regression analysis and multivariate Cox analysis, in unaltered form and after logarithmic transformation. Survival was calculated using the Kaplan-Meier method. For external validation data on 271 patients from Brazil were used.
Results Logarithmic transformation resulted in improvement of the predictive value of all three components of the original model. In the Cox analysis ln(bilirubin) ($P<0.001$) and ln(creatinine) ($P=0.030$) were significant, while ln(International Normalised Ratio) ($P=0.216$) was not. A score consisting of 10.1xln(ln(bilirubin in μmol/l)) + 8.9xln(ln(creatinine in μmol/l)) was derived from this model. The modified score was superior when compared to the MELD-score using logistic regression analysis in the modelling dataset. Minor differences were found for the Cox model c-statistics, that was 85% using the MELD-score and 84% for the simplified model. These findings were partly confirmed in the validation dataset.
Conclusion The use of log-transformed data led to simplification of the original model by deletion of the methodologically dubious International Normalised Ratio, without a significant loss of predictive value. To determine its general applicability our modified EMERALD-score requires further testing in patients enlisted for liver transplantation.

INTRODUCTION

Identifying predictors of survival for patients with liver diseases is important because they provide insight in disease mechanisms and can be used as an aid in decision making. Survival models can help in deciding when to offer liver transplantation to patients with progressive liver disease. Also, they can be used to give sicker patients a higher priority on the transplant waiting list. A number of models have been developed to predict survival of patients with chronic liver diseases. The Child-Pugh model[1] is the oldest and the most frequently used one. Besides bilirubin, albumin and prothrombin time it uses two subjective parameters, namely clinical grading of ascites and encephalopathy, which can be seen as a disadvantage. Moreover, the Child-Pugh model treats bilirubin, albumin and prothrombin time as categorical variables, and disregards the

differences within the categories. Some of the newer models are specific for certain diseases such as Primary Biliary Cirrhosis[2] or Primary Sclerosing Cholangitis[3] and, therefore, are not suitable for general use. Others rely on invasive procedures like liver biopsy or on tests that are not widely used[4-8].

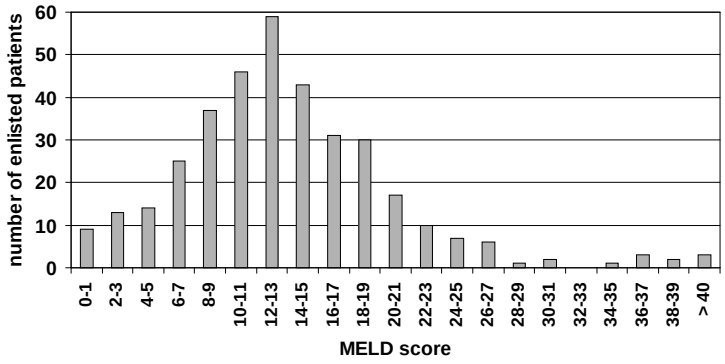
Recently the Model for End-stage Liver Disease[9] (MELD) was developed to predict 3-month survival based on three readily available biochemical tests: bilirubin, creatinine and prothrombin time expressed as International Normalised Ratio (INR). The MELD-score is being used in clinical research as well as in liver transplantation waiting list and allocation systems[10-16]. Although the use of the MELD-score in the United States liver allograft allocation system has resulted in a reduction of both the number of newly registered patients and the waiting list mortality, it still has its shortcomings, as highlighted in a recent editorial[17]. The MELD-score was not specifically developed for patients with inborn errors of bilirubin metabolism, intrinsic renal disease or anticoagulant therapy with coumarin-derivatives, and gives false predictions in these cases. Also, MELD may underestimate mortality in patients with refractory ascites. One of the proposed remedies is the addition of extra factors, such as serum sodium[18]. Another approach is a critical reappraisal of the predictive value of each of the individual MELD-score components, alone and in combination. We, therefore, studied the value of the MELD-score in predicting the outcome of our chronic liver disease patients awaiting liver transplantation. We also analysed the contribution of each of the MELD-score components. Based on this second analysis we developed a simplified score that possibly offers advantages over the original version. Finally we subjected this simplified score to external validation.

PATIENTS AND METHODS

All consecutive patients with chronic liver diseases enlisted for transplantation at our center between October 1, 1986, and October 1, 2003, were entered in the study. Clinical data and biochemical test results at the time of enlistment were retrieved from our liver transplantation database. All biochemical tests were done using standard automated techniques. Of the 372 patients entered in the study 13 were excluded because no INR was available. The final study group consisted of 215 males and 144 females with a median age of 50 years (range 16-68 years). The primary indication for transplantation was chronic viral hepatitis in 95 patients, alcoholic cirrhosis in 42, Primary Biliary Cirrhosis in 39, Primary Sclerosing Cholangitis in 47, cryptogenic cirrhosis in 36 and hepatocellular carcinoma in 32, various other liver diseases were present

in 68. The median MELD score was 13 (range 0-64). The distribution of the MELD scores is shown in figure 1.

Figure 1: distribution of MELD-scores in 359 patients enlisted for liver transplantation in Rotterdam between 1986 and 2003



Of the 359 patients 257 were transplanted and 14 were removed from the waiting list. The main reason for removal from the list was tumor progression in patients with hepatocellular carcinoma. At the closing date of the study, 46 patients were still on the waiting list. The total number of patients who died on the waiting list was 42, with 27 deaths during the first three months after enlistment and 10 between four and six months. The waiting time was at least three months for 176 patients and at least six months for 102 patients. All deaths were directly attributable to liver failure. Over 90% of the follow-up was contributed by patients enlisted from 1997 onwards, along with 30 of the 42 deaths (71%).

The data used for external validation came from a group 271 of patients enlisted for liver transplantation in Porto Alegre, Southern Brazil, between January, 2001, and August, 2003. This group consisted of 165 males and 106 females with a median age of 52 years (range 17-74 years). The primary indication for transplantation was chronic viral hepatitis in 151 patients, alcoholic cirrhosis in 31, Primary Biliary Cirrhosis in 3, Primary Sclerosing Cholangitis in 2, cryptogenic cirrhosis in 13 and hepatocellular carcinoma in 51, various other liver diseases were present in 20. The median MELD score was 13 (range 2-49). Here 170 patients were transplanted and at the closing date of the study 33 patients were still on the waiting list. There were 68 deaths on the waiting list, 32 during the first three months after enlistment and 20 between four and six months. The

waiting time was at least three months for 214 patients and at least six months for 169 patients (table 1).

Table 1: characteristics in the patient groups used for development and validation of the new liver transplantation waiting list survival model

Variable		Modelling dataset	Validation dataset
Patients	n	359	271
Male/Female	n / n	215 / 144	165 / 106
Age in years	median (range)	50 (16 – 68)	52 (17 – 74)
Chronic viral hepatitis	n (%)	95 (26%)	151 (56%)
Alcoholic liver disease	n (%)	42 (12%)	31 (11%)
PBC or PSC	n (%)	86 (24%)	5 (2%)
Cryptogenic cirrhosis	n (%)	36 (10%)	13 (5%)
Hepatocellular carcinoma	n (%)	32 (9%)	51 (19%)
Other liver diseases	n (%)	68 (19%)	20 (7%)
MELD-score	median (range)	13 (0 – 64)	13 (2 – 49)
Transplanted	n (%)	257 (72%)	170 (63%)
Dead on waiting list at <3 months	n (%)	27 (8%)	32 (12%)
>3 months on waiting list	n (%)	176 (49%)	214 (79%)
Dead on waiting list at <6 months	n (%)	37 (10%)	52 (19%)
>6 months on waiting list	n (%)	102 (28%)	169 (62%)
Dead on waiting list total	n (%)	42 (12%)	68 (25%)
Alive and waiting at end of study	n (%)	46 (13%)	33 (12%)

The predictive value of each of the components of the MELD-score was tested by multivariate logistic regression analysis with 3-month survival as end-point, and by multivariate Cox regression analysis. The time of enlistment was the starting point of the analysis. In the Cox analysis, patients were censored at the moment of transplantation, at removal from the waiting list for other reasons, or when still alive and waiting on October 1, 2003, the closing date of the study. Since the distributions of the values for bilirubin, creatinine and INR were skewed, all factors were tested again after logarithmic transformation. A step-backward approach was used to arrive at a modified model. For each patient a score was derived from this modified model in a manner analogous to that used to calculate the MELD-score, by adding the natural logarithms of the relative risks for the components of the model and multiplying the sum by 10. Survival was calculated for different risk groups according to both scores using the Kaplan-Meier method. The value of both scores in predicting survival at 3 and at 6 months was compared by logistic regression analysis and in predicting overall mortality by Cox regression analysis. We also compared the Receiver Operating Characteristic (ROC) curves at both time points

and the c-statistics of the two models. The method described by Harrell[19] was used for calculation of the c-statistics. All statistical tests were done using STATA (version 5.0, Stata Corporation, 702 University Drive East, College Station, TX 77840 USA).

RESULTS

First, the original MELD-score was tested in the 203 patients that either died within three months or had a follow-up of at least three months. Using univariate logistic regression analysis with 3-month survival as the end-point, the MELD-score proved to be a highly significant predictor with a hazard ratio of 1.21 (95% CI 1.12-1.31, P<0.001) and a value of 0.857 for the area under the ROC curve. Then the three individual components of the MELD-score were entered in a similar analysis. The hazard ratio for bilirubin in mg/dl was 1.08 (95% CI 1.03-1.12, P=0.001) for creatinine in mg/dl 1.25 (95% CI 0.70-2.26, P=0.453) and for the INR 2.12 (95% CI 0.90-4.98, P=0.085). The corresponding hazard ratio's in a Cox analysis were 1.06 (1.04-1.08, P<0.001), 0.81 (95% CI 0.54-1.21, P=0.302) and 1.85 (95% CI 1.21-2.84, P=0.004). In the original model the hazard ratio's were 1.46, 2.61 and 3.06, respectively (table 2).

Table 2: Logistic regression-analysis and Cox-analysis of Model for End-stage Liver Disease components in patients awaiting liver transplantation.

VARIABLE	Original MELD odds ratio	Logistic regression analysis odds ratio (95% CI)	Cox analysis hazard ratio (95% CI)
Patients		N = 203	n = 359
Bilirubin	1.46[1,2]	1.08 (1.03 to 1.12)[1,2]	1.06 (1.04 to 1.08)[1]
Creatinine	2.61[1,2]	1.25 (0.70 to 2.26)[1,2]	0.81 (0.54 to 1.21)[1]
INR	3.06[2]	2.12 (0.90 to 4.98)[2]	1.86 (1.21 to 2.84)

[1]) Calculated using concentrations in mg/dl
[2]) Calculated with 3-month survival as endpoint

The linearity and the predictive value for each of the individual MELD-score components improved significantly after logarithmic transformation. In a second multivariate Cox-model using log-transformed data the hazard ratio for ln(bilirubin in μmol/l) was 2.49 (95% CI 1.78-3.49, P<0.001), for ln(creatinine in μmol/l) 1.93 (95% CI 1.07-3.49, P=0.030) and for ln(INR) 2.06 (95% CI 0.65-6.50, P=0.216). When the INR was dropped from the model both bilirubin and creatinine remained significant, with P-values <0.001 and hazard ratio's of 2.74 (95% CI 2.04-3.68) and 2.43 (95% CI 1.53-3.88), respectively (table 3). A modified risk score consisting of 10.1xln(ln(bilirubin in μmol/l)) + 8.9xln(ln(creatinine in μmol/l)) was derived

from this model, that was called the Erasmus Model for End-stage Resistant-to-therapy All-aetiology Liver Disease (EMERALD).

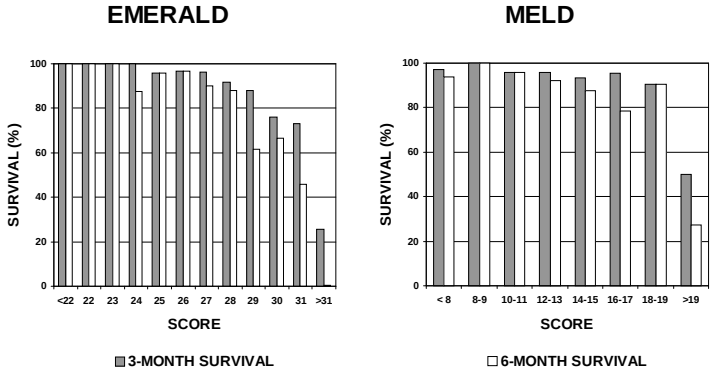
Table 3: Multivariate Cox-analysis of Model for End-stage Liver Disease components in 359 patients awaiting liver transplantation.

VARIABLE	Original MELD odds ratio	Cox analysis hazard ratio (95% CI)	Final Cox model hazard ratio (95% CI)	Brazil dataset hazard ratio (95% CI)
Bilirubin	1.46[1]	2.49 (1.78 to 3.49)[2]	2.74 (2.04 to 3.68)[2]	2.14 (1.56 to 2.96)[2]
Creatinine	2.61[1]	1.93 (1.07 to 3.49)[2]	2.43 (1.53 to 3.88)[2]	5.04 (2.86 to 8.90)[2]
INR	3.06	2.06 (0.65 to 6.50)[3]	--	--

[1]) Calculated using concentrations in mg/dl
[2]) Calculated using log-transformed concentrations in μmol/l
[3]) Calculated using log-transformed values

For each individual patient the MELD- and EMERALD-score was calculated and rounded to the nearest integer. Next, different risk categories were formed based on both scores, with cut-off points that were chosen so that each category contained at least 10 patients (figure 2). For

Figure 2: EMERALD versus MELD, survival at 3 and at 6 months for different scores in 359 patients enlisted for liver transplantation in Rotterdam between 1986 and 2003

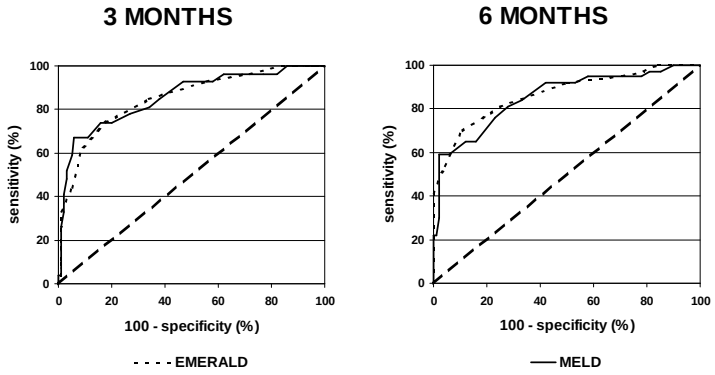


EMERALD-scores up to 24 the survival at three months was 100%, with a gradual decline to 26% for scores of 32 or more. At six months a similar pattern was seen, with a decline to a survival of 46% for patients with a

score of 31, and 0% for scores of 32 or more. The survival at three months was 91-100% for MELD-scores up to 19, and declined to 50% for scores of 20 or more. At six moths these figures were 79-100% and 27%, respectively.

The EMERALD-score was compared to the MELD-score in a multivariate logistic model with both 3- and 6-month survival as end-point and in a multivariate Cox model. For survival at 3 months the MELD-score odds ratio was 1.09 (P=0.141), against 1.51 (P=0.024) for the EMERALD-score. With 6-month survival as the end-point these figures were 1.13 (P=0.063) versus 1.71 (P=0.005). In the Cox model the hazard ratio for the MELD-score was 1.02 (P=0.468) and for the EMERALD-score 1.51 (P=0.001). We also calculated the sensitivity and the specificity of both scores. The ROC curves for the two scores predicting three-month and six-month mortality were almost identical (figure 3). The areas under the curve were 86% and 85% for the MELD-score, respectively, versus 85% and 87% for the EMERALD-score. The Cox model c-statistics were 85% for MELD and 84% for EMERALD.

Figure 3: receiver operating characteristics for EMERALD- and MELD-scores with 3-month and 6-month survival as endpoint in 359 patients enlisted for liver transplantation in Rotterdam, 1986-2003



In the validation dataset we checked the predictive value of ln(bilirubin in µmol/l) (hazard ratio 2.14, 95% CI 1.55-2.96, P<0.001), and ln(creatinine in µmol/l) (hazard ratio 5.05, 95% CI 2.86-8.90, P=<0.001) using Cox regression analysis. Here too we compared both scores in multivariate models. For survival at 3 months the MELD-score odds ratio was 1.20 (P=0.002), against 1.00 (P=0.982) for the EMERALD-score. With 6-month survival as the end-point these figures were 1.15 (P=0.004) versus 1.04

(P=0.787). In the Cox model the hazard ratio for the MELD- and EMERALD-score was 1.11 (P=<0.001) and 1.07 (P=0.294), respectively (table 4).

Table 4: multivariate comparisons of the MELD- and EMERALD-scores in the modelling and validation datasets using different endpoints

Statistical test	Endpoint	Score	Modelling dataset P	Validation dataset P
Logistic regression analysis	3-month mortality	MELD	0.141	0.002
		EMERALD	0.024	0.982
Logistic regression analysis	6-month mortality	MELD	0.063	0.004
		EMERALD	0.005	0.787
Cox regression analysis	overall mortality	MELD	0.593	<0.001
		EMERALD	<0.001	0.294

Finally we calculated the area under the ROC curve for both scores. For MELD with 3-month mortality as endpoint this value was 78%, against 74% for EMERALD. With 6-month mortality as endpoint values of 71% and 70%, respectively, were found. Here the Cox model c-statistics were 70% for MELD and 68% for EMERALD (table 5).

Table 5: comparison of the performance of the MELD- and EMERALD-scores in predicting 3-month, 6-month and overall mortality in the modelling dataset and the validation dataset.

End-point	Data	z-score		Area under the receiver operating characteristic curve	
		MELD	EMERALD	MELD	EMERALD
3-month mortality	Modelling set	4.92[1]	5.31[1]	0.86	0.85
	Validation set	5.08[1]	4.37[1]	0.78	0.74
6-month mortality	Modelling set	5.05[1]	5.25[1]	0.85	0.87
	Validation set	4.78[1]	4.19[1]	0.71	0.70
overall mortality	Modelling set	9.87[1]	9.02[1]	0.85[2]	0.84[2]
	Validation set	8.38[1]	4.89[1]	0.70[2]	0.68[2]

[1]) P<0.001
[2]) c-statistics

DISCUSSION

For validation of the MELD-score and of its individual components in a liver transplantation waiting list setting, we used logistic regression analysis in

our cohort of patients, with 3-month survival as end-point. Our study confirms the predictive value of the MELD-score, with an area under the ROC curve similar to that found in one study[16] but lower than that found in another[18]. However, of the hazard ratios for the three MELD-score components calculated from the model specifications, only that for the INR was found to lie within the 95% confidence interval found in the present study, and only the serum bilirubin concentration proved to be significant in our patients. These findings can be explained by the fact that our patient group differs from those used for development and validation of the MELD-score.

Compared to logistic regression analysis, Cox analysis has the advantage of allowing incomplete follow up, so more patients can be included and a longer period can be studied. This last point is important since at the moment waiting times for liver transplantation exceed 3 months for many patients. The result of our Cox analysis was similar to that of the logistic regression analysis, but the INR regained its significance. Logarithmic transformation improved the performance of each of the individual MELD-score components, but in a multivariate Cox-model only serum bilirubin and creatinine concentrations remained as independent predictors.

The INR is included in the MELD-score, but is not a factor in our simplified score. Apart from its lack of significance, there are two other points that make the INR less suitable for use in establishing priority on transplantation waiting lists. First, it has not been proven that calculation of the INR is the proper way to standardise prothrombin time measurements in patients with liver failure[20,21]. Second, the INR can be influenced by factors not directly related to liver failure, such as vitamin K deficiency, treatment with oral anticoagulants or intravenous administration of coagulation factors.

We, therefore, propose a modification of the MELD-score based on a simplified model derived from a Cox-analysis in an actual waiting list patient cohort, consisting of only the log-transformed serum bilirubin and creatinine concentrations, that solves at least one of the problems of the original version. An earlier study by others using logistic regression analysis in a different patient group resulted in a similar model also containing log-transformed serum bilirubin and creatinine concentrations[22]. In another study mentioned earlier[18] the serum sodium concentration was found to be an independent predictor of death when added to the original MELD-score. Identification of an additional risk factor is of course useful, but does not necessarily lead to a significantly better predictive model. In fact, the improvement reached by adding the serum sodium to the MELD-score can at best be called modest, with an increase of the area under the ROC curve by less than 2 percent points.

Like all new scoring systems ours requires external validation. This was done in collaboration with the group from Porto Alegre in Southern Brazil. Although the prognostic value of the two log-transformed components of our model was confirmed, the overlap between the 95% confidence intervals of the hazard ratios was less than 50% for the serum creatinine concentration. The area under the receiver operating characteristic curve for the EMERALD-score was about equal to that for the MELD-score in the modelling dataset as well as in the validation dataset with both 3- and 6-month mortality as endpoint. The same can be said for the Cox model c-statistics. The EMERALD-score performed less well in the validation dataset than in the modelling dataset, but so did the MELD-score. There are, however, differences between the two patient groups, not only in the distribution of the indications for transplantation but also in waiting times and waiting list mortality. Although these differences may explain the results of our comparison, further testing and probably some adjustment of our model remains necessary.

Still, our simplified score has advantages over the original MELD-score. It was developed in a more relevant patient population, and operates over a longer time period. Also, it eliminates the problems associated with the use of the International Normalised Ratio. On the other hand, it still is not clear how patients with inborn errors of bilirubin metabolism, intrinsic renal disease or a decline of their renal function due to other factors should be dealt with. Calculation of our modified score requires a double logarithmic transformation of both bilirubin and creatinine values, but this can be done, for instance, using web-based tools like the one for calculating the MELD-score (http://www.mayoclinic.org/gi-rst/mayomodel5.html). Our modified score is not perfect, and it does not correctly identify all patients who will and will not survive until transplantation. Nevertheless, the use of log-transformed values for bilirubin and creatinine probably will improve our ability to predict the fate of patients on the waiting list for liver transplantation.

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CHAPTER 3b

THE OPTIMAL TIMING OF LIVER TRANSPLANTATION IN PATIENTS WITH CHRONIC CHOLESTATIC LIVER DISEASE

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SUMMARY

The current opinion is that liver transplantation for chronic cholestatic liver disease should be done before the terminal, high-risk stage. However, most studies do not take waiting list mortality into account. We analysed 113 consecutive patients with chronic cholestatic liver disease, stratified according to estimated survival. Overall and post-transplantation survival was calculated using the Kaplan-Meier method. Including patients who died awaiting transplantation lowered the one-year survival by 19% in the high-risk category. In this group survival at 4 years was 45%, with an estimated survival benefit of 45%. For the intermediate- and low-risk groups these numbers were 56% and 36% versus 81% and 7%. Including the waiting list period in the analysis of the benefits of liver transplantation strengthens the case for early transplantation. Our study confirms that liver transplantation should be considered before the high-risk stage of chronic cholestatic liver disease is reached.

INTRODUCTION

For patients with chronic liver disease and a poor prognosis or a low quality of life, liver transplantation is the treatment of choice. A patient-centred approach leads to priority for the sickest patients on the transplantation waiting lists. There are, however, more ways to determine the optimal timing of transplantation for patients with chronic liver disease. When viewed from the perspective of the donor, the aim should be a maximal survival after transplantation. Yet another goal is a maximal survival benefit, calculated as the difference between estimated survival without transplantation and estimated or actual survival with transplantation. Each of these approaches requires estimation of the risk of dying without transplantation, which can be done for groups but is unreliable for individual patients. Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC) are chronic cholestatic liver diseases that are routinely treated with Ursodeoxycholic acid but, nevertheless, usually are progressive. PBC and PSC can serve as prototypes to study the effect of liver transplantation, since survival models are available for both[1,2].

The current opinion in the United States[3] as well as in Europe[4] is that in patients with chronic cholestatic liver disease transplantation should be carried out before they reach the terminal, high-risk stage of their disease, as the larger number of life-years gained by transplantation in the high-risk category is offset by a lower survival after transplantation. However, only one study on this issue has included patients who died on the waiting list for transplantation[5]. Patients that die awaiting liver transplantation could have an important impact on survival estimates, and including them might

strengthen the case for early transplantation. We therefore studied the survival in our series of 113 patients with cholestatic liver disease enlisted for liver transplantation. We calculated the 1- 2-, 3- and 4-year survival for all patients and for transplanted patients only in three different risk categories. We also compared the estimated and the actual survival of all patients at 1, 2, 3 and 4 years for the different risk categories.

METHODS

Study design and study population

We included all consecutive patients with cholestatic liver disease who were accepted as candidates for liver transplantation from October, 1986, through September, 2004. Indications for liver transplantation were end-stage liver disease as evidenced by a score > 8 points in the Child-Pugh classification[6]. Patients in earlier stages of their disease were also enlisted because of life threatening complications like spontaneous bacterial peritonitis, recurrent bacterial cholangitis and recurrent oesophageal variceal bleeding, or a severely diminished quality of life because of pruritus or fatigue. Persistent extrahepatic infectious foci, extrahepatic malignancy including cholangio-carcinoma and other diseases that directly influence the prognosis with or without liver transplantation were considered as absolute contra-indications.

The time of entry for this study was defined as the date of enlistment for liver transplantation. Patient characteristics and the most recent clinical and laboratory data available at the moment of inclusion needed to apply the Mayo models for survival of PBC and PSC patients were extracted from the patient files. The moment of liver transplantation was defined as the time and date of reperfusion of the transplanted organ. The follow up of all 73 surviving patients is complete until 30 September 2004, the closing date of this study.

Statistics

The Mayo risk score at entry in the study was calculated for all PBC patients {[0.871xln(bilirubin in mg/dl)] – [2.53xln(albumin in g/dl)] + [0.039x(age in years)] + [2.38xln(prothrombin time in s)] + [0.859x(edema score)]} and for all PSC patients {[0.03x(age in years)] + [0.54xln(bilirubin in mg/dl)] + [0.54xln(AST in U/l)] + [1.24x(variceal bleeding Y=1/N=0)] – [0.84x(albumin in g/dl)]}.

Patients were classified as high risk with an estimated median survival of up to one year when they scored more than 8.2 points in the Mayo PBC formula or more than 3.9 points in the Mayo PSC formula. The intermediate risk category with an estimated median survival of 1 to 3 years was formed by patients with a score of 6.8 to 8.2 in the Mayo PBC

model or 2.6 to 3.9 points in the Mayo PSC model. The low risk group with an estimated median survival > 3 years comprised the remaining patients.

The survival probabilities without transplantation for each individual patient at 1, 2, 3 and 4 years were estimated from the risk score using the appropriate model. The 1, 2, 3 and 4 year survival for the total group and for the transplanted patients only was estimated using the Kaplan-Meier method.

RESULTS

Included were 113 patients, 48 males and 65 females, with a median age of 49 years (range 15 to 67 years). Over two-thirds of the patients were enlisted in the second half of the study period, and <10% in the period before 1990. The liver disease was PBC in 46 patients and PSC in 67 patients. Liver transplantation was performed in 85 patients. At least one retransplantation was necessary in 14 patients. There were 2 peroperative deaths and 27 postoperative deaths in this series. Of the PBC patients 18 fell in the high-risk category, 16 in the intermediate risk category and 12 in the low risk category against 4, 22 and 41 of the PSC patients, respectively.

At the closing date of the study 14 patients were still on the waiting list, three were removed from the waiting list because of extrahepatic malignancies, and 11 died while waiting. The median waiting time for transplantation was 23 days (range 2-104 days) in the high-risk group, 40 days (3-593 days) in the intermediate-risk group, and 166 days (7-459 days) in the low-risk group (table 1). The median follow up of the 73 survivors was 1810 days (range 18-5499 days).

Table 1: Waiting times and outcomes in the different risk categories.

Risk category	**High**	**Intermediate**	**Low**
Estimated median survival	< 1 year	1-3 years	> 3 years
Total	22	38	53
PBC 18	16	12	
PSC 4	22	41	
Still waiting or removed, n=	1	4	12
Waiting time in days, median (range)	375 (-)	113 (18-246)	320 (44-949)
Deaths on the waiting list, n=	7	2	2
Waiting time in days, median (range)	30 (6-89)	- (129-390)	- (212-446)
Transplanted, n=	14	32	39
Waiting time in days, median (range)	23 (2-104)	40 (3-593)	166 (7-459)
Per- and post-operative deaths, n=	6	15	8
All deaths, n=	13	17	10

The 1-year survival calculated according to the intention-to-treat principle was 45% in the high-risk group, 69% in the intermediate risk category and 94% in the low risk category. When only transplanted patients are considered the 1-year survival rises from 45% to 64% in the high-risk category, with no major changes in the other two groups (table 2).

Table 2: Effect of patient selection on survival in the different risk groups.

Risk category	**High**	**Intermediate**	**Low**
All candidates, n=	22	38	53
- Actual 1-year survival, %	- 45	- 69	- 94
- (95% confidence interval)	- (24-64)	- (51-82)	- (82-98)
Transplanted patients, n=	14	32	39
- Survival 1 year post OLT, %	- 64	- 69	- 89
- (95% confidence interval)	- (34-83)	- (49-82)	- (74-96)

Note: The actual 1-year survival percentages were calculated using the Kaplan-Meier method.

In the high-risk group the survival at 2, 3 and 4 years remains 45%. The survival at 2, 3 and 4 years was 63%, 63% and 56% in the intermediate-risk group, versus 84%, 84% and 81% in the low-risk group. The largest survival benefit of transplantation is found in the high risk category, here the difference between estimated survival without liver transplantation and actual survival is 18% at 1 year, 38% at 2 years and 45% at 3 and 4 years. These figures are -3%, 14%, 32% and 36% in the intermediate risk group, and 0%, -3%, 4% and 7% in the low risk group, respectively (table 3).

Table 3: Comparison of the estimated survival without transplantation with the actual survival in the different risk categories.

Risk category	**High**	**Intermediate**	**Low**
All candidates, n=	22	38	53
Median estimated survival at			
1 year, % (range)	27 (0-49)	72 (50-83)	94 (86-100)
2 years, % (range)	7 (0-24)	49 (22-69)	87 (70-100)
3 years, % (range)	0 (0-6)	31 (7-49)	80 (57-100)
4 years, % (range)	0 (0-2)	20 (2-39)	74 (44-100)
Actual survival at			
1 year, % (95% CI)	45 (24-64)	69 (51-82)	94 (82-98)
2 years, % (95% CI)	45 (24-64)	63 (45-77)	84 (69-92)
3 years, % (95% CI)	45 (24-64)	63 (45-77)	84 (69-92)
4 years, % (95% CI)	45 (24-64)	56 (37-71)	81 (65-90)
Median survival benefit at			
1 year, %	18	-3	0
2 years, %	38	14	-3
3 years, %	45	32	4
4 years, %	45	36	7

Note: The estimated survival probabilities were calculated using the Mayo-models for PBC and PSC. The actual survival was calculated using the Kaplan-Meier method.

DISCUSSION

There were two questions that led to this study. The first one is about the effect of including the waiting list period in the analysis of the survival of liver transplantation candidates. Our data on patients with chronic cholestatic liver disease show a considerable difference between the total group and the transplanted patients in the category with the highest risk. In the patient group with an estimated survival of 1 year or less, the actual 1-year survival decreases by 19% when patients who die without transplantation are included. The magnitude of the effect of including the waiting period in the analysis of survival depends on the waiting time, which is relatively short in our high-risk patients. This effect probably will be larger when the waiting time increases. In the intermediate and the low risk categories, with an estimated median survival of 1 year or more, survival is not significantly influenced by the waiting list mortality. Here, too, a larger effect might well be found with longer waiting times.

The second question is what the overall outcome is for the different risk categories in terms of absolute survival and survival benefit. As expected, the highest absolute survival is found in our low-risk patients, but in this group there appears to be no meaningful survival benefit at a follow up of up to 4 years. In our study the effect of the waiting list mortality is negligible in the intermediate-risk group, but the postoperative mortality approaches that in the high-risk category. The largest survival benefit of liver transplantation is found in the group with the lowest estimated survival, even when patients who die without transplantation are included. This gain comes at the price of a one-year mortality of 55% in our high-risk patients.

The final point is what the implications of our study are for the waiting list policy. It would be unfair to deny high-risk patients the chance of liver transplantation because of an increased postoperative mortality, and the largest survival benefit is found in this group. Although the current postoperative survival for high-risk patients may be higher than in our series, it is likely to remain worse than in the other groups. The effect of the waiting list mortality will not disappear, and can only become stronger with longer waiting times. When high-risk patients are informed about their prognosis, the waiting list mortality certainly should be included.

When a lower postoperative mortality than in our series can be attained, intermediate-risk patients are the most attractive candidates for liver transplantation. Both waiting list mortality and postoperative mortality will be lower than in high-risk patients, and there is a substantial survival benefit, certainly on the longer term. Thus two of the three goals mentioned in the introduction would be reached. For selected low-risk patients with a

relatively good prognosis but a poor quality of life, liver transplantation also seems worthwhile, since it does not diminish survival on the short term and may well improve it on the longer term. In general, a policy of transplantation in an early disease stage would reduce the waiting list mortality and improve both overall and post-transplantation survival. Whenever possible, transplantation should not be postponed until the terminal, high-risk stage of chronic liver disease is reached.

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ORIGINAL ARTICLE

The optimal timing of liver transplantation in patients with chronic cholestatic liver disease

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Keywords
liver transplantation, primary biliary cirrhosis, primary sclerosing cholangitis, survival.

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Summary

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Introduction

For patients with chronic liver disease and a poor prognosis or a low quality of life, liver transplantation is the treatment of choice. A patient-centred approach leads to priority for the sickest patients on the transplantation waiting lists. There are, however, more ways to determine the optimal timing of transplantation for patients with chronic liver disease. When viewed from the perspective of the donor, the aim should be a maximal survival after transplantation. Yet another goal is a maximal survival benefit, calculated as the difference between estimated survival without transplantation and estimated or actual survival with transplantation. Each of these approaches requires estimation of the risk of dying without transplantation, which can be done for groups but is unreliable for individual patients. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic liver diseases that are routinely treated with ursodeoxycholic acid but, nevertheless, usually are progressive. PBC and PSC can serve as prototypes to study the effect of liver transplantation, as survival models are available for both [1,2].

The current opinion in the United States as well as in Europe is that in patients with chronic cholestatic liver disease transplantation should be carried out before they reach the terminal, high-risk stage of their disease, as the larger number of life-years gained by transplantation in the high-risk category is offset by a lower survival after transplantation [3,4]. However, only one study on this issue has included patients who died on the waiting list for transplantation [5]. Patients that die awaiting liver transplantation could have an important impact on survival estimates, and including them might strengthen the

case for early transplantation. We therefore studied the survival in our series of 113 patients with cholestatic liver disease enlisted for liver transplantation. We calculated the 1-, 2-, 3- and 4-year survival for all patients and for transplanted patients only in three different risk categories. We also compared the estimated and the actual survival of all patients at 1, 2, 3 and 4 years for the different risk categories.

Methods

Study design and study population

We included all consecutive patients with cholestatic liver disease who were accepted as candidates for liver transplantation from October, 1986, through September, 2004. Indications for liver transplantation were end-stage liver disease as evidenced by a score >8 points in the Child-Pugh classification [6]. Patients in earlier stages of their disease were also enlisted because of life threatening complications like spontaneous bacterial peritonitis, recurrent bacterial cholangitis and recurrent oesophageal variceal bleeding, or a severely diminished quality of life because of pruritus or fatigue. Persistent extrahepatic infectious foci, extrahepatic malignancy including cholangiocarcinoma and other diseases that directly influence the prognosis with or without liver transplantation were considered as absolute contra-indications.

The time of entry for this study was defined as the date of enlistment for liver transplantation. Patient characteristics and the most recent clinical and laboratory data available at the moment of inclusion needed to apply the Mayo models for survival of PBC and PSC patients were extracted from the patient files. The moment of liver transplantation was defined as the time and date of reperfusion of the transplanted organ. The follow-up of all 73 surviving patients is complete until 30 September 2004, the closing date of this study.

Statistics

The Mayo risk score at entry in the study was calculated for all PBC patients $\{[0.871 \times \ln(\text{bilirubin in mg/dl})] - [2.53 \times \ln(\text{albumin in g/dl})] + [0.039 \times (\text{age in years})] + [2.38 \times \ln(\text{prothrombin time in s})] + [0.859 \times (\text{oedema score})]\}$ and for all PSC patients $\{[0.03 \times (\text{age in years})] + [0.54 \times \ln(\text{bilirubin in mg/dl})] + [0.54 \times \ln(\text{AST in U/l})] + [1.24 \times (\text{variceal bleeding Y} = 1/\text{N} = 0)] - [0.84 \times (\text{albumin in g/dl})]\}$.

Patients were classified as high risk with an estimated median survival of up to 1 year when they scored more than 8.2 points in the Mayo PBC formula or more than 3.9 points in the Mayo PSC formula. The intermediate risk category with an estimated median survival of 1–3 years was formed by patients with a score of 6.8–8.2 in the Mayo PBC model or 2.6–3.9 points in the Mayo PSC model. The low risk group with an estimated median survival >3 years comprised the remaining patients.

The survival probabilities without transplantation for each individual patient at 1, 2, 3 and 4 years were estimated from the risk score using the appropriate model. The 1, 2, 3 and 4 year survival for the total group and for the transplanted patients only was estimated using the Kaplan–Meier method.

Results

Included were 113 patients, 48 males and 65 females, with a median age of 49 years (range 15–67 years). Over two-thirds of the patients were enlisted in the second half of the study period, and <10% in the period before 1990. The liver disease was PBC in 46 patients and PSC in 67 patients. Liver transplantation was performed in 85 patients. At least one retransplantation was necessary in 14 patients. There were two peroperative deaths and 27 postoperative deaths in this series. Of the PBC patients 18 fell in the high-risk category, 16 in the intermediate risk category and 12 in the low risk category against 4, 22 and 41 of the PSC patients, respectively. At the closing date of the study 14 patients were still on the waiting list, three were removed from the waiting list because of extrahepatic malignancies, and 11 died while waiting. The median waiting time for transplantation was 23 days (range 2–104 days) in the high-risk group, 40 days (3–593 days) in the intermediate-risk group, and 166 days (7–459 days) in the low-risk group (Table 1). The median follow up of the 73 survivors was 1810 days (range 18–5499 days).

The 1-year survival calculated according to the intention-to-treat principle was 45% in the high-risk group, 69% in the intermediate risk category and 94% in the low risk category. When only transplanted patients are considered the 1-year survival rises from 45% to 64% in the high-risk category, with no major changes in the other two groups (Table 2). In the high-risk group the survival at 2, 3 and 4 years remains 45%. The survival at 2, 3 and 4 years was 63%, 63% and 56% in the intermediate-risk group, vs. 84%, 84% and 81% in the low-risk group, respectively. The largest survival benefit of transplantation is found in the high risk category, here the difference between estimated survival without liver transplantation and actual survival is 18% at 1 year, 38% at 2 years and 45% at 3 and 4 years. These figures are −3%, 14%, 32% and 36% in the intermediate risk group, and 0%, −3%, 4% and 7% in the low risk group, respectively (Table 3).

Table 1. Waiting times and outcomes in the different risk categories.

Risk category	High	Intermediate	Low
Estimated median survival	<1 year	1–3 years	>3 years
Total	22	38	53
PBC	18	16	12
PSC	4	22	41
Still waiting or removed (*n*)	1	4	12
Waiting time in days [median (range)]	375	113 (18–246)	320 (44–949)
Deaths on the waiting list (*n*)	7	2	2
Waiting time in days [median (range)]	30 (6–89)	129, 390	212, 446
Transplanted (*n*)	14	32	39
Waiting time in days [median (range)]	23 (2–104)	40 (3–593)	166 (7–459)
Per- and postoperative deaths (*n*)	6	15	8
All deaths (*n*)	13	17	10

Table 2. Effect of patient selection on survival in the different risk categories.

Risk category	High	Intermediate	Low
All candidates (*n*)	22	38	53
Actual 1-year survival [% (95% confidence interval)]	45 (24–64)	69 (51–82)	94 (82–98)
Transplanted patients (*n*)	14	32	39
Survival 1 year post OLT [% (95% confidence interval)]	64 (34–83)	69 (49–82)	89 (74–96)

Note: The actual 1-year survival percentages were calculated using the Kaplan–Meier method.

Table 3. Comparison of the estimated survival without transplantation with the actual survival in the different risk categories.

Risk category	High	Intermediate	Low
All candidates (*n*)	22	38	53
Median estimated survival [% (range)]			
1 year	27 (0–49)	72 (50–83)	94 (86–100)
2 years	7 (0–24)	49 (22–69)	87 (70–100)
3 years	0 (0–6)	31 (7–49)	80 (57–100)
4 years	0 (0–2)	20 (2–39)	74 (44–100)
Actual survival [% (95% CI)]			
1 year	45 (24–64)	69 (51–82)	94 (82–98)
2 years	45 (24–64)	63 (45–77)	84 (69–92)
3 years	45 (24–64)	63 (45–77)	84 (69–92)
4 years	45 (24–64)	56 (37–71)	81 (65–90)
Median survival benefit (%)			
1 year	18	–3	0
2 years	38	14	–3
3 years	45	32	4
4 years	45	36	7

Note: The estimated survival probabilities were calculated using the Mayo-models for PBC and PSC. The actual survival was calculated using the Kaplan–Meier method.

Discussion

There were two questions that led to this study. The first one is about the effect of including the waiting list period in the analysis of the survival of liver transplantation candidates. Our data on patients with chronic cholestatic liver disease show a considerable difference between the total group and the transplanted patients in the category with the highest risk. In the patient group with an estimated survival of 1 year or less, the actual 1-year survival decreases by 19% when patients who die without transplantation are included. The magnitude of the effect of including the waiting period in the analysis of survival depends on the waiting time, which is relatively short in our high-risk patients. This effect probably will be larger when the waiting time increases. In the intermediate and the low risk categories, with an estimated median survival of 1 year or more, survival is not significantly influenced by the waiting list mortality. Here, too, a larger effect might well be found with longer waiting times.

The second question is what the overall outcome is for the different risk categories in terms of absolute survival and survival benefit. As expected, the highest absolute survival is found in our low-risk patients, but in this group there appears to be no meaningful survival benefit at a follow up of up to 4 years. In our study the effect of the waiting list mortality is negligible in the intermediate-risk group, but the postoperative mortality approaches that in the high-risk category. The largest survival benefit of liver transplantation is found in the group with the lowest estimated survival, even when patients who die without transplantation are included. This gain comes at the price of a 1-year mortality of 55% in our high-risk patients.

The final point is what the implications of our study are for the waiting list policy. It would be unfair to deny high-risk patients the chance of liver transplantation because of an increased postoperative mortality, and the largest survival benefit is found in this group. Although the current postoperative survival for high-risk patients may be higher than in our series, it is likely to remain worse than in the other groups. The effect of the waiting list mortality will not disappear, and can only become stronger with longer waiting times. When high-risk patients are informed about their prognosis, the waiting list mortality certainly should be included.

When a lower postoperative mortality than in our series can be attained, intermediate-risk patients are the most attractive candidates for liver transplantation. Both waiting list mortality and postoperative mortality will be lower than in high-risk patients, and there is a substantial survival benefit, certainly on the longer term. Thus two of the three goals mentioned in the introduction would be reached. For selected low-risk patients with a relatively good prognosis but a poor quality of life, liver transplantation also seems worthwhile, as it does not diminish survival on the short term and may well improve it on the longer term. In general, a policy of transplantation in an early disease stage would reduce the waiting list mortality and improve both overall and post-transplantation survival. Whenever possible, transplantation should not be postponed until the terminal, high-risk stage of chronic liver disease is reached.

Appendix

The Rotterdam Liver Transplantation Group is formed by HLA Janssen, RJ de Knegt, J Kwekkeboom, RA de Man, HJ Metselaar, S de Rave, SW Schalm, Department of Gastroenterology and Hepatology; CHJ van Eijck, G. Kazemier, HW Tilanus, JNM Ijzermans, Department of Surgery; ThN Groenland, L Visser, Department of Anaesthesiology; PE Zondervan, Department of Pathology; W Weimar, Department of Internal Medicine, Erasmus Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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CHAPTER 4a

HETEROTOPIC VERSUS ORTHOTOPIC LIVER TRANSPLANTATION FOR CHRONIC LIVER DISEASE: A CASE-CONTROL COMPARISON OF SHORT-TERM AND LONG-TERM OUTCOMES

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Abbreviations:

HLT: Heterotopic Liver Transplantation
OLT: Orthotopic Liver Transplantation
RR: Relative Risk
CI: Confidence Interval
ELTR: European Liver Transplant Registry

SUMMARY

Background Between 1986 and 1990 we performed heterotopic liver transplantation (HLT) in 17 patients with chronic liver disease. In spite of theoretical advantages and favorable short-term results, we abandoned HLT because of doubts about the long-term outcome and the improved results of standard orthotopic liver transplantation (OLT). There are, however, no studies comparing the long-term survival after HLT and OLT for chronic liver disease.
Patients and methods We performed a case-control study of HLT vs. OLT, with long-term patient and graft survival as the main outcome measures. Known confounders and differences in baseline characteristics between HLT and OLT patients were corrected for.
Results At 1 year, 5 of the 17 HLT patients had died, compared with 9 of the 34 OLT patients (relative risk [RR] 1.15; 95% confidence interval [CI] 0.33-4.02; P=0.83). After correction for confounders, the long-term risk of graft failure (RR, 18.0; 95% CI, 1.5-223.5; P=0.02) and of death (RR, 5.2; 95% CI, 0.8-34.8; P=0.09) was higher after HLT than after OLT. The main causes of graft loss and death at more than 1 year after HLT were de novo malignancies and a variety of biliary complications.
Conclusions In conclusion, our data, from one of the largest single-center series of HLT available, showed no significant difference between HLT and OLT in 1-year survival. However, the long-term outcome of HLT was inferior. HLT cannot be recommended as an alternative to OLT for any of the indications we studied, even though only 1 of the late deaths was definitely related to the heterotopic technique.

INTRODUCTION

In 1988, we reported on the favorable short-term results of auxiliary partial liver transplantation in a small number of patients with end-stage chronic liver disease.[1] Originally, this procedure, which will be referred to as heterotopic liver transplantation (HLT), was developed for patients deemed too ill for standard orthotopic liver transplantation (OLT). Encouraged by the early successes, we subsequently did HLT's in less severely affected patients as well. In 1991, we described the short-term outcomes in our HLT series.[2] Later, 17 HLT's from the UK and another series of 10 patients from Turkey were reported.[3,4]

HLT has, however, never gained general acceptance. In our center, the technique of HLT was abandoned in 1990 because of the improved results of OLT, even in very ill patients, and the risk of hepatocellular carcinoma in the host liver, especially in patients with viral hepatitis. Yet little is known about the long-term outcome of HLT, and a formal comparison with OLT

has never been made. Therefore, we examined the long-term survival after HLT and performed a case-control study of HLT vs. OLT. Because the advantages of HLT over OLT were expected to become evident during and early after transplantation, and certainly within the first year, we also took 1-year survival as an outcome measure. Other outcome measures were peroperative and in-hospital mortality, incidence of graft primary non-function, and frequency of retransplantation.

PATIENTS AND METHODS

Study population – cases

Between 1986 and 1990, elective HLT's for chronic liver disease were performed in 17 patients. Indications were hepatitis B (n=2), hepatitis B+D (n=3), primary biliary cirrhosis (n=5), primary sclerosing cholangitis (n=2), alcoholic cirrhosis (n=2), autoimmune hepatitis (n=1), cryptogenic cirrhosis (n=1), and cirrhosis caused by metabolic liver disease (n=1).

Selection of controls

Between July 1989 and December 2002, 234 patients underwent OLT in our institution. Excluded were 74 patients with a diagnosis not represented in the HLT group, mainly hepatitis C or hepatocellular carcinoma. From the remaining 160 patients, 2 controls were selected for each HLT patient, matched for diagnosis and as far as possible for disease severity measured using the Child-Turcotte-Pugh score. When more than 2 matches were found, the earliest OLT's were chosen. The characteristics of cases and controls, together with data on the operations and on the follow-up, were retrieved from our liver transplantation database and from the patient files. The 126 potential controls who were not included in the study had less severe liver disease (Child-Turcotte-Pugh score median 8, range 5-15), underwent transplantation later (median 1998, range 1989-2002), and had a higher 1-year survival (86%) than the actual controls.

Statistics

The baseline characteristics of cases and controls were compared to identify possible confounders. Because of the matched study design, advanced statistical methods were used for these comparisons, mixed model analysis of variance for continuous factors and fixed-effects logistic regression analysis for categorical factors. When the number of endpoints was too small for logistic regression analysis, Fisher's exact test was used. For the analysis of 1-year survival we also used fixed-effects logistic regression. Overall survival was calculated using the Kaplan-Meier method, starting at the day of transplantation, until death or until January 1, 2003, the closing date of the study. A stratified Cox proportional hazard rate model was used to analyze the long-term patient and graft survival. In

the Cox analysis, the year of transplantation, the Child-Turcotte-Pugh score, and the peroperative blood loss were entered as covariates. A score based on a recent European Liver Transplant Registry (ELTR) study, which identified a number of factors predicting mortality after liver transplantation, was included as a time-dependent variable.[5] Graft failure was defined as either retransplantation or patient death, regardless of clinical or biochemical graft function. All calculations were done using Stata (version 5.0; Stata, College Station, TX) SPSS (version 11.0.1.1; SPSS, Chicago, IL) and SAS (version 8.02; SAS Institute, Cary, NC) statistical software.

RESULTS

Matching criteria and baseline characteristics

Matching was successful for etiology, but not for disease severity. The Child-Turcotte-Pugh score was slightly higher in the HLT group than in the OLT group (median 11, range 8-14 vs. median 10, range 8-13, P<0.001). The age and gender distributions showed no significant differences between cases and controls. The other baseline characteristics we studied were year of transplantation, peroperative blood loss, and the relative risk (RR) of dying after transplantation as predicted by a truncated ELTR model.[5] The year of transplantation (median 1988 vs. 1994, range 1986-1990 vs. 1989-2002, P<0.001) and the peroperative blood loss (median 6.5 vs. 10.2 L, range 3.0-40.0 L vs. 2.5-95.0 L, P=0.03) also differed. Matched controls were transplanted at a median of 6.0 years (range 0.7-15.2 years) after the HLT cases.

Of the predictive factors identified by the ELTR study, 8 were relevant for our analysis. Euro-Collins solution was used for preservation in the first 7 heterotopic grafts. University of Wisconsin fluid was used in the remaining 10 heterotopic and in all of the 34 orthotopic grafts (P<0.001). Also, 16 of the 17 heterotopic grafts were reduced in size vs. 0 in the OLT group (P<0.001). The only full-size heterotopic graft came from a child. The other 6 relevant factors are retransplantation, the use of ABO blood group-compatible instead of ABO blood group-identical grafts, recipient age over 59 years, cold ischemic time of 12 hours or more, donor age over 55 years, and the combination of a female donor and a male recipient. For these 6 factors, no significant differences were found between cases and controls. The combined RR of death after transplantation, calculated using a truncated version of the ELTR model containing all 8 factors mentioned here, was considerably higher in cases than in controls (median 2.14 vs. 1.17, range 1.00-2.97 vs. 1.00-1.86, respectively, P=0.001). These data are summarized in Table 1.

Table 1: Patient characteristics and possible confounders according to type of transplantation.

	Heterotopic	Orthotopic	P
n	17	34	--
Gender (male/female)	11 / 6	17 / 17	0.25*
Recipient age in years, median (range)	48 (20-60)	50.5 (27-65)	0.06†
Year of transplantation, median (range)	1988 (1986-1990)	1994 (1989-2002)	<0.001†
Child-Turcotte-Pugh score, median (range)	11 (8-14)	10 (8-13)	<0.001†
ELTR relative risk, median (range)	2.14 (1.00-2.97)	1.17 (1.00-1.86)	0.001†
Partial graft	16	0	<0.001*
Preservation fluid non-UW	7	0	<0.001*
Retransplantation	2	1	0.26*
Cold ischemic time ≥12 hours	8	11	0.30‡
Recipient age ≥60 years	1	5	0.31
Donor age >55 years	0	2	0.55*
ABO-compatible graft	3	8	0.65‡
Donor female / recipient male	3	7	0.80‡
Blood loss in L, median (range)	6.5 (3.0-40.0)	10.2 (2.5-95.0)	0.03†

Abbreviations: ELTR, European Liver Transplant Registry; UW, University of Wisconsin.
* Fisher's exact test for categorical variables when logistic regression analysis inappropriate.
† Mixed model analysis of variance for continuous variables.
‡ Fixed effects logistic regression analysis for categorical variables.

Postoperative course and 1-year follow-up

There was no significant difference between HLT and OLT in the number of primary non-functioning grafts (0 of 17 vs. 1 of 34, P=1.00), the need for early retransplantation (1 of 17 vs. 1 of 34, P=0.62), or the in-hospital mortality (5 of 17 vs. 7 of 34, P=0.50). At 1 year, 12 of the 17 HLT patients were alive (survival 71%) compared with 25 of the 34 OLT patients (74%). The RR of death within 1 year for HLT vs. OLT was 1.15 (95% confidence interval [CI] 0.33-4.02, P=0.83, fixed effects logistic regression analysis). This risk did not change significantly after addition of any of the possible confounders to the model.

Long-term follow-up

Between 1 year after transplantation and the closing date of the study, 10 HLT patients died, compared with only 4 in the OLT group. The median patient survival after HLT was 2.00 years (95% CI, 1.15-2.85 years), whereas it exceeded the maximal follow-up of 12.8 years after OLT. The

RR of death after HLT was 5.2 (95% CI, 0.8-34.8; P=0.09; multivariate stratified time-dependent Cox analysis, corrected for all possible confounders). The RR of graft failure after HLT was 18.0 (95% CI, 1.5-223.5; P=0.02).

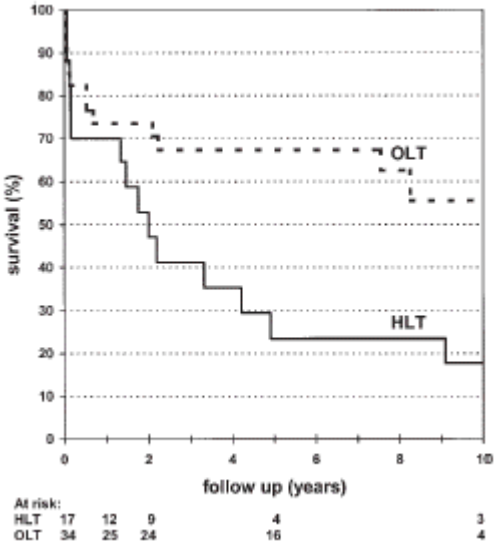

Figure 1: Survival after heterotopic liver transplantation (HLT) and orthotopic liver transplantation (OLT). One-year mortality HLT vs. OLT relative risk (RR) 1.15; 95% confidence interval (CI) 0.33-4.02; P=0.83; fixed effects logistic regression analysis. Overall mortality HLT vs. OLT RR 5.2; 95% CI 0.8-34.8; P=0.09; stratified time-dependent Cox analysis, corrected for all possible confounders.

Two HLT patients were alive at the closing date of the study, 1 with α-1-antitrypsin deficiency at 15.2 years after transplantation, and 1 with hepatitis B+D, who was followed for 14.7 years. In the HLT group, 4 patients survived for more than 5 tears, and 3 of these for more than 10 years (Fig. 1). The causes of graft failure or death at more than 1 year after transplantation in the HLT patients were biliary complications in 3, de novo extrahepatic malignancies in 3, hepatocellular carcinoma in 1, pulmonary embolism complicated by bronchopneumonia in 1, chronic rejection in 1, and sepsis in 1 (Table 2). Of the late deaths, 1 was definitely related, 6 were possibly related, and 3 were not related to the HLT procedure.

Details on the HLT patients with biliary complications and de novo malignancies are given in Table 3. Two of the late biliary complications were found in primary sclerosing cholangitis patients and the 3rd in an autoimmune hepatitis patient. One can be classified as primary sclerosing cholangitis recurrence, 1 as an ischemic type biliary lesion, and 1 as an anastomotic stricture. Of the 4 de novo malignancies, 3 were located in the digestive tract. The only hepatocellular carcinoma occurred in the first HLT patient, who underwent transplantation because of a chronic hepatitis B, he remained infected and developed cirrhosis of the graft within 1 year. All tumors were diagnosed within 4 years after transplantation.

Table 2: Follow-up beyond 1 year after transplantation for heterotopic and orthotopic procedures.

	Heterotopic	Orthotopic	P
n	17	34	--
Alive at 1 year	12	25	0.83*
Retransplantation at >1 year	1	0	0.32†
Death/graft failure at >1 year	10	4	<0.001†
Causes of death/graft failure at >1 year			
De novo malignancy	4‡	--	0.01†
Biliary complications	3§	--	0.03†
Chronic rejection	1‖	--	0.32†
Sepsis	1‖	--	0.32†
Pulmonary embolism/pneumonia	1‖	--	0.32†
Hepatitis B recurrence	--	2	0.55†
Femur neck fracture	--	1	1.00†
Unknown	--	1	1.00†

* Univariate fixed effects logistic regression analysis.
† Fisher's exact test.
‡ One definitely and 3 possibly related to HLT technique.
§ All 3 possibly related to HLT technique.
‖ Not related to HLT technique.

Of the 4 OLT patients who died after more than 1 year, 2 had hepatitis B recurrences, 1 died after a femur neck fracture, and 1 died of an unknown cause. In the OLT group, in which 61 patients were followed for more than 5 years, no graft losses due to late biliary complications and no deaths due to de novo malignancies were observed. The frequency of late biliary complications and of de novo malignancies was higher after HLT than after OLT (P=0.028 and P=0.007, respectively, Fisher's exact test).

DISCUSSION

Our formal comparison of HLT and OLT confirms the general opinion that the long-term outcome after HLT is inferior, even though the 1-year survival appears to be similar. A definite answer to the question as to whether the short-term results of HLT and OLT are equal cannot be given, because of the limitations of our study. One is the relatively small number of cases and controls, leading to a low power and wide CIs.[6] Also, the comparison between our HLT and OLT groups is not as simple as in the average randomized controlled trial, due to the matched study design, the differences in baseline characteristics, and the presence of other potential confounders. Differences between HLT and OLT were found for year of transplantation, disease severity, type of preservation fluid, and

peroperative blood loss. The use of a partial grafts, confined to the HLT group, is also an independent risk factor.[5] These factors and other known confounders were incorporated in the statistical models used to compare the 2 groups. However, it should be noted that most known confounders are disadvantageous for the HLT patients, and a 1-year survival lower than in the OLT group would have been expected.

Table 3: Heterotopic liver transplantation: late biliary complications and de novo malignancies.

Late biliary complications	**Case 1**	**Case 2**	**Case 4**	
Localization of biliary lesion	Intrahepatic	Intrahepatic	Extrahepatic	
Type of biliary lesion	Small duct	Large duct	Anastomotic	
Biliary lesion found after (years)	2.0	1.0	2.2	
Death or graft failure after (years)	3.3	8.9	2.2	
Potential risk factors				
Original liver disease	PSC/AIH	PSC	AIH	
Preservation fluid	Euro-Collins	UW	UW	
Cold ischemic time (hours)	5.0	12.5	13.5	
Warm ischemic time (minutes)	42	50	75	
Hepatic artery	Patent	Stenotic	Patent	
De novo malignancies	**Case 1**	**Case 2**	**Case 3**	**Case 4**
Tumor origin	Pancreas	Colon	Esophagus	Liver
Tumor diagnosed after (years)	1.8	1.3	3.7	2.0
Death after (years)	1.8	1.5	4.2	2.0
Potential risk factors				
Original liver disease	ALC	PBC	ALC	HBV
Age (years)	59	60	48	35
Gender	Male	Female	Male	Male

Abbreviations: PSC, primary sclerosing cholangitis; ALC, alcoholic cirrhosis; AIH, auto-immune hepatitis; PBC, primary biliary cirrhosis; UW, University of Wisconsin; HBV, hepatitis B virus infection.

The divergence in survival that occurs at more than 1 year after transplantation is mainly caused by a higher frequency of late biliary complications and de novo malignancies in HLT patients. Given the diversity of the late biliary complications after HLT, the difference with OLT could be a chance finding. The use of partial grafts for HLT is a possible explanation, but recent comparisons of right lobe and full-size grafts in OLT do not show a difference in the number of biliary complications.[7-9] There are, however, no studies that specifically address the problem of

late biliary complications with partial liver grafts, so in our patients they are at most possibly related to the technique of HLT.

The higher de novo tumor frequency in the HLT group probably is not related to a longer follow-up, since at least 50% of the OLT patients have been followed for a period longer than the maximal interval between HLT and the diagnosis of malignancy. A possible but rather speculative explanation for the higher number of de novo malignancies after HLT is the growth promoting effect of implanting a partial liver. The influence on the environment of such a large regenerating organ might be an additional risk factor for patients already prone to cancer development for other reasons, such as chronic viral hepatitis or alcohol abuse.[10] Support for this hypothesis has been found in an animal experiment, at least for intrahepatic metastases.[11] On the other hand, there is no evidence of excess mortality from de novo malignancies after transplantation of split or reduced size livers in the overall ELTR data (update June 2003), but these figures include pediatric cases, and it is not clear how many individuals had a higher than average risk of developing de novo malignancies. Thus, only the 1 hepatocellular carcinoma in our series can be considered as definitely related to HLT, whereas the other 3 tumors are only possibly related to the technique.

In conclusion, our study strongly suggests that HLT is equal to OLT in the short term but inferior in the long term. The exact cause of the divergence between HLT and OLT that occurs at more than 1 year after transplantation remains uncertain, but the use of partial liver grafts for HLT could play a role. Apart from ELTR data indicating a poorer outcome, little is known about the survival at more than 2 years after transplantation of partial liver grafts. One publication cites a 77% 5-year survival, but here the median follow-up is only 22.6 months.[7] The unexpected divergence we find in our study of HLT vs. OLT implies that more data on the long-term follow-up after other forms of partial liver transplantation are needed. In spite of the fact that survival of more than 10 years is possible after HLT, we found no advantage over OLT. HLT cannot be recommended as an alternative to OLT for any of the indications we studied.

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Heterotopic vs. Orthotopic Liver Transplantation for Chronic Liver Disease: A Case-Control Comparison of Short-Term and Long-Term Outcomes

Sjoerd de Rave,[1] Bettina E. Hansen,[2] Theo H.N. Groenland,[3] Geert Kazemier,[4] Robert A. de Man,[1] Herold J. Metselaar,[1] Onno T. Terpstra,[4] Hugo W. Tilanus,[4] Jan H.N.M. IJzermans,[4] and Solko W. Schalm[1]

Between 1986 and 1990 we performed heterotopic liver transplantation (HLT) in 17 patients with chronic liver disease. In spite of theoretical advantages and favorable short-term results, we abandoned HLT because of doubts about the long-term outcome and the improved results of standard orthotopic liver transplantation (OLT). There are, however, no studies comparing the long-term survival after HLT and OLT for chronic liver disease. We performed a case-control study of HLT vs. OLT, with long-term patient and graft survival as the main outcome measures. Known confounders and differences in baseline characteristics between HLT and OLT patients were corrected for. At 1 year, 5 of the 17 HLT patients had died, compared with 9 of the 34 OLT patients (relative risk [RR], 1.15; 95% confidence interval [CI], 0.33-4.02; $P = 0.83$). After correction for confounders, the long-term risk of graft failure (RR, 18.0; 95% CI, 1.5-223.5; $P = 0.02$) and of death (RR, 5.2; 95% CI, 0.8-34.8; $P = 0.09$) was higher after HLT than after OLT. The main causes of graft loss and death at more than 1 year after HLT were de novo malignancies and a variety of biliary complications. In conclusion, our data, from 1 of the largest single-center series of HLTs available, showed no significant difference between HLT and OLT in 1-year survival. However, the long-term outcome of HLT was inferior. HLT cannot be recommended as an alternative to OLT for any of the indications we studied, even though only 1 of the late deaths was definitely related to the heterotopic technique. (*Liver Transpl 2005;11:396-401.*)

In 1988, we reported on the favorable short-term results of auxiliary partial liver transplantation in a small number of patients with end-stage chronic liver disease.[1] Originally, this procedure, which will be referred to as heterotopic liver transplantation (HLT), was developed for patients deemed too ill for standard orthotopic liver transplantation (OLT). Encouraged by the early successes, we subsequently did HLTs in less severely affected patients as well. In 1991, we described the short-term outcomes in our HLT series.[2] Later, 17 HLTs from the UK and another series of 10 patients from Turkey were reported.[3,4]

HLT has, however, never gained general acceptance. In our center, the technique of HLT was abandoned in 1990 because of the improved results of OLT, even in very ill patients, and the risk of hepatocellular carcinoma in the host liver, especially in patients with viral hepatitis. Yet little is known about the long-term outcome of HLT, and a formal comparison with OLT has never been made. Therefore, we examined the long-term survival after HLT and performed a case-control study of HLT vs. OLT. Because the advantages of HLT over OLT were expected to become evident during and early after transplantation, and certainly within the first year, we also took 1-year survival as an outcome measure. Other outcome measures were perioperative and in-hospital mortality, incidence of graft primary nonfunction, and frequency of retransplantation.

Patients and Methods

Study Population—Cases

Between 1986 and 1990, elective HLTs for chronic liver disease were performed in 17 patients. Indications were hepatitis B virus (n = 2), hepatitis B + D (n = 3), primary biliary cirrhosis (n = 5), primary sclerosing cholangitis (n = 2), alcoholic cirrhosis (n = 2), autoimmune hepatitis (n = 1), cryptogenic cirrhosis (n = 1), and cirrhosis caused by metabolic liver disease (n = 1).

Abbreviations: HLT, heterotopic liver transplantation; OLT, orthotopic liver transplantation; RR, relative risk; CI, confidence interval; ELTR, European Liver Transplant Registry.

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Selection of Controls

Between July 1989 and December 2002, 234 patients underwent OLT in our institution. Excluded were 74 patients with a diagnosis not represented in the HLT group, mainly hepatitis C or hepatocellular carcinoma. From the remaining 160 patients, 2 controls were selected for each HLT patient, matched for diagnosis and as far as possible for disease severity measured using the Child-Turcotte-Pugh score. When more than 2 matches were found, the earliest OLTs were chosen. The characteristics of cases and controls, together with data on the operations and on the follow-up, were retrieved from our liver transplantation database and from the patient files. The 126 potential controls who were not included in the study had less severe liver disease (Child-Turcotte-Pugh score median 8; range 5-15), underwent transplantation later (median 1,998; range 1,989-2,002), and had a higher 1-year survival (86%) than the actual controls.

Statistics

The baseline characteristics of cases and controls were compared to identify possible confounders. Because of the matched study design, advanced statistical methods were used for these comparisons: mixed model analysis of variance for continuous factors and fixed-effects logistic regression analysis for categorical factors. When the number of endpoints was too small for logistic regression analysis, Fisher's exact test was used. For the analysis of 1-year survival we also used fixed-effects logistic regression. Overall survival was calculated using the Kaplan-Meier method, starting at the day of transplantation, until death or until January 1, 2003, the closing date of the study. A stratified Cox proportional hazard rate model was used to analyze the long-term patient and graft survival. In the Cox analysis, the year of transplantation, the Child-Turcotte-Pugh score, and the perioperative blood loss were entered as covariates. A score based on a recent European Liver Transplant Registry (ELTR) study, which identified a number of factors predicting mortality after liver transplantation, was included as a time-dependent variable.[5] Graft failure was defined as either retransplantation or patient death, regardless of clinical or biochemical graft function. All calculations were done using STATA (version 5.0; Stata, College Station, TX), SPSS (version 11.0.1; SPSS, Chicago, IL), and SAS (version 8.02; SAS Institute, Cary, NC) statistical software.

Results

Matching Criteria and Baseline Characteristics

Matching was successful for etiology, but not for disease severity. The Child-Turcotte-Pugh score was slightly higher in the HLT group than in the OLT group (median 11, range 8-14 vs. median 10, range 8-13; $P < 0.001$). The age and gender distributions showed no significant differences between cases and controls. The other baseline characteristics we studied were year of transplantation, perioperative blood loss, and the relative risk (RR) of dying after transplantation as predicted by a truncated ELTR model.[5] The year of transplantation (median 1988 vs. 1994; range 1986-1990 vs. 1989-2002; $P < 0.001$) and the perioperative blood loss (median 6.5 vs. 10.2 L; range 3.0-40.0 vs. 2.5-95.0 L; $P = 0.03$) also differed. Matched controls were transplanted at a median of 6.0 years (range 0.7-15.2 years) after the HLT cases. Of the predictive factors identified by the ELTR study, 8 were relevant for our analysis. Euro-Collins solution was used for preservation in the first 7 heterotopic grafts, University of Wisconsin fluid was used in the remaining 10 heterotopic and all of the 34 orthotopic grafts ($P < 0.001$). Also, 16 of the 17 heterotopic grafts were reduced in size vs. 0 in the OLT group ($P < 0.001$). The only full-size heterotopic graft came from a child. The other 6 relevant factors are retransplantation, the use of ABO blood group–compatible instead of ABO blood group–identical grafts, recipient age over 59 years, cold ischemic time of 12 hours or more, donor age over 55 years, and the combination of a female donor and a male recipient. For these 6 factors, no significant differences were found between cases and controls. The combined RR of death after transplantation, calculated using a truncated version of the ELTR model containing all 8 factors mentioned here, was considerably higher in cases than in controls (median 2.14 vs. 1.17, range 1.00-2.97 vs. 1.00-1.86, respectively; $P = 0.001$). These data are summarized in Table 1.

Postoperative Course and 1-Year Follow-Up

There was no significant difference between HLT and OLT in the number of primary nonfunctioning grafts (0 of 17 vs. 1 of 34; $P = 1.00$), the need for early retransplantation (1 of 17 vs. 1 of 34; $P = 0.62$), or the in-hospital mortality (5 of 17 vs. 7 of 34; $P = 0.50$). At 1 year, 12 of the 17 HLT patients were alive (survival 71%) compared with 25 of the 34 OLT patients (74%). The RR of death within 1 year for HLT vs. OLT was 1.15 (95% confidence interval [CI], 0.33-4.02; $P = 0.83$, fixed-effects logistic regression analysis). This risk did not change significantly after addition of any of the possible confounders to the model.

Long-Term Follow-Up

Between 1 year after transplantation and the closing date of the study, 10 HLT patients died, compared with only 4 in the OLT group. The median patient survival after HLT was 2.00 years (95% CI, 1.15-2.85 years),

Table 1. Patient Characteristics and Possible Confounders According to Type of Transplantation

	Heterotopic	Orthotopic	*P*
n	17	34	—
Gender (male/female)	11 / 6	17 / 17	0.25*
Recipient age in years, median (range)	48 (20-60)	50.5 (27-65)	0.06†
Year of transplantation, median (range)	1988 (1986-1990)	1994 (1989-2002)	<0.001†
Child-Turcotte-Pugh score, median (range)	11 (8-14)	10 (8-13)	<0.001†
ELTR relative risk, median (range)	2.14 (1.00-2.97)	1.17 (1.00-1.86)	0.001†
Partial graft	16	0	<0.001*
Preservation fluid non-UW	7	0	<0.001*
Retransplantation	2	1	0.26*
Cold ischemic time ≥ 12 hours	8	11	0.30‡
Recipient ≥ 60 years	1	5	0.31‡
Donor age > 55 years	0	2	0.55*
ABO-compatible graft	3	8	0.65‡
Donor female / recipient male	3	7	0.80‡
Blood loss in L, median (range)	6.5 (3.0-40.0)	10.2 (2.5-95.0)	0.03†

Abbreviations: ELTR, European Liver Transplant Registry; UW, University of Wisconsin.
*Fisher's exact test for categorical variables when logistic regression analysis inappropriate.
†Mixed model analysis of variance for continuous variables.
‡Fixed effects logistic regression analysis for categorical variables.

whereas it exceeded the maximal follow-up of 12.8 years after OLT. The RR of death after HLT was 5.2 (95% CI, 0.8-34.8; $P = 0.09$; multivariate stratified time-dependent Cox analysis, corrected for all possible confounders). The RR of graft failure after HLT was 18.0 (95% CI, 1.5-223.5; $P = 0.02$).

Two HLT patients were alive at the closing date of the study, 1 with α-1-antitrypsin deficiency at 15.2 years after transplantation, and 1 with hepatitis B + D, who was followed for 14.7 years. In the HLT group, 4 patients survived for more than 5 years and 3 of these for more than 10 years (Fig. 1). The causes of graft failure or death at more than 1 year after transplantation in the HLT patients were biliary complications in 3, de novo extrahepatic malignancies in 3, hepatocellular carcinoma in 1, pulmonary embolism complicated by bronchopneumonia in 1, chronic rejection in 1, and sepsis in 1 (Table 2). Of the late deaths, 1 was definitely related, 6 were possibly related, and 3 were not related to the HLT procedure.

Details on the HLT patients with biliary complications and de novo malignancies are given in Table 3. Two of the late biliary complications were found in primary sclerosing cholangitis patients and the 3rd in an autoimmune hepatitis patient. One can be classified as primary sclerosing cholangitis recurrence, 1 as an ischemic type biliary lesion, and 1 as an anastomotic stricture. Of the 4 de novo malignancies, 3 were located in the digestive tract. The only hepatocellular carcinoma occurred in the first HLT patient, who underwent transplantation because of a chronic hepatitis B; he remained infected and developed cirrhosis of the graft within 1 year. All tumors were diagnosed within 4 years after transplantation.

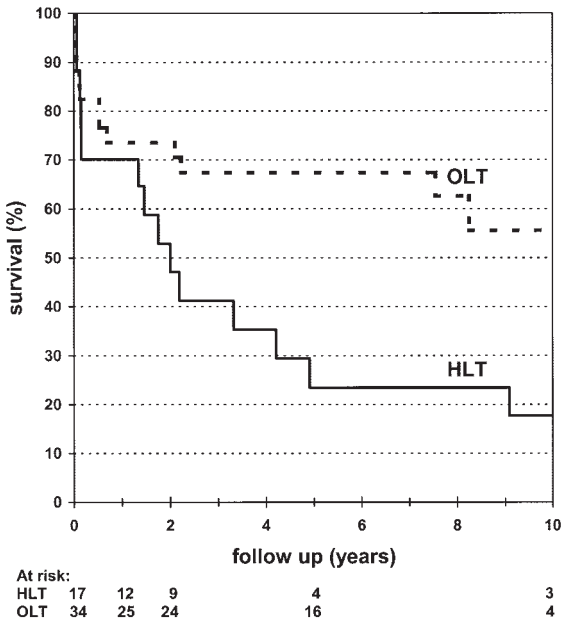

Figure 1. Survival after heterotopic liver transplantation (HLT) and orthotopic liver transplantation (OLT). One-year mortality HLT vs. OLT (RR, 1.15; 95% CI, 0.33-4.02; $P = 0.83$; fixed-effects logistic regression analysis). Overall mortality HLT vs. OLT (RR, 5.2; 95% CI, 0.8-34.8; $P = 0.09$; stratified time-dependent Cox analysis, corrected for all possible confounders).

Table 2. Follow-up Beyond 1 Year After Transplantation for Heterotopic and Orthotopic Procedures

	Heterotopic	Orthotopic	*P*
n	17	34	—
Alive at 1 year	12	25	0.83*
Retransplantation at > 1 year	1	0	0.32†
Death/graft failure at > 1 year	10	4	<0.001†
Causes of death/graft failure at > 1 year			
De novo malignancy	4‡	—	0.01†
Biliary complications	3§	—	0.03†
Chronic rejection	1‖	—	0.32†
Sepsis	1‖	—	0.32†
Pulmonary embolism/pneumonia	1‖	—	0.32†
Hepatitis B recurrence	—	2	0.55†
Femur neck fracture	—	1	1.00†
Unknown	—	1	1.00†

*Univariate fixed effects logistic regression analysis.
†Fisher's exact test.
‡One definitely and 3 possibly related to HLT technique.
§All 3 possibly related to HLT technique.
‖Not related to HLT technique.

Of the 4 OLT patients who died after more than 1 year, 2 had hepatitis B recurrences, 1 died after a femur neck fracture, and 1 died of an unknown cause. In the OLT group, in which 16 patients were followed for more than 5 years, no graft losses due to late biliary complications and no deaths due to de novo malignancies were observed. The frequency of late biliary complications and of de novo malignancies was higher after

Table 3. Heterotopic Liver Transplantation: Late Biliary Complications and De Novo Malignancies

	Case 1	Case 2	Case 3	
Late biliary complications				
Localization of biliary lesion	Intrahepatic	Intrahepatic	Extrahepatic	
Type of biliary lesion	Small duct	Large duct	Anastomotic	
Biliary lesion found after (years)	2.0	1.0	2.2	
Death or graft failure after (years)	3.3	8.9	2.2	
Potential risk factors				
Original liver disease	PSC/AIH	PSC	AIH	
Preservation fluid	Euro-Collins	UW	UW	
Cold ischemic time (hours)	5.0	12.5	13.5	
Warm ischemic time (minutes)	42	50	75	
Hepatic artery	Patent	Stenotic	Patent	
	Case 1	**Case 2**	**Case 3**	**Case 4**
De novo malignancies				
Tumor origin	Pancreas	Colon	Esophagus	Liver
Tumor diagnosed after (years)	1.8	1.3	3.7	2.0
Death after (years)	1.8	1.5	4.2	2.0
Potential risk factors				
Original liver disease	ALC	PBC	ALC	HBV
Age (years)	59	60	48	35
Gender	Male	Female	Male	Male

Abbreviations: PSC, primary sclerosing cholangitis; ALC, alcoholic cirrhosis; AIH, auto-immune hepatitis; PBC, primary biliary cirrhosis; UW, University of Wisconsin; HBV, hepatitis B virus infection.

HLT than after OLT ($P = 0.028$ and $P = 0.007$, respectively, Fisher's exact test).

Discussion

Our formal comparison of HLT and OLT confirms the general opinion that the long-term outcome after HLT is inferior, even though the 1-year survival appears to be similar. A definite answer to the question as to whether the short-term results of HLT and OLT are equal cannot be given, because of the limitations of our study. One is the relatively small number of cases and controls, leading to a low power and wide CIs.[6] Also, the comparison between our HLT and OLT groups is not as simple as in the average randomized controlled trial, due to the matched study design, the differences in baseline characteristics, and the presence of other potential confounders. Differences between HLT and OLT were found for year of transplantation, disease severity, type of preservation fluid, and perioperative blood loss. The use of a partial grafts in the HLT group is also an independent risk factor.[5] These factors and other known confounders were incorporated in the statistical models used to compare the 2 groups. However, it should be noted that most known confounders are disadvantageous for the HLT patients, and a 1-year survival lower than in the OLT group would have been expected.

The divergence in survival that occurs at more than 1 year after transplantation is mainly caused by a higher frequency of late biliary complications and de novo malignancies in HLT patients. Given the diversity of the late biliary complications after HLT, the difference with OLT could be a chance finding. The use of partial grafts for HLT is a possible explanation, but recent comparisons of right lobe and full-size grafts in OLT do not show a difference in the number of biliary complications.[7-9] There are, however, no studies that specifically address the problem of late biliary complications with partial liver grafts, so in our patients they are at most possibly related to the technique of HLT.

The higher de novo tumor frequency in the HLT group probably is not related to a longer *follow-up*, since at least 50% of the OLT patients have been followed for a period longer than the maximum interval between HLT and the diagnosis of malignancy. A possible but rather speculative explanation for the higher number of de novo malignancies after HLT is the growth promoting effect of implanting a partial liver. The influence on the environment of such a large regenerating organ might be an additional risk factor for patients already prone to cancer development for other reasons, such as chronic viral hepatitis or alcohol abuse.[10] Support for this hypothesis has been found in an animal experiment, at least for intrahepatic metastases.[11] On the other hand, there is no evidence of excess mortality from de novo malignancies after transplantation of split or reduced size livers in the overall ELTR data (update June 2003), but these figures include pediatric cases, and it is not clear how many individuals had a higher than average risk of developing de novo malignancies. Thus, only the 1 hepatocellular carcinoma in our series can be considered as definitely related to HLT, whereas the other 3 tumors are only possibly related to the technique.

In conclusion, our study strongly suggests that HLT is equal to OLT in the short term but inferior in the long term. The exact cause of the divergence in survival between HLT and OLT that occurs at more than 1 year after transplantation remains uncertain, but the use of partial liver grafts for HLT could play a role. Apart from ELTR data indicating a poorer outcome, little is known about the survival at more than 2 years after transplantation of partial liver grafts.[5] One publication cites a 77% 5-year survival after right lobe split-liver transplantation, but here the median follow-up is only 22.6 months.[7] The unexpected divergence we find in our study of HLT vs. OLT implies that more data on the long-term follow-up after other forms of partial liver transplantation are needed. In spite of the fact that survival of more than 10 years is possible after HLT, we found no advantage over OLT. HLT cannot be recommended as an alternative to OLT for any of the indications we studied.

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CHAPTER 4b

SURVIVAL OF MORE THAN TEN YEARS AFTER HETEROTOPIC LIVER TRANSPLANTATION FOR END-STAGE CHRONIC LIVER DISEASE: A REPORT OF THREE CASES

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SUMMARY

We studied three patients who survived for more than 10 years after Heterotopic Liver Transplantation because of end-stage chronic liver disease. Two patients had hepatitis B and D infections. Although their grafts rapidly became infected too, and severe fibrosis of the graft developed within five years, the liver function has remained normal or near normal during a follow-up of at least 10 years, and no signs of portal hypertension have occurred. One of these two patients died of sepsis 11.5 years after transplantation, the other was alive at 16.5 years, with moderate renal dysfunction as the main long-term complication. The remaining patient had α-1-antitrypsin deficiency and was cured after transplantation. She was alive at 17 years post-transplantation, with complications that can be ascribed to long-term immunosuppression, such as overweight, hypertension, osteopenia and recurrent basal cell skin cancers. Near-complete atrophy of the native liver was found on imaging in all patients. Hepatocellular carcinoma did not occur. Although in general the results of Heterotopic Liver Transplantation are inferior to those of Orthotopic Liver transplantation, these cases show that Heterotopic Liver Transplantation for end-stage chronic liver disease can result in long-term survival with normal clinical and biochemical graft function.

INTRODUCTION

Heterotopic Liver Transplantations (HLT) have been performed since 1964[1]. Although we have reported favourable short-term results of HLT in our first 6 chronic liver disease patients, the procedure has never become a generally accepted alternative for the standard Orthotopic Liver Transplantation (OLT)[2]. Long-term survivors of HLT have been described, but the maximum follow up of these patients was 6.5 years[3-6]. We have recently compared the long-term survival of our 17 HLT patients with chronic liver disease with that of 34 matched OLT patients[7]. In the HLT group, 3 patients have survived for more than 10 years. Here we report the clinical course of these 3 exceptional long-term survivors in more detail.

PATIENTS AND METHODS

Our initial report on Auxiliary Partial Liver Transplantation described 6 patients[2]. Patient A died of hepatocellular carcinoma 2.0 years after transplantation, patient C died during attempted retransplantation for recurrence of his Primary Sclerosing Cholangitis after 3.3 years and patient E died of pulmonary embolism complicated by bronchopneumonia after 1.3 years. Patients B, D and F survived for more than 10 years, these

are the subject of the present report. Clinical and laboratory data were retrieved from our liver transplantation database and from the patient files. All biochemical measurements were done using standard automated techniques. Clinical data on the 3 patients are summarised in table 1.

Table 1: Clinical data on the three patients who survived for more than 10 years after heterotopic liver transplantation (HLT).

Patient	B	D	F
Sex	Male	Female	Male
Age	40	53	32
Liver disease	Chronic hepatitis B+D	α-1-antitrysin deficiency	Chronic hepatitis B+D
Child-Pugh score	13	12	8
Disease course	Recurrence in graft	Cured	Recurrence in graft
Graft function	Normal (11 years)	Normal (17 years)	Normal (16 years)
Graft fibrosis	Cirrhosis (5.0 years)	None (5.0 years)	Severe (4.5 years)
Native liver	Atrophic	Atrophic	Atrophic
Late complications	None	Bacterial cholangitis Basal cell skin cancers Hypertension Overweight Osteopenia Femur neck fracture	Biliary stricture (7 mths) Recurrent upper and lower respiratory tract infections Renal dysfunction
Outcome	Died (sepsis)	Alive	Alive
Follow up (yrs)	11.5	17.0	16.5

Data on laboratory measurements, Body Mass Index and abdominal ultrasound results at yearly follow up after heterotopic liver transplantation in table 2. Magnetic Resonance Images (MRI) of the grafts and the native livers of patients B, D and F obtained 3.2, 12.5 and 11.5 years after HLT, respectively, are shown in figure 1a, 1b and 1c.

CASES

Patient B was a 40-year old male who was transplanted for end-stage cirrhosis due to a chronic hepatitis B and D infection. He had an uneventful postoperative course and was discharged after 29 days. Initially his maintenance immunosuppressive regimen consisted of corticosteroids and Cyclosporin-A, after 2.5 years Cyclosporin-A was replaced by Azathioprin because of hypertension. Hepatitis B s-antigen became positive in the graft at 3 weeks and c-antigen at 9 weeks. The s-antigen has been positive in the graft throughout, the c-antigen became negative at 5 years. Delta-antigen was already detectable in the graft at 1 week and has

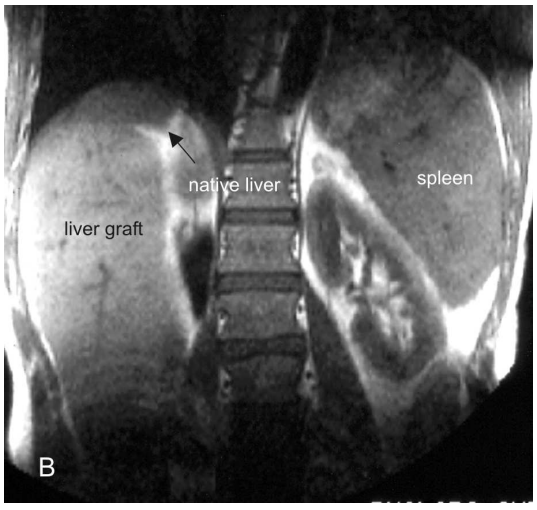
remained positive ever since. Progressive fibrosis was seen in biopsies taken from the liver graft between 6 months and 4 years after transplantation and cirrhosis was found at 5 years. Nevertheless, the function of the graft has always been normal or nearly normal. Values found during yearly follow-up were between 17 and 36 μmol/l for bilirubin, between 34 and 43 g/l for albumin, and between 0.9 and 1.2 for the prothrombin time International Normalised Ratio (INR). Repeated imaging showed atrophy of the host liver, and no evidence of hepatocellular carcinoma. The spleen has remained enlarged, but there have been no complications of portal hypertension. Apart from an inguinal hernia requiring surgical repair he has had no other important medical problems until he unexpectedly died from a gram-negative sepsis 11.5 years after transplantation.

Table 2: Laboratory measurements, Body Mass Index and abdominal ultrasound results at yearly follow up after heterotopic liver transplantation for the 3 patients who survived for more than 10 years.

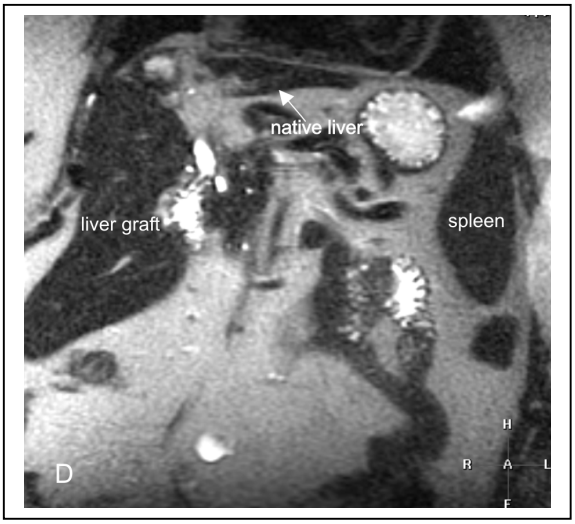
	Normal values	Patient B		Patient D		Patient F	
		median (range)	year 11	median (range)	year 17	median (range)	year 16
Laboratory measurements							
Albumin (g/l)	35-50	37 (34-43)	36	43 (37-48)	40	40 (34-43)	43
Bilirubin (μmol/l)	≤ 17	24 (17-36)	24	25 (10-33)	10	19 (15-30)	30
Alanine amino-transferase (U/l)	M < 41 F < 31	30 (21-109)	30	22 (14-33)	20	45 (23-259)	32
Creatinine (μmol/l)	M 65-115 F 55-90	95 (80-108)	103	83 (67-159)	80	138 (123-184)	136
Platelet count (x 10^9/l)	150-400	92 (68-139)	78	105 (82-133)	94	112 (92-136)	122
Leukocyte count (x 10^9/l)	3.5-10.0	7.8 (5.7-10.9)	7.1	4.2 (3.4-6.9)	3.9	3.8 (2.5-5.5)	3.7
Prothrombin time (INR, -/-)	≤ 1.4	1.1 (0.9-1.2)	1.2	1.0 (0.9-1.1)	1.1	1.3 (1.1-1.4)	1.4
Antithrombin-III (U/ml)	0.80-1.20	0.67 (0.52-1.16)	0.67	0.88 (0.47-1.04)	0.79	0.71 (0.51-0.90)	0.65
Other measurements							
Body Mass Index (kg/m^2)	18.0-25.0	23.2 (22.3-24.6)	22.7	33.1 (26.5-34.7)	28.7	21.2 (19.9-24.9)	24.8
Spleen size on US (cm)	≤ 12	15.4 (14.0-18.0)	15.0	15.0 (14.0-16.2)	15.6	16.0 (14.0-17.9)	15.8

Patient D was a 53-year old female with α-1-antitrypsin deficiency. She quickly recovered from the transplantation and left the hospital 24 days later. It did, however, take 6 months for her ascites to resolve completely. Because of hypertension her maintenance immunosuppression was switched from corticosteroids and Cyclosporin-A to a low-dose triple drug regimen also containing Azathioprin at 1 year and to corticosteroids and Azathioprin at 2 years. The serum α-1-antitrypsin concentration rose from 0.18 g/l before to 2.31 g/l one week after transplantation, and has remained normal thereafter. In the latest biopsy of the graft, taken at 5 years after transplantation, no major abnormalities were seen. The function of the graft has been normal ever since the transplantation, with values at yearly follow-up between 10 and 33 μmol/l for bilirubin, between 37 and 48 g/l for albumin, and between 0.9 and 1.1 for the INR. The native liver atrophied, as shown by repeated imaging. After the first six months there have been no signs or symptoms of portal hypertension, although the spleen size has not returned to normal. She was put on Sirolimus monotherapy at 15 years because of recurrent basal cell skin cancers. Other late complications have been recurrent staphylococcal infections of the skin, overweight and osteoporosis, with a fracture of the left femoral neck at 15.7 years. She has been hospitalised twice on suspicion of acute bacterial cholangitis at 12.4 and 12.9 years, but has been doing well otherwise. This patient has been followed postoperatively for 17 years.

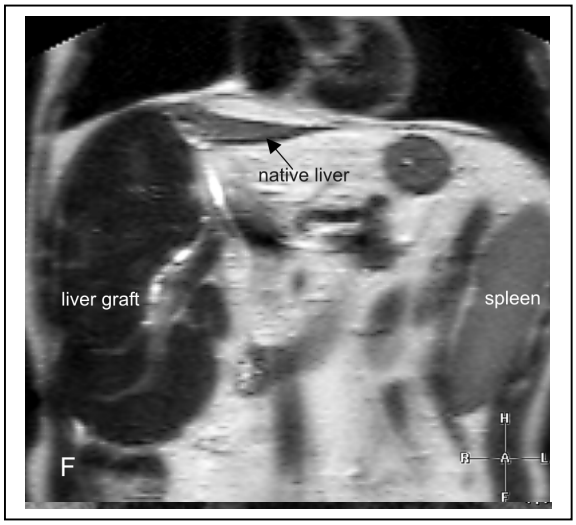
Figure 1: Magnetic Resonance Imaging of the abdomen after Heterotopic Liver Transplantation in 3 long-term survivors, coronal view. The images were selected to enable an optimal comparison between the grafts and the native livers.



Patient B, 3.2 years after transplantation. A T1-weighted spin-echo sequence is shown. As usual, the signal intensity of the graft is higher than that of the spleen. The native liver (arrow) has almost disappeared and has a lower signal intensity than the graft, due to atrophy and fibrosis.



Patient D, 12.5 years after transplantation. T2-weighted single-shot turbo spin-echo sequence, higher signal intensities indicating fat and fluid. The graft signal intensity equals that of the spleen, due to the technique used. The remnant of the native liver (arrow) has a somewhat increased signal intensity, mainly due to atrophy.



Patient F, 11.5 years after transplantation. T2-weighted single-shot turbo spin-echo sequence. The signal intensity of the graft is lower than that of the spleen, as expected in this sequence. As in patient D, the native liver (arrow) is atrophic, with a markedly increased signal intensity.

Patient F was a 32-year old male who also suffered from a chronic hepatitis B and D infection. He had no major postoperative complications and was discharged after 21 days. He has been on corticosteroids and Cyclosporin-A for 10 years, and on Cyclosporin-A monotherapy thereafter. The hepatitis B s-antigen became positive in the graft at 3 weeks and the c-antigen at 7 weeks. The s-antigen has remained positive, while expression of the c-antigen reached a peak in the third month and then declined, but remained detectable. Delta antigen was first detected in the graft at 3 weeks and remained positive thereafter. Fibrosis in the graft progressed from minimal at 7 months to severe at 4.5 years. Like in patient B, the function of the graft has always been normal or nearly normal. Here values during yearly follow-up were between 15 and 30 μmol/l for bilirubin,

between 34 and 43 g/l for albumin, and between 1.1 and 1.4 for the INR. In this patient too, repeated imaging showed atrophy of the host liver, without evidence of hepatocellular carcinoma. The spleen has remained enlarged, but there have been no other signs of portal hypertension. A biopsy of the graft at 3 months was complicated by bleeding, sepsis, respiratory failure and renal failure, requiring several laparotomies, ventilatory support and haemodialysis. The renal function did recover after several weeks, but has not returned to normal. At 7 months another laparotomy was performed because of a biliary anastomotic stricture. Later on several admissions have been necessary because of recurrent upper and lower respiratory infections. This patient was still alive at 16.5 years after transplantation.

DISCUSSION

Long-term survival for up to 17 years after HLT is possible, as illustrated by our experience, even though the overall results of HLT are inferior to those of OLT[7]. We describe a follow up of 45 patient-years, with a maximum more than twice that published so far. HLT has resulted in long-lasting correction of the metabolic defect and of the liver function in our patient with α-1-antitrypsin deficiency. The graft function has also remained normal or near normal in the 2 patients with hepatitis B and D infections of the graft, in spite of the development of severe fibrosis or cirrhosis of the graft within 5 years. The spleen has remained enlarged in all 3 patients, but no other signs or symptoms of portal hypertension have occurred.

One of the reasons we abandoned HLT was the risk of hepatocellular carcinoma in the remaining cirrhotic liver in general and the even greater risk in specific diagnostic categories like chronic viral hepatitis and haemo-chromatosis. Hepatocellular carcinoma was looked for systematically in the 2 patients with chronic viral hepatitis, but was not found. As shown by imaging, the native liver has atrophied in all cases. It seems possible that the near-total atrophy of the native liver already seen at 3 years has played a role in the protection of even our high-risk patients against the development of hepatocellular carcinoma of recipient origin. In the third patient there is no clinical suspicion of hepatocellular carcinoma at more than 16 years, her own liver has also atrophied. In all 3 cases the quality of life generally has been good. Notwithstanding its limitations, HLT did prove to be worthwhile for at least some of our chronic liver disease patients.

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CHAPTER 5a

THE IMPORTANCE OF ORTHOTOPIC LIVER TRANSPLANTATION IN ACUTE HEPATIC FAILURE

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SUMMARY

Selection of patients with acute hepatic failure for liver transplantation remains difficult, and there is no definite proof of a survival effect. We therefore did a retrospective study in 75 consecutive patients referred over a 12 year period. In two thirds we identified a cause, mostly viruses or drugs. Patients were grouped by the Clichy and King's College criteria. In 20 there was no indication for transplantation. Of the 5 with autoimmune hepatitis 3 died, significantly differing from the other 15 (P=0.009). The remaining 55 met our criteria, except 1. All 9 patients with absolute contraindications died. Of the 46 enlisted, 7 died without transplantation. One year survival after transplantation was 69%, compared with 58% by "intention to treat". For patients enlisted, transplantation reduced mortality by 78% (P=0.069). The Clichy and King's College criteria reliably predict survival without transplantation, except in autoimmune hepatitis. Our study strongly suggests that transplantation improves survival.

INTRODUCTION

Acute hepatic failure (AHF) is defined as a syndrome of severe hepatic dysfunction and hepatic encephalopathy in individuals with no evidence of preexisting liver disease. AHF is a medical emergency and the outcome can generally be determined in the first 12-24 hours after admission. O'Grady, Schalm and Williams[13] proposed to divide AHF into three groups, based on differences in clinical features and prognosis. Hyperacute hepatic failure is the term used to describe patients who develop encephalopathy within 7 days after the onset of jaundice. The most frequent causes are acetaminophen intoxications and acute hepatitis A virus (HAV) or herpes simplex virus (HSV) infections. About one third of the patients presenting with hyperacute hepatic failure survive without transplantation. AHF includes patients with an interval from jaundice to encephalopathy of 8-28 days. There is a high incidence of cerebral edema in this group, and survival without transplantation is less than 10%. Subacute hepatic failure describes those patients with an interval of 5-12 weeks between the appearance of jaundice and the onset of encephalopathy. Although the frequency of cerebral edema is low, the outcome is also poor, with a survival of approximately 15%.[13]

The most frequent causes of AHF are hepatotropic viruses and drugs, but there is a large variety of other etiologic factors. In approximately 30% of all cases, no cause can be identified. Some conditions can be effectively treated by means other than liver transplantation, for instance N-acetyl-cysteine in cases of paracetamol intoxication or portosystemic shunting in Budd-Chiari syndrome. For most other causes of AHF, medical therapy is

supportive only, aimed at prevention of complications such as infections and cerebral edema. In general, the mortality of patients with AHF treated without liver transplantation is high and ranges between 60 and 80%.[10]

An early and accurate assessment of the individual patient is critical in deciding whether liver transplantation is indicated in the treatment of AHF. To identify patients with hepatitis B induced AHF who die without liver transplantation, Benhamou and Bernuau have developed the Clichy criteria, which predict which patients could benefit from orthotopic liver transplantation (OLT). Patients with hepatic encephalopathy (grade 3 to 4) and concentrations of coagulation factor V less than 20% in patients in the age group below 30 years and less than 30% in patients in the age group above 30 years die in 80% of all cases.[2] In a retrospective study, Pauwels et al. have found a low predictive value for these criteria in patients with AHF by non-viral causes.[15]

O'Grady and Williams have analyzed 588 patients with AHF at King's College Hospital and proposed their criteria for liver transplantation. In acetaminophen-induced AHF, survival correlated with arterial blood pH, peak prothrombin time, serum creatinine and grade of encephalopathy. In other patients, non-A-non-B hepatitis or idiosyncratic drug reactions, age less than 10 or more than 40 years, jaundice for more than 7 days before the onset of encephalopathy, serum bilirubin more than 300 µmol/l and a prothrombin time of more than 50 seconds were associated with a poor prognosis.[12]

In this study we report the outcome in 75 patients with AHF referred for emergency liver transplantation. We also did a retrospective assessment of the applicability of the Clichy and the King's College criteria, and evaluated the effect of OLT on survival in patients put on the high urgency waiting list.

PATIENTS AND METHODS

From 1 April 1987 until 1 January 1999, 83 patients with acute liver failure were referred for OLT. Two patients died before the indication for transplantation could be established. Six other patients were not considered suitable candidates because of advanced age (n=2), ongoing chronic alcohol abuse (n=2) and liver failure secondary to severe nonhepatic disease (n=2). These 8 patients were not included in this analysis.

For the remaining 75 patients, emergency liver transplantation was considered. Diagnostic evaluation included routine hematological and biochemical tests, measurement of coagulation parameters, virological and

immunological screening, toxicologic and metabolic tests, abdominal ultrasound, and a CT scan of the brain, to assess cerebral edema. Clotting factor V was determined by measurement of prothrombin time in plasma deficient of factor V. Arterial blood was used to determine pH values and lactate levels in patients with acetaminophen-induced AHF. The grade of encephalopathy was assessed using the Opolon criteria[14] and by spectral analysis of the electroencephalogram.[16]

All patients with grade 3 or grade 4 encephalopathy were admitted to the ICU. According to protocol they were intubated, ventilated, received antibiotic prophylaxis and, if necessary, were treated with intravenous glucose, vasopressive drugs and mannitol. In each patient the indication for emergency liver transplantation was weighed against absolute or relative contra-indications (i.e. extrahepatic infection, sepsis, malignancies, or HIV-positivity). Prior to publication of the King's College and Cliichy criteria the indication was based mainly on clinical judgement. Candidates for emergency liver transplantation were placed on the Eurotransplant high-urgency waiting list after consent was obtained from the nearest relative. Only blood group-compatible donors were accepted. Patients without an indication or not fit for liver transplantation received continuing conservative treatment according to protocol and were re-evaluated twice daily until recovery or death.

Table 1: Indications for emergency liver transplantation according to the Clichy and King's College criteria. Of the 55 patients considered as candidates for emergency liver transplantation, six are not included. Three were anhepatic at the moment of enlistment, and in another three, who did meet the King's College criteria, no factor V measurement was made.

		Clichy criteria met	**Clichy criteria not met**
King's College criteria met	**Total**	n = 37	n = 2
	Hepatitis B	n = 5	n = 0
	Other causes	n = 32	n = 2
King's College criteria not met	**Total**	n = 9	n = 1
	Hepatitis B	n = 4	n = 0
	Other causes	n = 5	n = 1

Twenty patients met neither the Clichy nor the King's College criteria for enlistment (group 1), and in nine patients absolute contraindications for transplantation were present (group 2). Group 3 consisted of 46 patients who were enlisted for emergency liver transplantation, of whom 7 died on the waiting list (group 3a) and 39 underwent OLT (group 3b). Three of the seven patients in group 3a were anhepatic at the moment of enlistment after total hepatectomy because of liver trauma. In three other group 3 patients the Clichy criteria could not be applied because no factor V measurement

was available. One patient with venoocclusive disease met only one of the two Clichy criteria and two of the five King's College criteria, but was nevertheless accepted for emergency liver transplantation. Of the other 48 patients, two met only the King's College criteria and nine only the Clichy criteria, while the remaining 37 met both (Table 1). Grade 3 or 4 encephalopathy was present in 49 of the 51 group 3 patients that could be evaluated.

Group 1 consisted of 4 men and 16 women with a median age of 41 years (range 17-57 years), group 2 of 6 men and 3 women with a median age of 45 years (27-62), group 3a of 4 men and 3 women with a median age of 40 years (16-55), and group 3b of 15 men and 24 women with a median age of 37 years (16-62). The largest diagnostic categories were acute viral hepatitis (n=18), drug induced hepatitis (n=12), acetaminophen intoxication (n=11), autoimmune hepatitis (n=6), and acute liver failure of unknown etiology (n=19). The other indications were irreparable liver trauma (n=3), Wilson's disease (n=3), Budd-Chiari syndrome (n=2), and acute fatty liver of pregnancy (n=1). These data are summarized in Table 2.

For comparisons between groups, Fisher's exact test was used. The effect of liver transplantation on survival in patients put on the high urgency waiting list was investigated using Cox regression, with transplantation as time-dependent variable. Calculations were done using the Logxact program (1993, CYTEL Software Corporation, Cambridge, Mass., USA).

RESULTS

Follow up in group 1 patients (no indication, n=20), most of whom were sent back to the referring clinician after recovery, is limited to a median of 14 days (range 2-1,859 days). Three of the five patients with autoimmune hepatitis in this group died: one at day 14 after admission of uncontrollable bleeding from a duodenal ulcer, one at day 25 of sepsis as a complication of immunosuppressive treatment and one at home, at 91 days from admission and after successful treatment of her liver disease, of an unknown cause. No deaths were observed in the 15 patients with other diagnoses (P=0.009, Fisher's exact test). All patients in group 2 (absolute contraindictions, n=9) died at a median of 2 days (range 0-11) after admission. The main causes of death in this group were irreversible shock and multiorgan failure.

In group 3 (enlisted, n=46), 7 patients, including the 3 anhepatic patients, died while waiting for transplants at a median of 2 days (range 0-7) after enlistment. Causes of death were cerebral edema in three cases, uncontrollable bleeding in two and irreversible shock and sepsis in one

each. The median stay on the waiting list for the 39 transplanted patients was 1 day (range 0-5 days). The median follow up in the 27 survivors of transplantation was 2 years and 6 months (range 6 days to 9 years and 6 months), with 23 patients followed up for at least 1 year, 17 for at least 2 years and 9 for at least 5 years.

Table 2: Etiology of liver disease and demographics in 75 patients with acute hepatic failure (AHF) according to indications and contraindications for liver transplantation. Group 1, criteria not met (n = 20); group 2, absolute contraindications (n = 9); group 3a, listed, died on list (n = 7); group 3b, transplanted (n = 39).

	Total	**1**	**2**	**3a**	**3b**
Indication		No	Yes	Yes	Yes
Contraindication			Yes	No	No
Death on waiting list				Yes	No
Total number	75	20	9	7	39
Male/female	29/46	4/16	6/3	4/3	15/24
Age (years)					
Median	39	41	45	40	37
Range	16-62	17-57	27-64	16-55	16-62
Cause known	56	18	7	7	24
- Acute viral hepatitis	- 18	- 2	- 4	- 2	- 10
- Acute hepatitis B	- 12	- 1	- 4	-	- 7
- Acute hepatitis A	- 2	- 1	-	-	- 1
- Acute EBV hepatitis	- 2	-	-	- 1	- 1
- Acute HSV hepatitis	- 1	-	-	- 1	-
- Acute hepatitis E	- 1	-	-	-	- 1
- Drug-induced hepatitis	- 23	- 10	- 3	- 2	- 8
- Acetaminophen	- 11	- 9	- 2	-	-
- NSAID	- 2	-	-	- 1	- 1
- Ecstasy	- 2	-	-	-	- 2
- Other drugs	- 8	- 1	- 1	- 1	- 5
- Other causes	- 15	- 6	-	- 3	- 6
- Autoimmune hepatitis	- 6	- 5	-	-	- 1
- Wilson's disease	- 3	-	-	-	- 3
- Liver trauma	- 3	-	-	- 3	-
- Budd-Chiari syndrome	- 2	-	-	-	- 2
- Acute fatty liver in pregnancy	- 1	- 1	-	-	-
Cause unknown	19	2	2		15

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

All but one of the 12 deaths after transplantation occurred within 6 months, at a median of 14 days (range 2-159 days) after enlistment. Death after transplantation was caused by sepsis in 3 patients, by cerebral edema in 2 patients and by a variety of other causes in 6 patients. The one remaining patient died of a pulmonary malignancy after 6 years and 3 months. The causes of death in the different patient groups are listed in Table 3. The actual survival of transplanted patients at 1 year, 2 years, and 5 years was 69% compared with 58% when calculated according to the intention-to-treat principle. Cox regression, comparing mortality of transplanted patients with that of those still on the waiting list, showed a relative death rate of 0.22 (95% confidence interval 0.03-1.47, P=0.069).

Table 3: Causes of death in 31 patients with acute hepatic failure according to indication and contraindications for liver transplantation.

Group	Total	1	2	3a	3b
Total number	75	20	9	7	39
Number of deaths	31	3	9	7	12
- Causes of death					
Irreversible shock/MOF	10		8	1	1
Sepsis	6	1	1	1	3
Cerebral edema	5			3	2
Uncontrollable bleeding	3	1		2	
Aorto-enteral fistula/MRSA	1				1
Veno-occlusive disease	1				1
Primary nonfunctioning graft	1				1
Pneumonia (Legionella)	1				1
Cardiac tamponade	1				1
Unknown	1	1			
Bronchuscarcinoma (late)	1				1

Abbreviations: MOF, multiorgan failure; MRSA, methicillin-resistant *Staphylococcus Aureus*.

DISCUSSION

OLT has changed the prognosis of patients with AHF and is recommended when spontaneous recovery appears unlikely. A large U.S. series from the late 1980s and early 1990s showed a 63% 1-year survival after liver transplantation for AHF[4], with a 68% survival at 2 months reported in the largest contemporary European study.[5] In a more recent U.S. multicenter study, the 1-year survival had increased to 76%,[17] while in Europe it remained about 70%.[6,11] Auxiliary liver transplantation, originally advocated as an alternative therapy for end-stage chronic liver disease,[19] has theoretical advantages over the conventional orthotopic procedure and

results in an approximately 60% survival,[3,18] but is an accepted treatment for acute liver failure in selected cases only. Other therapies, such as artificial hepatic support systems and hepatocyte transplantation, are still in an experimental stage or only serve as a bridge to OLT.[7,9]

We describe our single-centre experience with acute liver failure over a 12-year period, which differs from other reports in at least one important aspect. Recently 295 cases seen in 13 centers were reported from the USA,[12] with acetaminophen-induced acute liver failure as the most frequent diagnosis. In the UK acetaminophen even accounts for the majority of cases.[1,14] Acetaminophen intoxication was the cause of acute liver failure in only 11 of our 75 patients (15%), with only two, both with an absolute contraindication, meeting the criteria for transplantation. In our series the Clichy and King's College criteria accurately predicted survival without transplantation for all patients, with the exception of three out of five presenting with acute autoimmune hepatitis, who died of causes not directly related to the primary liver disease. The chance of finding a difference like the one in this study, when in fact the survival in these two subgroups is equal, is less than 1%.

The outcome in the 39 patients who were transplanted most probably would have been worse without transplantation than the 69% 1-year survival observed in this group, given the results of our Cox regression analysis and the results of medical treatment reported in the pre-transplantation era.[8] Mortality among the patients on the waiting list for emergency liver transplantation and in the postoperative period does, however, remain a serious problem. Most deaths are due to irreversible complications already present at or shortly after enlistment, such as cerebral edema or infection. Of our 46 patients enlisted for emergency liver transplantation 18 (39%) died on the waiting list (n=7) or in the postoperative period (n=11). As expected, death in these patients was mainly caused by infections (n=6) and by cerebral edema (n=5). Various other causes accounted for the remaining 7 deaths. A totally different pattern is seen in patients with contraindications for transplantation, most of whom died of irreversible shock or multiorgan failure.

Our study confirms that, in patients that do meet either the Clichy or the King's College criteria, emergency liver transplantation improves survival, although due to the small number of end points the difference with the patients that died on the waiting list was only of borderline significance. In the group of patients enlisted for emergency liver transplantation the short-term mortality remains relatively high, but might be improved by measures aimed at preventing cerebral edema and infections. Of special interest might be the outcome in the five patients with acute autoimmune hepatitis without an indication, three of whom died. In acute autoimmune hepatitis, the selection criteria for emergency liver transplantation currently in use

appear not be appropriate. In these patients treatment with immuno-suppressive drugs seems to be a hazardous course, and a different approach may be warranted. From this retrospective study in a relatively modest number of patients we conclude that the combined King's College and the Clichy criteria are useful in deciding which patients with acute liver failure will or will not benefit from emergency liver transplantation in most diagnostic categories.

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ORIGINAL ARTICLE

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Abstract Selection of patients with acute hepatic failure for liver transplantation remains difficult, and there is no definite proof of a survival effect. We therefore did a retrospective study in 75 consecutive patients referred over a 12-year period. In two-thirds we identified a cause, mostly viruses or drugs. Patients were grouped by the Clichy and King's College criteria. In 20 there was no indication for transplantation. Of the 5 with autoimmune hepatitis, 3 died, significantly differing from the other 15 ($P = 0.009$). The remaining 55 met our criteria, except 1. All 9 patients with absolute contraindications died. Of the 46 enlisted, 7 died without transplantation. One-year survival after transplantation was 69%, compared with 58% by "intention to treat." For patients enlisted, transplantation reduced mortality by 78% ($P = 0.069$). The Clichy and King's College criteria reliably predict survival without transplantation, except in autoimmune hepatitis. Our study strongly suggests that transplantation improves survival.

Keywords Acute hepatic failure · Liver transplantation · Survival

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Patients and methods

From 1 April 1987 until 1 January 1999, 83 patients with acute liver failure were referred for OLT. Two patients died before the indication for transplantation could be established. Six other patients were not considered suitable candidates because of advanced age ($n=2$), ongoing chronic alcohol abuse ($n=2$), and liver failure secondary to severe nonhepatic disease ($n=2$). These 8 patients were not included in this analysis.

For the remaining 75 patients, emergency liver transplantation was considered. Diagnostic evaluation included routine hematological and biochemical tests, measurement of coagulation parameters, virological and immunological screening, toxicologic and metabolic tests, abdominal ultrasound, and a CT scan of the brain, to assess cerebral edema. Clotting factor V was determined by measurement of prothrombin time in plasma deficient of factor V. Arterial blood was used to determine pH values and lactate levels in patients with acetaminophen-induced AHF. The grade of encephalopathy was assessed using the Opolon criteria [14] and by spectral analysis of the electroencephalogram [16]. All patients with grade 3 or grade 4 encephalopathy were admitted to the ICU. According to protocol they were intubated, ventilated, received antibiotic prophylaxis, and if necessary were treated with intravenous glucose, vasopressive drugs, and mannitol. In each patient the indication for emergency liver transplantation was weighed against absolute or relative contraindications (i.e., extrahepatic infection, sepsis, malignancies, or HIV positivity). Prior to publication of the King's College and Cliichy criteria, the indication was based mainly on clinical judgement. Candidates for emergency liver transplantation were placed on the Eurotransplant high-urgency waiting list after consent was obtained from the nearest relative. Only blood group-compatible donors were accepted. Patients without an indication or not fit for liver transplantation received continuing conservative treatment according to protocol and were reevaluated twice daily until recovery or death.

Twenty patients met neither the Clichy nor the King's College criteria for enlistment (group 1), and in nine patients absolute contraindications for transplantation were present (group 2). Group 3 consisted of 46 patients who were enlisted for emergency liver transplantation, of whom 7 died while waiting for a transplant (group 3a) and 39 underwent orthotopic liver transplantation (group 3b). Three of the seven patients in group 3a were anhepatic at the moment of enlistment after total hepatectomy because of liver trauma. In 3 other group 3 patients, the Clichy criteria could not be applied because no factor V measurement was available. One patient with veno-occlusive disease met only one of the two Clichy criteria and two of the five King's College criteria, but was nevertheless accepted for emergency liver transplantation. Of the other 48 patients, two met only the King's College criteria and nine only the Clichy criteria, while the remaining 37 met both (Table 1). Grade III or grade IV encephalopathy was present in 49 of the 51 group 3 patients that could be evaluated.

Group 1 consisted of 4 men and 16 women with a median age of 41 years (range 17–57 years), group 2 of 6 men and 3 women with a median age of 45 years (27–62), group 3a of 4 men and 3 women with a median age of 40 years (16–55), and group 3b of 15 men and 24 women with a median age of 37 years (16–62). The largest diagnostic categories were acute viral hepatitis ($n=18$), drug-induced

Table 1 Indication for emergency liver transplantation according to the Clichy and King's College criteria. Of the 55 patients considered as candidates for emergency liver transplantation, six are not included. Three were anhepatic at the moment of enlistment and, in another three who did meet the King's College criteria, no factor V measurement was made

		Clichy criteria met	Clichy criteria not met
King's College criteria met	Total	$n=37$	$n=2$
	Hepatitis B	$n=5$	$n=0$
	Other causes	$n=32$	$n=2$
King's College criteria not met	Total	$n=9$	$n=1$
	Hepatitis B	$n=4$	$n=0$
	Other causes	$n=5$	$n=1$

hepatitis ($n=12$), acetaminophen intoxication ($n=11$), autoimmune hepatitis ($n=6$), and acute liver failure of unknown etiology ($n=19$). The other indications were irreparable liver trauma ($n=3$), Wilson's disease ($n=3$), Budd-Chiari syndrome ($n=2$), and acute fatty liver of pregnancy ($n=1$). These data are summarized in Table 2.

For comparisons between groups, Fisher's exact test was used. The effect of liver transplantation on survival in patients put on the high-urgency waiting list was investigated using Cox regression, with transplantation as time-dependent variable. Calculations were done using the Logxact program (1993; CYTEL Software Corporation, Cambridge, Mass., USA).

Results

Follow-up in group 1 patients (no indication, $n=20$), most of whom were sent back to the referring clinician after recovery, is limited to a median of 14 days (range 2–1,859 days). Three of the five patients with autoimmune hepatitis in this group died: one at day 14 after uncontrollable bleeding from a duodenal ulcer, one at day 25 of sepsis as a complication of immunosuppressive treatment, and one at home, at 91 days from admission and after successful treatment of her liver disease, of an unknown cause. No deaths were observed in the 15 patients with other diagnoses ($P=0.009$, Fisher's exact test). All patients in group 2 (absolute contraindictions, $n=9$) died at a median of 2 days (range 0–11) after admission. The main causes of death in this group were irreversible shock and multiorgan failure.

In group 3 (enlisted, $n=46$), 7 patients, including the 3 anhepatic patients, died whilst waiting for transplants at a median of 2 days (range 0–7) after enlistment. Causes of death were cerebral edema in three cases, uncontrollable bleeding in two, and irreversible shock and sepsis in one each. The median stay on the waiting list for the 39 transplanted patients was 1 day (range 0–5 days). The median follow-up in the 27 survivors of transplantation was 2 years and 6 months (range 6 days to 9 years and 6 months), with 23 patients followed up for at least 1 year, 17 for at least 2 years, and 9 for at least 5 years. All but one of the 12 deaths after transplantation occurred within 6 months, at a median of 14 days (range 2–159 days) after enlistment. Death after transplantation was caused by sepsis in 3 patients, by cerebral edema in 2 patients, and by a variety of other causes in 6 patients. The one remaining patient died of a pulmonary malignancy after 6 years and 3 months. The causes of death in the different patient groups are listed in Table 3. The actual survival of transplant patients at 1 years, 2 years, and 5 years was 69% compared with 58% when calculated according to the intention-to-treat principle. Cox regression, comparing mortality of transplanted patients with that of those still on the waiting list, showed a relative death rate of 0.22 (95% confidence interval 0.03–1.47, $P=0.069$).

Discussion

OLT has changed the prognosis of patients with AHF and is recommended when spontaneous recovery appears unlikely. A large US series from the late 1980s and early 1990s showed a 63% 1-year survival after liver transplantation for AHF [4], with a 68% survival at 2 months reported in the largest contemporary European study [5]. In a more recent US multicenter study, the 1-year survival had increased to 76% [17], while in Europe it remained at about 70% [6, 11]. Auxiliary liver transplantation, originally advocated as an alternative therapy for end-stage chronic liver disease [19], has theoretical advantages over the conventional orthotopic procedure and results in an approximately 60% survival [3, 18], but is an accepted treatment for acute liver failure in selected cases only. Other therapies such as artificial hepatic support systems and hepatocyte transplantation are still at an experimental stage or only serve as a bridge to OLT [7, 9].

We describe our single-centre experience with acute liver failure over a 12-year period, which differs from other reports in at least one important aspect. Recently 295 cases seen in 13 centers were reported from the USA [12], with acetaminophen-induced acute liver failure as the most frequent diagnosis. In the UK, acetaminophen even accounts for the majority of cases [1, 14]. Acetaminophen intoxication was the cause of acute liver failure in only 11 of our 75 patients (15%), with only 2, both with an absolute contraindication, meeting the criteria for transplantation.

In our series the Clichy and King's College criteria accurately predicted survival without transplantation for all patients, with the exception of three out of five presenting with acute autoimmune hepatitis, who died of causes not directly related to the primary liver disease. The chance of finding a difference like the one in this study, when in fact the survival in these two subgroups is equal, is less than 1%.

Table 2 Etiology of liver disease and demographics in 75 patients with acute hepatic failure (*AHF*) according to indication and contraindications for liver transplantation. Group 1, criteria not met ($n=20$); group 2, absolute contraindications ($n=9$); group 3a, listed, died on list ($n=7$); group 3b, listed, transplanted ($n=39$) (*NSAID* nonsteroidal anti-inflammatory drug)

Group	Total	1	2	3a	3b
Indication		No	Yes	Yes	Yes
Contraindication			Yes	No	No
Death on waiting list				Yes	No
Total number	75	20	9	7	39
Male/female	29/46	4/16	6/3	4/3	15/24
Age (years)					
Median	39	41	45	40	37
Range	16–62	17–57	27–62	16–55	16–62
Acute viral hepatitis	18	2	4	2	10
Acute hepatitis B	12	1	4		7
Acute hepatitis A	2	1			1
Acute EBV hepatitis	2			1	1
Acute HSV hepatitis	1			1	
Acute hepatitis E	1				1
Drug-induced hepatitis	23	10	3	2	8
Acetaminophen	11	9	2		
NSAID	2			1	1
Ecstasy	2				2
Other drugs	8	1	1	1	5
Other causes	15	6		3	6
Autoimmune hepatitis	6	5			1
Wilson's disease	3				3
Liver trauma	3			3	
Budd-Chiari syndrome	2				2
Acute fatty liver in pregnancy	1	1			
Cause unknown	19	2	2		15

The outcome in the 39 patients who received transplants most probably would have been worse without transplantation than the 69% 1-year survival observed in this group, given the results of our Cox regression analysis and the results of medical treatment reported in the pretransplantation era [8]. Mortality among the patients on the waiting list for emergency liver transplantation and in the postoperative period does, however, remain a serious problem. Most deaths are due to irreversible complications already present at or shortly after enlistment, such as cerebral edema or infection. Of our 46 patients enlisted for emergency liver transplantation, 18 (39%) died on the waiting list ($n=7$) or in the postoperative period ($n=11$). As expected, death in these patients was mainly caused by infections ($n=6$) and by cerebral edema ($n=5$). Various other causes accounted for the remaining 7 deaths. A totally different pattern is seen in patients with contraindications for transplantation, most of whom died of irreversible shock or multiorgan failure.

Our study confirms that, in patients that do meet either the Clichy or the King's College criteria, emergency liver transplantation improves survival, although due to the small number of end points the difference to the patients that died on the waiting list was only of borderline significance. In the group of patients enlisted for emergency liver transplantation, the short-term mortality remains relatively high, but might be improved by measures aimed at preventing cerebral edema and infections. Of special interest might be the outcome in the five patients with acute autoimmune hepatitis without an indication, three of whom died. In acute autoimmune hepatitis, the selection criteria for emergency liver transplantation currently in use appear not be appropriate. In these patients treatment with immunosuppressive drugs seems to be a hazardous course, and a different approach may be warranted. From this retrospective study in a relatively modest number of patients, we conclude that the combined King's College and the Clichy criteria are useful in deciding which patients with acute liver failure will or will not benefit from emergency liver transplantation in most diagnostic categories.

Table 3 Causes of death in 21 patients with acute hepatic failure according to indication and contraindications for liver transplantation. *MOF* multiorgan failure, *MRSA* methicillin-resistant *Staphylococcus aureus*

Group	Total	1	2	3a	3b
Total number	75	20	9	7	39
Number of deaths	31	3	9	7	12
Causes of death					
Irreversible shock/MOF	10		8	1	1
Sepsis	6	1	1	1	3
Cerebral edema	5			3	2
Uncontrollable bleeding	3	1		2	
Aorto-enteral fistula/MRSA	1				1
Veno-occlusive disease	1				1
Primary nonfunctioning graft	1				1
Pneumonia (Legionella)	1				1
Cardiac tamponade	1				1
Unknown	1	1			
Bronchuscarcinoma (late)	1				1

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CHAPTER 5b

LONG-TERM FOLLOW UP AFTER TRANSPLANTATION FOR ACUTE LIVER FAILURE: RESULTS AT 5 AND AT 10 YEARS

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SUMMARY

Background Little is known about the long-term sequelae of acute liver failure treated by liver transplantation. We therefore studied the clinical course of patients who survived at least 10 years.
Methods From 65 patients transplanted for acute liver failure between 1989 and 2002 we selected those that had a complete follow-up of at least 10 years. In this group of 10 patients we conducted a retrospective study aimed at general health aspects and specific complications, including graft dysfunction, hypertension, renal dysfunction, obesity, diabetes, dyslipidemia and bone loss at 5 and at 10 years.
Results Of the 10 patients seven were functioning normally at both time points, limitations due to pre-existing diseases were present in three. Frequent complications were obesity, dyslipidemia, hypertension and mild renal dysfunction. One or more of these problems were found in nine patients at 5 years and in all 10 at 10 years. Other complications were either uncommon or absent.
Conclusions In spite of some frequent late postoperative complications, liver transplantation leads to complete rehabilitation in the majority of patients with acute liver failure who survive the initial period after the operation.

INTRODUCTION

Liver transplantation is regarded as an effective treatment of acute liver failure, resulting in survival rates between 60% and 80%[1-5]. Yet little is known about long-term sequelae in surviving patients. Studies on long-term outcomes after transplantation for acute liver failure have concentrated mainly on survival, and only few on retransplantation, hepatitis B virus reinfection and neuropsychologic function[1,6]. We, therefore, decided to study the clinical course after transplantation, and especially the prevalence of late complications in our long-term survivors of acute liver failure.

PATIENTS AND METHODS

Until the end of 2002 we performed orthotopic liver transplantations in 65 patients with acute liver failure. Of these 65, 18 were done prior to November, 1994. In this group of 18, there were five deaths within two weeks after transplantation, and one at five months. One patient died from a pulmonary tumour at 6 years after transplantation, and one was lost to follow up after 7 years. The study group was formed by the ten remaining patients, that have been followed for at least 10 years. These were two

males and eight females with a median age at transplantation of 33 years (range 20-50 years). All 10 patients were included in an earlier report, where more details on the severity of the liver disease were given[5]. The causes of liver failure were acute hepatitis B in four patients, acute hepatitis A in one, drug-induced hepatitis in two, Wilson's disease in one, Budd-Chiari syndrome in one and unknown in the last patient. One patient was retransplanted after three days because of hepatic artery thrombosis, a second patient had to be retransplanted after five months because of ischemic type biliary lesions.

After transplantation, all patients had yearly check-ups, consisting of a routine clinical visit, recording of medication, length, weight and blood pressure, biochemical tests, virological tests, and measurement of bone mass. We chose the 5- and 10-year time-points for this study. Liver biopsies were not done on a protocol basis but only when indicated. Data were retrieved from our liver transplantation database and from patient files. All laboratory measurements were done using standard automated methods. Hypertension was defined as the use of one or more antihypertensive drugs. Diabetes was diagnosed according to current international standards[7]. Values for triglycerides or cholesterol above the desired range are referred to as dyslipidemia. Bone mass was measured by dual photon absorptiometry.

RESULTS

General health, treatment and pregnancies The number of patients that could be classified as "alive and well" was seven at both 5 and 10 years. Two patients suffered from chronic psychiatric disorders and one had progressive multiple sclerosis, these diseases were already present before transplantation in all cases. Readmissions were concentrated in the first year after transplantation with a median of 17.5 days (range 0-76 days), and accounted for a median of 5.4 hospital-days per year (range 0.0-23.6 days/year) in the first 5 years after transplantation, and for 0.3 days/year (range 0.0-8.6 days/year) in the next 5 years (table 1). All four patients with acute hepatitis B were treated with hepatitis B immunoglobulin only during the first year after transplantation, none developed reinfection of the graft although antibodies to the hepatitis B surface-antigen remained positive in only two. At 5 years all ten patients were treated with calcineurin-inhibitors, three were on a triple immuno- suppressive regimen, four on a two-drug regimen and three on mono-therapy. At 10 years these numbers were ten, two, one and seven. There have been four pregnancies in three patients, one ending in intra-uterine foetal death and three in delivery of a healthy child.

Table 1: Clinical and anthropometric data on long-term survivors at 5 and at 10 years after transplantation for acute liver failure.

	5 years		10 years	
	median (range)	**n=**	**median (range)**	**n=**
Readmissions (days/year)	5.4 (0.0-23.6)	10	0.3 (0.0-8.6)	10
Immunosuppressive drugs	2 (1-3)	10	1 (1-2)	10
CNI[1] + STE[2] + AZA[3]		3		2
CNI + STE		4		1
CNI monotherapy		3		7
Hypertension		7		8
Diabetes		0		0
Body Mass Index (kg/m^2)	26 (21-36)	10	25 (20-34)	10
BMI > 25 / > 30		6/3		4/2
BMD L2-L4 (g/cm)	1.19 (1.01-1.35)	10	1.23 (1.04-1.38)	10
Z-score < -1 / < -2		1/0		1/0
BMD femoral neck (g/cm)	0.94 (0.67-1.22)	10	0.94 (0.71-1.22)	10
Z-score < -1 / < -2		5/1		3/1

1) CNI: Calcineurin inhibitors
2) STE: Corticosteroids
3) AZA: Azathioprine
4) BMD: Bone Mineral Density (dual photon absorptiometry)
5) Z-score: difference from age- and sex-matched controls in S.D.

Graft function and histology The function of the liver grafts was measured by serum concentrations of bilirubin, albumin and coagulation factors. At 5 years, the graft function was normal in all but two of the patients, who had slightly elevated bilirubin levels. At 10 years bilirubin was also above normal in two patients, one of these and one additional patient had an antithrombin-III level just below the normal range. Mild liver enzyme abnormalities, mainly of the cholestatic type, were found in two of the patients at 5 years and in five at 10 years (table 2). Measurements of the spleen size were available for five patients at 5 years (median length 9.9 cm, range 7.7-13.0 cm), and for six at 10 years (9.6 cm, 7.6-13.0 cm). There was only one patient with a spleen size >12.0 cm both at 5 and at 10 years. No other signs or symptoms of portal hypertension were found in any of the patients. Between 5 and 10 years after transplantation four liver biopsies were done in 3 patients, these showed signs of nodular regenerative hyperplasia and mild ductopenia at 7.4 years in one, moderate fibrosis in another one at 8.2 years, and only minimal abnormalities at 8.0 years in the last patient.

Hypertension and renal dysfunction Hypertension requiring drug treatment was present in seven patients at 5 years and in eight at 10 years (table 1). At 5 years serum creatinine concentrations were above normal in

four of the seven hypertensive patients and in one of the three normotensive patients. At 10 years these figures were six of the eight and one of the two. The median serum creatinine concentration was 96 μmol/l (range 72-152 μmol/l) at 5 years and 115 μmol/l (range 82-154 μmol/l) at 10 years (table 2).

Table 2: Laboratory measurements in long-term survivors at 5 and at 10 years after transplantation for acute liver failure.

	normal range – or – ***target range***	**5 years**		**10 years**	
		median (range)	**normal**	**median (range)**	**normal**
Bilirubin (μmol/l)	<17	11 (9-24)	9/10	10 (7-31)	8/10
Albumin (g/l)	35-50	44 (39-49)	10/10	41 (39-48)	10/10
Prothrombin time (INR, -/-)	≤1.4	0.9 (0.9-1.0)	7/7	1.0 (0.9-1.1)	10/10
Antithrombin-III (U/ml)	0.80-1.20	1.10 (0.85-1.40)	10/10	1.10 (0.77-1.19)	8/10
All liver enzymes			3/7		5/10
Alkaline phosphatase (U/l)	<120	60 (26-158)	7/9	84 (53-129)	9/10
γ-glutamyl transferase (U/l)	M <50 F <35	29 (17-181)	5/8	40 (20-135)	5/10
Aspartate amino-transferase (U/l)	M < 37 F <31	16 (12-40)	9/10	27 (20-29)	10/10
Alanine amino-transferase (U/l)	M <41 F <31	19 (11-55)	9/10	23 (13-41)	9/10
Creatinine (μmol/l)	M 65-115 F 55-90	96 (72-152)	5/10	115 (82-154)	3/10
Triglycerides (mmol/l)	*≤2.0*	1.54 (1.33-3.00)	3/5	1.36 (0.93-2.72)	8/9
Cholesterol (mmol/l)	*≤5.0*	6.2 (4.8-6.6)	1/5	5.4 (3.5-6.6)	1/10
HDL-cholesterol (mmol/l)	*≥1.55*	1.51 (0.87-1.61)	2/4	1.58 (0.94-2.71)	5/10
Haemoglobin (mmol/l)	M 8.6-10.5 F 7.5-9.5	8.5 (6.9-9.8)	8/10	8.5 (6.7-10.2)	7/10
Leukocyte count ($x10^9$/l)	3.5-10.0	8.1 (5.0-9.9)	10/10	7.3 (6.0-8.5)	10/10
Platelet count ($x10^9$/l)	150-400	238 (182-317)	10/10	219 (161-330)	10/10

Obesity, diabetes and dyslipidemia At 5 years the median Body Mass Index (BMI) was 26 kg/m^2 (range 21-36 kg/m^2), and at 10 years 25 kg/m^2 (20-34 kg/m^2). At 5 years six patients had a BMI > 25 kg/m^2 and three of

these a BMI > 30 kg/m^2. At 10 years these figures were four and two. Between 5 and 10 years weight was gained by three patients and lost by three patients, while four remained stable. Diabetes was found in none of the patients (table 1). Hypercholesterolemia was found in four out of five patients at 5 years and in nine out of ten at 10 years. Hypertriglyceridemia was present in one patient with a BMI >30 kg/m^2 at 5 as well as at 10 years, in one other patient triglycerides were elevated at 5 years but normal at 10 years. The median serum cholesterol was 6.2 mmol/l (range 4.8-6.6 mmol/l) at 5 years and 5.4 mmol/l (3.5-6.6 mmol/l) at 10 years. For the serum triglycerides these figures were 1.54 mmol/l (1.33-3.00 mmol/l) and 1.36 mmol/l (0.93-2.72 mmol/l) (table 2).

Bone loss Bone mineral mass of the lumbar spine at the level of L2 to L4 and of the femoral neck was measured routinely in all patients. To prevent or treat bone loss Calcium and vitamin D were prescribed to three patients at 5 years and at 10 years. The median lumbar spine Bone Mineral Density (BMD) at 5 years was 1.19 g/cm (range 1.01-1.35 g/cm) and 1.23 g/cm (1.04-1.38 g/cm) at 10 years. For the femoral neck these figures were 0.94 g/cm (0.67-1.22 g/cm) and 0.94 (0.71-1.22 g/cm). At 5 and at 10 years, only one female patient had a lumbar spine BMD of more than 1 S.D. below the mean for age- and sex-matched controls (Z-score), she was the only one with frank osteopenia of the femoral neck, with a Z-score < -2 (table 1).

DISCUSSION

We observed a survival of more than 10 years in 10 of our 18 patients with acute liver failure who underwent emergency orthotopic liver transplantation. No objective quality of life measurements were done, but the subjective quality of life has been good in most of these 10 patients. Some frequent long-term complications were found, the main ones being obesity, dyslipidemia, hypertension and mild renal dysfunction. In various combinations these problems were present in nine of the patients at 5 years and in all ten at 10 years, with a mean number of complications per patient of 2.2 at 5 years and of 2.8 at 10 years. At 10 years the biochemical graft function was normal in all but three of the patients but only minimal abnormalities were found in these three. Histological abnormalities of the graft were found in two patients at 7.4 and 8.2 years after transplantation. None has developed signs or symptoms of portal hypertension. Osteopenia was uncommon in our patients.

No overt neuropsychological complications developed after transplantation in our 10 long-term survivors. However, we did not use specific tests of neuropsychologic function like others have done[6]. Nevertheless, most of

our patients have been able to lead a fairly normal life for at least 10 years after transplantation, without clear limitations due to the original disease, the operation or the long-term immunosuppressive treatment. The three patients that did not function at a normal level all had pre-existing psychiatric or neurologic diseases. We conclude that for patients with acute liver failure emergency liver transplantation not only improves survival, but also leads to complete rehabilitation in most patients that survive the operation. However, obesity, dyslipidemia, hypertension and renal dysfunction are common and increase over time. Most of these problems are related to the immunosuppressive therapy, especially the treatment with calcineurin inhibitors. Changes in and minimisation of immunosuppression might lead to a decrease in the prevalence or the severity of these complications.

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CHAPTER 6

FACTORS PREDICTING EARLY ACUTE REJECTION AFTER LIVER TRANSPLANTATION IN PATIENTS TREATED WITH CALCINEURIN INHIBITORS

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SUMMARY

Background Individualised immunosuppressive treatment after liver transplantation requires an estimate of the risk of acute rejection. We therefore studied 120 potential risk factors in patients that were mainly treated with calcineurin inhibitors and did not receive anti-lymphocyte antibodies or Interleukin-2-receptor blocking antibodies.
Patients and methods Data on all consecutive patients meeting the inclusion criteria for the study were extracted from our liver transplantation database and from patient files. The study group consisted of 95 males and 89 females with a median age of 47 years (range 16-70 years). There were 68 acute rejections in the first 3 months after transplantation. Statistical methods used were Kaplan-Meier survival estimates and univariate as well as multivariate Cox regression analysis.
Results Age under 50 years and the presence of the HLA-DR6 and DR7 antigens in recipients were associated with an increased risk of early acute rejection. Other factors that significantly increased the risk were peroperative cryoprecipitate use and postoperative intravenous Cyclosporin treatment. Anti-hepatitis B immunoglobulin treatment was associated with a lower risk. A score containing four of these factors, without cryoprecipitate use and intravenous Cyclosporin treatment, turned out to have a c-statistic of 0.660, very near the optimum.
Conclusions Our study suggests that it is possible to define patient groups at different risks of acute rejection using a limited number of four factors known at the moment of transplantation. Confirmation of pur findings would pave the road for individualised immunosuppression after liver transplantation.

INTRODUCTION

The calcineurin inhibitors Cyclosporin and Tacrolimus are currently used by virtually all liver transplantation centers to prevent acute rejections. Still, in two large studies comparing both agents incidences of acute rejection of 40%[1] and 76%[2] were found. In our center the incidence of Early Acute Rejection (EAR) in the first three months after liver transplantation has dropped from 39% to 18% after the introduction of interleukin-2-receptor blocking antibodies as part of the primary immunosuppressive therapy in 1998. These data imply that interleukin-2-receptor blocking antibodies are very effective in preventing acute rejection, but also that between 25% and 60% of patients could have been treated with a two-drug regimen consisting of corticosteroids and calcineurin inhibitors, and received an additional immunosuppressive agent in spite of the fact that they were not at risk for acute rejection. Given these figures it seems important to identify patients that have a low risk of acute rejection and can be spared the

potential danger of over-immunosuppression, and patients with a high risk that might benefit from an intensified immunosuppressive regimen containing interleukin-2-receptor blocking antibodies.

Recipient factors, donor factors and factors related to matching of donor and recipient, the operative procedure and postoperative events that can be used to predict acute rejection after liver transplantation have been identified in earlier studies[3-14]. There are a number of differences between these studies, for instance in the immunosuppressive treatment that was used. It is, therefore, not surprising that the outcomes of these studies are different, and that conflicting results have been reported[15-20]. To address this problem, and to identify factors associated with EAR in a patient group treated mainly with calcineurin inhibitors, we studied our liver transplantation patients treated with an immunosuppressive regimen not containing anti-lymphocyte antibodies or interleukin-2-receptor blocking antibodies.

PATIENTS AND METHODS

All consecutive patients that underwent orthotopic liver transplantation in our center between 1990 and 2004 who were not treated with anti-lymphocyte antibodies or interleukin-2-receptor blocking antibodies were entered in the analysis. The study comprised 199 transplantations in 184 patients. In two cases late retransplantations were included while the primary ones were not. Of all transplantations, 157 (79%) were done in the 6-year period between 1993 and 1999. Data were extracted from patient files and from our liver transplantation database. All biochemical measurements were done using standard automated tests. Human Leukocyte Antigen (HLA) typing of recipients and donors was done by the National Reference Centre for Histocompatibility Testing in Leiden, the Netherlands, using standard lymphocytotoxicity tests.

There were 95 male and 89 female recipients with a median age of 47 years (range 16 to 70 years). Acute liver failure was the indication for primary transplantation in 39 patients, active chronic hepatitis B in 17, hepatitis C in 19, primary biliary cirrhosis in 15, primary sclerosing cholangitis in 28, alcoholic liver disease in 17, cryptogenic liver disease in 13, hepatocellular carcinoma in 10, and a variety of other liver diseases in 26. Two diagnoses were found in 19 patients and three in 2 patients. Postoperative treatment consisted of corticosteroids and either Cyclosporin (n=136) or Tacrolimus (n=42). Cyclosporin was given intravenously 118 times. Calcineurin inhibitors were not used in 19 cases of intraoperative death or immediate postoperative graft failure, and for

other reasons in 2 cases. Azathioprine or Mofetil-mycophenolate was used as additional immunosuppressive agent in 120 patients.

EAR was defined as deterioration of liver graft function in the first 3 months after liver transplantation with no other identifiable cause and a compatible liver graft histology, responding to high-dose corticosteroids or anti-lymphocyte immunoglobulins. Incidences of EAR were calculated according to the Kaplan-Meier method. Of the 199 transplantations 68 (42%) were followed by EAR (table 1). The effects of different factors on

Table 1: Characteristics of patients in the study group.

	All patients	**Complete data**
Number of patients	184	137
Males / Females	95 / 89	71 / 66
Number of transplantations	199	147
Primary transplantation only	182	135
Primary transplantation and retransplantation	15	10
Retransplantation only	2	2
Age in years, median (range)	47 (16 – 70)	48 (16 – 67)
Liver disease		
Acute liver failure	41	26
Chronic hepatitis B	26	19
Chronic hepatitis C	27	21
Primary biliary cirrhosis	18	15
Primary sclerosing cholangitis	33	28
Alcoholic liver disease	23	19
Cryptogenic liver disease	38	26
Other liver diseases (diagnostic restgroup)	44	28
Hepatocellular carcinoma	11	7
Primary immunosuppressive treatment		
Cyclosporin (intravenous)	136 (118)	114 (101)
Tacrolimus	42	32
No calcineurin inhibitors	21	1
Azathioprine	118	98
Acute rejections	68 (42%)	60 (44%)

the incidence of EAR were calculated using the Cox proportional hazard rate model. A first round of screening by univariate analysis was done in all patients. Factors with a P-value ≤ 0.20 and factors found to be significant in multivariate analyses by others were entered in a multivariate Cox model using a step-forward approach and excluding patients with incomplete data. Here categorical factors with at less than 20 cases in either category were not analysed. In the multivariate analysis P-values <0.05 were considered significant. Finally, different risk scores were calculated by dropping the least influential factors from the final Cox-model in a stepwise fashion. C-statistics were calculated for these models according to the method described by Harrell[21]. All statistical tests were done using STATA (version 5.0, Stata Corporation, 702 University Drive East, College Station, TX 77840 USA).

RESULTS

The variables found to be of possible predictive value in the first round of univariate testing can be divided in recipient factors, donor factors and other factors related to matching, operative procedure and postoperative treatment (table 2). There were 5 recipient factors with P < 0.05 and 13 with a P between 0.05 and 0.20. For donor factors these numbers were 0 and 4, and for other factors 11 and 5. In the subsequent step-forward multivariate Cox-analysis we added another 13 factors identified as independent predictors in earlier studies that used multivariate tests. A cold ischemic time > 15 hours occurred only 15 times in our series and was not included in the analysis. Also not used for multivariate testing were 100 other factors, mainly specific HLA-types (n=51) and immunological factors (n=22), 71 with univariate P-values >0.20 and 29 with too few cases in either category.

In the second round of testing 52 (26%) of the 199 transplantations were excluded because of incomplete data. Of these 52, 23 did not survive with a functioning graft for long enough to be at risk of acute rejection. In 19 cases HLA-typing was incomplete or missing, and various other data were not recorded in the remaining 10 cases. The frequencies of postoperative intravenous Cyclosporin treatment and EAR were lower in dropped cases than in those with complete data (P≤0.001, logistic regression analysis). For other relevant factors no significant differences were found.

The multivariate Cox analysis resulted in a model consisting of postoperative intravenous Cyclosporin treatment (HR 4.01, 95% CI 1.88 – 8.54, P<0.001), HLA-DR6 in the recipient (HR 2.07, 95% CI 1.21 – 3.53,P=0.008), HLA-DR7 in the recipient (HR 2.15, 95% CI 1.18 – 3.94, P=0.013), peroperative cryoprecipitate use (HR 1.14 for each unit, 95% CI

Table 2: Factors possibly predicting acute rejection in the first 3 months after liver transplantation identified by screening using univariate Cox regression analysis or in earlier studies.

P <0.100	Rejection	HR (95% CI)	P
Recipient factors			
HLA-DR6 positive	30 / 69	1.87 (1.14 – 3.06)	0.013
Acute liver failure	19 / 41	1.86 (1.10 – 3.17)	0.022
Diagnostic restgroup	9 / 44	0.44 (0.24 – 0.89)	0.022
HLA-B12 positive	19 / 38	1.88 (1.10 – 3.21)	0.022
HLA-DR1 positive	4 / 26	0.36 (0.13 – 0.99)	0.049
Other factors			
Postoperative intravenous Cyclosporin treatment	56 / 118	3.72 (1.72 – 6.63)	<0.001
Period 1990 – 1996 (versus 1997 – 2004)	47 / 104	2.17 (1.30 – 3.64)	0.003
Postoperative intravenous or oral Cyclosporin treatment	60 / 135	2.83 (1.36 – 5.93)	0.006
Postoperative Tacrolimus treatment	7 / 42	0.35 (0.16 – 0.76)	0.008
Number of HLA-A mismatches	1: 27 / 82 2: 34 / 72	1.72 (1.14 – 2.59)	0.010
Waiting time (in days)	--	0.995 (0.991 – 0.999)	0.013
Postoperative anti-Cytomegalovirus immunoglobulin treatment	14 / 23	2.12 (1.17 – 3.82)	0.013
Anti-Cytomegalovirus IgG donor positive and recipient negative	15 / 31	1.98 (1.11 – 3.51)	0.020
Duration of transplantation (in minutes)	--	1.002 (1.000 – 1.004)	0.023
HLA-A partial or complete match	24 / 80	0.58 (0.35 – 0.97)	0.037
Postoperative Azathioprine treatment	52 / 118	1.81 (1.03 – 3.17)	0.038

1.02 – 1.26, P=0.016), postoperative anti-hepatitis B virus immunoglobulin treatment (HR 0.34, 95% CI 0.12 – 0.95, P=0.039) and recipient age under 50 years (HR 1.79, 95% CI 1.02 – 3.14, P=0.43). The final Cox model is shown in table 3. A risk score was calculated by adding the natural logarithms of the hazard ratio's for the factors. Intravenous Cyclosporin treatment was not used for the calculation of this risk score because this factor is unknown at the time of transplantation. The other factors were dropped one by one according to their influence on the c-statistics, leading to scores containing 5, 4, 3 and 2 factors (table 4). The score containing 5 factors ([recipient HLA-DR6 x 0.76] + [recipient HLA-DR7 x 0.56] + [peroperative cryoprecipitate use in U x 0.14] – [postoperative anti-hepatitis B virus immunoglobulin treatment x 1.01] + [recipient age under 50 years x 0.62]) appeared to be the optimal one, with 0.665 as the c-

Table 2: continued

P 0.050-0.200	Rejection	HR (95% CI)	P
Recipient factors			
Preoperative serum bilirubin < 85 μmol/l	41 / 100	1.62 (1.00 – 2.64)	0.050
Age < 50 years	46 / 112	1.65 (0.99 – 2.75)	0.054
Ln(preoperative serum bilirubin in μmol/l)	--	1.21 (0.99 – 1.47)	0.069
Anti-Cytomegalovirus IgG positive	37 / 127	0.64 (0.39 – 1.04)	0.071
HLA-DR3 positive	17 / 57	0.61 (0.35 – 1.07)	0.085
Edema present	24 / 88	0.65 (0.39 – 1.07)	0.088
Chronic Hepatitis B (s- antigen positive)	5 / 26	0.47 (0.19 – 1.16)	0.100
HLA-DR7 positive	19 / 44	1.55 (0.90 – 2.61)	0.112
Preoperative serum bilirubin in μmol/l	--	1.0007 (0.9998 – 1.0017)	0.123
Blood group B or AB	16 / 33	1.55 (0.88 – 2.71)	0.128
Chronic viral infection (Cytomegalovirus / hepatitis B / hepatitis C)	39 / 132	0.68 (0.42 – 1.12)	0.129
HLA-B7 positive	6 / 25	0.53 (0.23 – 1.22)	0.136
Cryptogenic cirrhosis	16 / 38	1.53 (0.87 – 2.68)	0.139
Donor factors			
HLA-B35 positive	17 / 40	1.56 (0.90 – 2.71)	0.111
HLA-B8 positive	10 / 39	0.59 (0.30 – 1.16)	0.129
HLA-DR6 positive	22 / 51	1.46 (0.88 – 2.43)	0.145
HLA-A3 positive	20 / 61	0.69 (0.41 – 1.16)	0.162
Other factors			
Postoperative anti-hepatitis B virus immunoglobulin treatment	6 / 27	0.45 (0.20 – 1.05)	0.064
Peroperative cryoprecipitate use (in units)	--	1.102 (0.986 – 1.232)	0.085
HLA-class 1 partial or complete match	34 / 102	0.67 (0.41 – 1.09)	0.105
Donor-recipient ethnic mismatch	10 / 43	0.60 (0.31 – 1.17)	0.135
Peroperative red blood cell concentrate use (in units)	--	1.015 (0.993 – 1.037)	0.197

statistic. The c-statistic was 0.660 for a score with 4 factors, without peroperative cryoprecipitate use, and declined to 0.63 or lower for scores with 3 or 2 factors. Since cryoprecipitate was used only in a minority of cases we chose the four-factor score consisting of [recipient HLA-DR6 x 0.81] + [recipient HLA-DR7 x 0.64] – [postoperative anti-hepatitis B virus immunoglobulin treatment x 1.01] + [recipient age under 50 years x 0.56] for further calculations. EAR occurred in 8 of 47 patients (18%, 95% CI 9% to 33%) with a four-factor score up to 0, in 25 of 56 (48%, 95% CI 36% to

Table 2: continued

P >0.200	Rejection	HR (95% CI)	P
Recipient factors			
Disease category: 1) chronic viral hepatitis; 2) alcoholic liver disease; 3) hepatocellular carcinoma; 4) Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis	1) 10 / 38 2) 9 / 22 3) 5 / 10 4) 20 / 51	1.14 (0.91 – 1.43)	0.265
Preoperative kreatinine ≥176 µmol/l or on dialysis	8 / 22	1.45 (0.69 – 3.03)	0.324
Age category: 16-29 = 1 **- 30-39 = 2** **- 40-49 = 3** **- 50-59 = 4** **- 60+ = 5**	1: 11 / 26 2: 8 / 28 3: 27 / 58 4: 13 / 60 5: 9 / 27	0.91 (0.75 – 1.10)	0.325
Age (in years)	--	0.99 (0.97 – 1.01)	0.347
Preoperative ASAT >5x(ULN) **- ASAT >5xULN versus ASAT ≤ULN** **- ASAT >5xULN versus ASAT 1-5xULN**	22 / 58	1.25 (0.75 – 2.07) 1.62 (0.49 – 5.42) 1.24 (0.74 – 2.07)	0.396 0.432 0.421
Chronic hepatitis C	11 / 27	1.32 (0.69 – 2.51)	0.405
Female sex	34 / 96	1.21 (0.75 – 1.94)	0.437
Child-class A (cirrhotic patients only)	7 / 21	0.94 (0.42 – 2.11)	0.882
Donor factors			
Age ≥30 years	50 / 141	1.20 (0.70 – 2.06)	0.508
Other factors			
Partial HLA-class 1 match (in recipients chronically infected with hepatitis B-, hepatitis C- or Cytomegalo-virus)	22 / 73	0.77 (0.40 – 1.48)	0.433
HLA-class 2 partial or complete match	26 / 66	1.00 (0.61 – 1.65)	0.998

63%) with a score up to 1, and in 27 of 44 (67%, 95% CI 52% to 81%) with a score over 1. There was a small very high risk group of 7 patients scoring 1.45 or more and a 100% incidence of EAR.

DISCUSSION

Our study shows that it is possible to identify patient groups at low risk, intermediate risk, and high risk of acute rejection in the first 3 months after liver transplantation, as can also be concluded from earlier reports mentioned in the introduction. These studies do, however, differ from each other and from ours in the predictive factors that come out, and also in other ways. Most of the earlier studies[8-20] used only univariate tests. There are five[3-7] that used multivariate tests, but these still show considerable differences in other aspects. In- and exclusion criteria vary, as does the definition of EAR, and also the factors tested (table 5). Our study is by far

the most comprehensive one in this category, even though it is not the largest one. When compared to other studies using multivariate tests, ours confirms only the significance of recipient age, albeit modelled differently as recipient age under 50 years, with a borderline significant additional effect of the age category (HR 1.44, 95% CI 0.99 – 2.10, P=0.058).

Table 3: Final multivariate Cox models of factors predicting acute rejection in the first 3 months after liver transplantation.

	Hazard ratio	**95% confidence interval**	**P**
Final model (log likelihood = –259)			< 0.001
Postoperative intravenous Cyclosporin treatment	4.01	1.88 – 8.54	<0.001
Recipient HLA-DR6 positive	2.07	1.21 – 3.53	0.008
Recipient HLA-DR7 positive	2.15	1.18 – 3.94	0.013
Peroperative cryoprecipitate use (U)	1.14	1.02 – 1.26	0.016
Postoperative anti-hepatitis B virus immunoglobulin treatment	0.34	0.12 – 0.95	0.039
Recipient age < 50 years	1.79	1.02 – 3.14	0.043

Table 4: Coefficients, model log-likelihoods and model P-values derived from Cox models containing 6, 5, 4, 3 and 2 factors predicting acute rejection within 3 months after liver transplantation, with factors left out one by one according to their impact on the c-statistics.

Cox regression analysis					
	6 factor model	**5 factor model**	**4 factor model**	**3 factor model**	**2 factor model**
Recipient HLA-DR6 positive	0.73	0.76	0.81	0.66	0.74
Recipient age < 50 years	0.58	0.62	0.56	0.64	0.63
Postoperative anti-hepatitis B virus immunoglobulin treatment	– 1.08	– 1.01	– 1.01	– 1.08	--
Recipient HLA-DR7 positive	0.77	0.56	0.64	--	--
Peroperative cryoprecipitate use (U)	0.13	0.14	--	--	--
Intravenous Cyclosporin treatment	1.39	--	--	--	--
Model Log Likelihood	– 258.9	– 267.6	– 269.7	– 271.8	– 274.8
Model P (chi-square test)	<0.001	<0.001	<0.001	<0.001	0.001
c-statistics	--	0.665	0.660	0.648	0.623

None of the 11 remaining factors from the earlier reports on multivariate testing turned out to be significant in our analysis (table 6). Borderline significance was reached only by hepatitis C as the indication for transplantation (HR 1.77, 95% CI 0.90–3.49, P=0.096) and in the diagnostic rest-group (HR 0.4, 95% CI 0.21–1.07, P=0.073). Unlike earlier

Table 5: Characteristics of studies on acute rejection after liver transplantation using multivariate tests

reference	**3**	**4**	**5**	**6**	**7**	**current study**
year of publication	1998	1998	1998	2001	2004	
Multi-center / Single-center	M	S	S	S	S	S
start entry period	1990	1988	1989	1990	1999	1990
entry period duration (years)	4	7	8	9	4	15
exclusion criteria[1]	abcd	cefg	hijk	cghjm	cghjl	cn
induction immunosuppression[2]	var.	ATG	var.	CNI	triple	CNI
definition of rejection[3]	CH	CHT	CH	CH	CH	CHT
number of subjects	762	252	126	133	285	147
follow up period (in weeks)	6 (52)	52	22	6.5	26	13
number of acute rejections	-- (490)	--	46	47	117	60
% of acute rejections	48 (65)	43	36.5	35.3	41	44
statistical test[4]	cox	cox	lra	lra	cox	cox
recipient factors tested (n)	9	4	1	4	6	28
donor factors tested (n)	2	0	0	0	3	5
matching factors tested (n)	1	1	4	0	0	7
operative procedure factors tested (n)	3	4	0	1	3	5
postoperative factors tested (n)	7	0	0	2	2	6
total number of factors tested	22	9	5	7	14	51
number of factors in final model	8	1	1	5	2	6

Legend to table 5:

[1]) a: no informed consent
b: multi-organ transplantation
c: pediatric cases (age <16 years or <18 years)
d: death or graft failure within 3 days
e: cirrhosis not caused by virus, alcohol or cholestatic liver disease
f: metabolic liver disease
g: acute liver failure
h: retransplantation
i: patient or graft failure not caused by acute rejection within 1 or 2 weeks
j: no HLA-typing of donor and/or recipient
k: ABO-incomapatibility
l: non-cirrhotic liver disease
m: no CNI-inhibitors immediately after transplantation
n: use of IL2-receptor blocking agents

[2]) var.: variable
ATG: anti-thymocyte immunoglobulin followed by Cyclosporin
CNI: calcineurin inhibitors
triple: triple therapy with steriods, tacrolimus and mycophenolate-mofetil

[3]) C: clinical diagnosis. H: histological diagnosis.
T: anti-rejection treatment.

[4]) lra: logistic regression analysis. cox: cox regression analysis.

studies, we found no other significant effects of specific diseases. On the other hand, we found five additional significant factors, of which presence of the HLA-DR6 antigen in the recipient, peroperative cryoprecipitate use and postoperative treatment with anti-hepatitis B virus immunoglobulin have been implicated in studies using univariate tests[6,8,9,14]. The significance of the HLA-DR6 antigen is contradicted in two studies[6,15]. Likewise, in the first of these no effect of the HLA-DR7 antigen or of intravenous Cyclosporin treatment was found. Undoubtedly, some of the

Table 6: Predictors of acute rejection after liver transplantation identified by studies using multivariate analysis.

Reference	1	2	3	4	5	current study
Recipient factors [–(HR) / +(HR) / 0 / NT[1]]						
Female sex	NT	0	0	NT	+(1.79)	0
Age	NT	0	NT	- (0.92)	0	0
Age category	- (0.81)	NT	NT	NT	NT	0
Age ≤50 years	NT	NT	NT	NT	NT	+(1.79)
Current edema	- (0.71)	NT	NT	NT	NT	0
Creatinine ≥176 µmol/l (≥2 mg/dl) or on dialysis	- (0.48)	NT	NT	NT	NT	0
Child class A vs. B+C (cirrhotic patients only)	NT	NT	NT	+(5.22)	NT	0
Preoperative AST >5xULN vs. ≤ULN	+(1.92)	NT	NT	NT	NT	0
Preoperative AST >5xULN vs. 2-5xULN	+(1.52)	NT	NT	NT	NT	0
Underlying liver disease						
Disease category	NT	+(1.4)	NT	NT	NT	0
Hepatitis C vs. all others	0	NT	NT	NT	+(1.71)	0
Hepatitis C vs. alcoholic liver disease	NT	NT	NT	+(3.13)	0	NT
Autoimmune hepatitis + Primary Biliary Cirrhosis + idiopathic ductopenia vs. alcoholic liver disease	NT	NT	NT	+(16.1)	NT	NT
metabolic liver disease vs. alcoholic liver disease	NT	NT	NT	+(12.3)	NT	NT
Specific HLA-types						
DR6	NT	NT	NT	0	NT	+(2.07)
DR7	NT	NT	NT	0	NT	+(2.15)
Donor factors						
Age ≥30 years	+(1.27)	NT	NT	NT	NT	0
Operative procedure factors						
Cold ischemic time ≥15 hours	+(1.61)	NT	NT	NT	NT	NT[2]
Cryoprecipitate (U administered during LT)	NT	NT	NT	0	NT	+(1.14)
HLA matching factors						
Class 1 matches (in chronic virally infected patients only)	NT	NT	+(7.71)	NT	NT	0
Class 2 matches 0/1/2	- (0.74)	NT	0	0	NT	0
Postoperative factors						
Intravenous Cyclosporin treatment	NT	NT	NT	0	NT	+(4.01)
Anti-hepatitis B virus immunoglobulin treatment	NT	NT	NT	NT	NT	- (0.34)

1) NT: not tested
2) number too small

significant univariate test results have to be ascribed to chance. For the multivariate tests the situation is less clear. However, the number of 6 factors in our final Cox model is not unreasonable given the 60 endpoints in the group of patients with complete data sets we studied. Finally, each of the six factors in our final model was significant at all stages of our multivariate analysis.

An effect of the HLA-DR6 antigen is not found in all studies, as is also the case in renal transplantation[22,23]. This might be partly explained by the differences between the studies on liver transplantation, and the genetic background of the populations involved could also play a role. The same holds true for the new finding that the HLA-DR7 antigen in the recipient is associated with an increased risk of EAR. Older age probably is accompanied by a decline in immune-responsiveness, as suggested by for instance vaccination studies[24], but it could also partly substitute for other factors not included in our analysis.

Contrary to anti-hepatitis B virus immunoglobulin, postoperative treatment with anti-Cytomegalovirus immunoglobulin appeared to increase the risk of EAR in our patients, although significance was reached only in the univariate analysis. At first sight this seems to rule out a general effect of polyclonal immunoglobulins, but differences in immunoglobulin preparation and dose could well play a role[25]. The effect of anti-hepatitis B virus immunoglobulin probably is caused by inhibition of functional maturation of antigen-presenting dendritic cells and of proliferation of T-cells.

Intravenous CYA treatment is by far the strongest predictor in our model. When this factor is corrected for, there is no difference between Cyclosporin and Tacrolimus. The effect of intravenous Cyclosporin treatment, therefore, appears to be unrelated to the choice of drug. Rather, the need to give Cyclosporin intravenously probably indicates inadequate early immunosuppression. Finally, there is no obvious explanation for the effect of cryoprecipitate, but this was used in only a small number of transplantations.

The prognostic model described here may not seem very promising with a c-statistic as low as 0.66, but in our patient group it certainly seems possible to identify different risk groups using a four-factor score. However, this score lacks external validation and cannot be regarded as definitive. More work on the prediction of EAR after liver transplantation remains to be done, but such work has important implications. Low risk patients only require treatment with corticosteroids and calcineurin inhibitors, and could possibly benefit from a lower-than-usual level of immunosuppression. In the high-risk group additional treatment with IL-2-R blocking antibodies or other immunosuppressive agents might be beneficial. In any case, future studies on immunosuppression after liver transplantation should deal with risk factors for EAR in their design and in the analysis of outcomes.

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CHAPTER 7

EPILOGUE

LIVER TRANSPLANTATION IN ROTTERDAM: ACHIEVEMENTS AND CHALLENGES

S. de Rave

"The most important thing about a treatment is that it is effective, not merely that it ought to be effective." (R. Asher[1])

The main topic of this thesis is the outcome of liver transplantation using the conventional orthotopic technique or the alternative heterotopic technique. A model predicting waiting list mortality was tested and modified, and another model predicting early acute rejection was developed. In a separate study the results of orthotopic and heterotopic liver transplantation were compared. Last but not least, we tried to determine where improvements in the process are required. This resulted in a number of new hypotheses that have to be verified or falsified in future studies.

After many years of preparation, the Rotterdam clinical program started in 1986. The first liver transplantation in our centre was done on October 24. The recipient was a 35 year old male with end-stage chronic liver disease caused by hepatitis B. He received a partial liver graft placed in the right upper abdomen, below his own liver. This diseased organ was left in place. The operation took 6 hours and the peroperative blood loss was 6.5 litres. He left the Intensive Care Unit after 3 days and could be discharged after 28 days, without having experienced any serious complications.

The idea behind this heterotopic procedure was that avoidance of the hemodynamic and metabolic problems associated with the anhepatic phase of the conventional orthotopic procedure would make it easier for the recipient to survive the transplantation. Our hope was that potential short-term advantages of heterotopic liver transplantation would materialise and would lead to a better long-term prognosis. Heterotopic liver transplantation also served as a stepping stone to the conventional technique of orthotopic liver transplantation, with complete replacement of the diseased organ. Eventually, heterotopic liver transplantation fell into disuse. Since 1991 only orthotopic liver transplantations have been done. The yearly number of transplantations has risen to around 40 during the last decade.

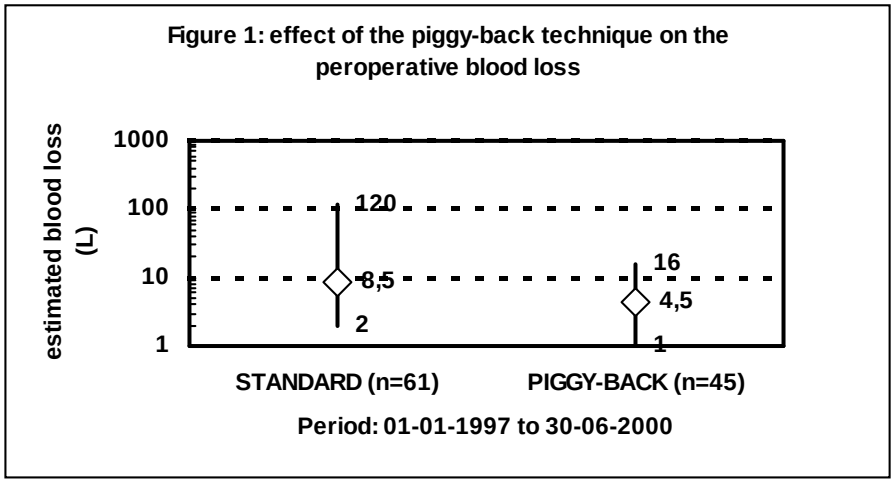
Here I want to highlight the fields where we have booked progress and those where more work still has to be done. Heterotopic liver transplantation may not have brought the results we would have liked, but ours is the largest of the series published so far, and our three long-term survivors are exceptional. On the positive side the improvements in the operative procedure have to be mentioned, together with the better-than-average results of transplantation for acute liver failure. One of the important problems that needs to be addressed is the waiting list mortality. Also, there has been much talk about individualised immunosuppression after transplantation, but no real progression. The treatment of chronic hepatitis C before as well as after liver transplantation is another area where more needs to be done. These points will be dealt with one by one in the remainder of this chapter.

Heterotopic liver transplantation

Do we have to close the book on heterotopic liver transplantation? At first sight the answer given by our comparison with orthotopic transplantation in chapter 4 is “yes”. This conclusion might be qualified as an achievement, but some notes have to be made. Due to its small size and the lack of a contemporary control group our study does not provide definitive evidence that the results of heterotopic liver transplantation are inferior to those of the orthotopic procedure, even though it is the best evidence currently available. Also we cannot exclude the possibility that the difference between the two groups is mainly caused by the use of partial grafts for heterotopic transplantation, in spite of correction for this factor in our analysis. Another point is that, in response to the shortage of donor organs, the use of partial liver grafts from cadaveric as well as living donors probably will increase. Perhaps it is time for a randomised trial of heterotopic versus orthotopic liver transplantation using partial grafts in adult patients not at risk for hepatocellular carcinoma or cholangio-carcinoma, which could be done in the setting of a living donor program. Maybe even left lobe grafts could be used for heterotopic transplantation, with the advantage of reducing the risk for the donors.

The operative procedure

The technique of liver transplantation certainly has evolved since the early, experimental days. Replacement of the liver may not yet be a routine procedure, but can no longer be called experimental or exceptional. The current surgical team has been active since 1991, and has managed to improve their liver transplantation skills on a number of points. An important one is the median warm ischemic time of the graft, that has more than halved since the period 1994-1998, when it was around 80 minutes. Equally important is the median peroperative blood loss, which also has halved since the same period, and currently is between 4 and 5 litres. Both



factors probably are related to the introduction of the piggyback technique, that leaves the recipient inferior caval vein intact (figure 1). This piggyback technique avoids the problems associated with interruption of the venous blood flow from the lower part of the body to the heart, and shortens the time needed for implantation of the donor liver. Another surgical achievement is the successful performance of two Living Related Donor Liver Transplantations in 2004.

Acute liver failure

The treatment of patients with acute liver failure requires quick and concerted action by specialists in the fields of intensive care medicine, hepatology and transplantation surgery. Such a co-operation has led to referral to our centre of 143 patients in the period 1986-2002, half of whom were actually placed on the emergency liver transplantation waiting list. Thanks to a relatively short median waiting time of 1 to 2 days, about 90% of the enlisted patients could be transplanted. The 66% 5-year survival after transplantation is better than the average reported by the ELTR for a similar period[2] (table 1), and can be seen as an achievement of the entire team.

Table 1: Comparison of 5-year survival after transplantation for different indications, Rotterdam versus ELTR

INDICATION	1988-2001	1986-2002	**5-YEAR SURVIVAL (95% CI)**	
	ELTR	**ROTTERDAM**	**ELTR**	**ROTTERDAM**
	N	**N**		
Acute liver failure	3709	65	59%	66% (53-76%)
Alcoholic cirrhosis	6950	33	72%	68% (48-82%)
Chronic hepatitis B	3050	43	70-85%	68% (51-80%)
Chronic hepatitis C	6436	30	67-85%	57% (36-74%)
PBC / PSC / SBC	5213	78	77%	71% (54-80%)
Hepatocellular carcinoma	3364	21	34-58%	31% (13-51%)
Autoimmune hepatitis	991	16	72%	87% (56-96%)

The waiting list

One of the major challenges of liver transplantation lies in the allocation of donor organs. A choice has to be made between a rule-of-rescue policy (the most endangered patient comes first), a policy based on utility (the greatest good for the greatest number), and a policy based on fairness (the patient that has the longest waiting time comes first)[3]. Politicians dictate waiting list criteria and priorities, but it is up to clinicians to provide the data that can support these political decisions. Involvement of physicians that treat liver transplantation candidates in policy-making leads

to conflicts of interest and is best avoided. Treating physicians are bound by the rule-of-rescue and, therefore, cannot chose. Policy-makers have more freedom of choice, but do need guidance.

The rule-of-rescue policy implies that the patient who most urgently needs a liver transplantation is treated first, and fulfils the obligation of the treating physicians. It forms the basis of emergency liver transplantation for acute liver failure, where it is not challenged. For patients with chronic liver disease the situation may be somewhat different. Here transplanting the most severe cases probably results in the largest possible gain of life-years, but also to the lowest postoperative survival and to an avoidable loss of valuable donor organs.

Thus the rule-of-rescue violates the utility principle, that guards against desperate attempts to treat very high-risk patients. Beyond that, the utility principle is mainly economic in its nature and its effects and therefore should not influence decisions on transplantation, according to a statement of the World Health Organisation[4]. By aiming at an optimal graft survival, reached by transplanting relatively low-risk patients, it will, however, be attractive to the public (the potential donors) and to patients that otherwise would have to wait a long time for transplantation or would not be transplanted at all.

Fairness is a dominant principle in many fields in our society, and cannot be discarded easily in liver graft allocation systems. The rule-of-rescue seems to satisfy the fairness principle, but under the latter equal sharing of the burden of disease and of the benefits of transplantation takes preference[5]. This implies a more or less equal distribution of waiting times, or – in other words – transplantation in order of enlistment. The fairness principle of course requires some discipline from physicians, by not placing patients on the waiting list too early.

In my view a balance should be found between the rule-of-rescue (with an upper limit for acceptable risk of dying after transplantation) and the fairness principle (with a lower limit for acceptable disease severity). Where this balance and these limits should lie has to be decided in an open, well-informed discussion. If it is not choice, what tasks should physicians undertake? First, they can develop models predicting mortality of liver transplantation candidates and thus set the criteria for disease severity. Example of such models are MELD and its modified versions. Second, they can develop models predicting mortality after liver transplantation based on preoperative patient and donor characteristics, setting the limits for high-risk patients. Models of this second type have already been described[6-11], as summarised in table 2. The problem with these models is that different measures for disease severity and different

cut-off points for recipient and donor age were used. Development of a model incorporating all relevant factors is one of the challenges that have to be met.

Tabel 2: Preoperative recipient and donor characteristics and other factors predicting death after liver transplantation in adult patients

Reference	6	7	8	9	10	11
Recipient						
- age	Yes	Yes	Yes	--	--	Yes
- renal function	--	Yes	Yes	--	Yes	--
- indication for transplantation	Yes	--	--	--	--	--
- disease severity	--	Yes	Yes	--	Yes	Yes
- prior transplantation	Yes	--	Yes	--	--	--
Donor						
- age	Yes	Yes	Yes	--	Yes	--
- sodium	--	Yes	--	--	--	--
- preservation fluid non-UW	Yes	--	--	--	--	--
Recipient and donor						
- recipient M / donor F	Yes	--	--	Yes	--	--
- ABO compatible, non-identical	Yes	--	--	--	--	--
Other factors						
- center volume	Yes	--	--	--	--	--

Immunosuppression

Acute rejection has been reported to influence both patient and graft survival at 6 months after liver transplantation[12]. In our own patient group the incidence of acute rejection in the first 3 months after transplantation has dropped from about 40% to 18% since the introduction of interleukin-2-receptor blocking antibodies as part of the primary immunosuppressive regimen in 1998. This does, however, imply that more than half of the patients are overtreated with immunosuppressive drugs. Overimmuno-suppression might lead to a higher incidence of severe infections and possibly also of post-transplantation lymphoproliferative disease, and thereby have a negative influence on the overall outcome. The induction of donor-specific tolerance is the Holy Grail of transplantation, and has the potential of making maintenance immunosuppression obsolete, but has yet to be found. In the mean time, identifying patients with a low risk of acute rejection, and reducing the amount of immunosuppressive drugs given after transplantation in this group seems a viable alternative. On the other hand there are high-risk patients, who might benefit from heavier immuno-suppression, but it still has to be proven that such an approach in this

patient group leads to a better survival. It seems possible to identify patient groups at low and at high risk of early acute rejection, but our results await external validation.

Hepatitis C

Liver transplantation for chronic hepatitis C is a subject that lies outside the scope of this thesis, but certainly deserves to be mentioned here as one of the challenges to be met. In Rotterdam the yearly number of patients transplanted for chronic hepatitis C has grown from 0 until 1993 to 4 (or just over 10% of the total number) in recent years. As shown in table 1 long-term survival after transplantation in this group is below our own average, most likely because of disease recurrence. A similar but smaller negative effect of hepatitis C on post-transplantation survival was also found in database-studies from Europe[2] and from the United States[13]. As stated in the editorial accompanying the latter report[14], "the coming and present challenges to maintaining and improving outcomes for recipients with HCV infection should focus our attention on maximising the efficacy and tolerability of antiviral therapies in this fragile population". Given our limited number of patients, the only way forward lies in joining large, multicenter trials.

Conclusion

We can only learn from our experiences if we are willing to draw conclusions from them. One has to be that heterotopic liver transplantation is not an alternative to conventional orthotopic transplantation of full-size liver grafts. The heterotopic technique might, however, have advantages in certain patient groups when partial grafts are used. Management of the waiting list remains a challenge, but physicians have a limited role in policy making. Treatment of patients with hepatocellular carcinoma still is far from optimal, and here lies an important area for future research. The same can be said of patients with chronic hepatitis C. The final point is the standard immunosuppressive treatment currently given to prevent acute rejection after transplantation. A more balanced approach, based on individualised treatment guided by estimates of the risk of early acute rejection, could lead to better outcomes. We may have booked some successes, like in the treatment of patients with acute liver failure, but more work still has to be done.

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CHAPTER 8

SUMMARY

In chapter 1 a brief description of the scientific strategy followed in the papers that form the main part of this thesis is given, along with a division in study categories. Here this division will be followed. There are 3 descriptive studies, 3 hypothesis-generating observational studies and 2 hypothesis-testing observational studies. The distinction between these study types is, however, not always very clear. Both the descriptive and the hypothesis-testing studies contain elements that can be regarded as hypothesis-generating.

The first descriptive study can be found in chapter 2. It marks the field by describing the group of patients referred to the Erasmus Medical Center Rotterdam department of Hepatology for liver transplantation from 1986 through 2002, as well as the treatment decisions and outcomes in this group. Also, the fields covered by the studies in the following chapters are pointed out. No attempt is made here to generate hypotheses.

Three exceptional patients that have survived for more than 10 years after heterotopic liver transplantation are described in chapter 4b. Heterotopic liver transplantation is a surgical technique designed to solve some of the problems of the conventional orthotopic procedure by avoiding the removal of the patient's own liver. Heterotopic transplantation has never become a viable alternative for orthotopic transplantation, and was abandoned even in Rotterdam after 23 were done in the 5-year period between 1986 and 1990. In this paper the possibility is raised that recipients of heterotopic liver grafts are protected from hepatocellular carcinoma development in their own liver by the nearly complete atrophy of this organ. Admittedly, this statement can hardly be called a hypothesis because it cannot really be tested.

Chapter 5b hosts the last descriptive paper. Here details are given on the long-term follow up of patients transplanted for acute liver failure. The main finding is that complete rehabilitation is the rule rather than the exception in patients that survive after transplantation, though there are some frequently occurring complications that become even more prevalent over

the period from 5 to 10 years after the operation. These complications are obesity, dyslipidemia, hypertension and a moderate decline of the renal function. The hypothesis that can be distilled a from our data is that modification and minimisation of the immunosuppressive treatment might reduce the number and severity of long-term complications.

The hypothesis-generating part starts with chapter 3a, where the Model for End-stage Liver Disease (MELD) developed by the Mayo Clinics in the United States is examined. The hypothesis arising from this study is that a simplified model containing only two of the factors used in MELD transformed into their natural logarithms predicts mortality on the waiting list for liver transplantation better than MELD does in its original form. In the same paper partial external validation of this new model is presented.

The effect of disease severity in patients with Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis on the outcome after enlistment for liver transplantation is the subject of study in chapter 3b. Here it is shown that the optimal timing of transplantation depends on the choice of the starting point for the analysis and of the outcome measure. The best absolute survival is found when low-risk patients are transplanted, but the largest survival benefit is found in the high-risk group. The resulting hypothesis is that transplanting patients with chronic cholestatic liver diseases before they reach a more advanced stage of their disease is the optimal strategy, at least from the perspective of the patient.

A type of study similar to that in chapter 3a is presented in chapter 6. Here we identify the factors associated with the occurrence of early acute rejection after liver transplantation in our patient group using the Cox proportional hazard rate model. The resulting hypothesis is that a risk score derived from this model can be used to separate patient groups with low and high risks of acute rejection, that could possibly benefit from a level of postoperative immunosuppression adjusted to this risk.

Two studies can be qualified as hypothesis-testing. In chapter 4a the claim that the results of heterotopic liver transplantation for end-stage chronic liver disease are superior to those of the conventional orthotopic procedure is examined in an observational study covering a relatively long period and using a case-control approach. This study has a number of shortcomings, but still provides the best evidence available that the hypothesis should be rejected, at least for the specific liver diseases forming the indication for transplantation in our patients. In hindsight, a somewhat more definitive answer would have been given by a less complex analysis of patient survival on an intention-to-treat basis, disregarding the crossover of one patient from the case group to the control group at the time of retransplantation. Apart from that, based on the observations in this study

two other hypotheses can be formulated. One is that the use of a partial liver graft in patients at a more-than-average risk of developing malignant diseases further increases this risk. The second one, explicitly stated in chapter 7, is that heterotopic transplantation may still be superior to orthotopic transplantation in the setting of a living related donor program.

Finally, in chapter 3a the hypothesis that emergency liver transplantation improves the survival for patients with acute liver failure is tested in another observational study. Although the alternative hypothesis that there is no effect cannot be rejected on statistical grounds, our data strongly suggest that the original hypothesis is correct. It should be noted that it is hard to reach statistical significance here because of the relatively small number of patients that died before they could be transplanted in our single-centre study. Our paper does, however, point out the optimal statistical method to test the hypothesis in a larger study that does not rely on historical controls.

To summarise the summary, the studies in this thesis have generated 6 more or less new hypotheses, that are again explicitly stated here:

1. After liver transplantation for acute hepatic failure the number of long-term complications increases with time, and modification or minimisation of the immunosuppressive treatment might reverse this trend.

2. A simplified version of the MELD-score predicts survival on the waiting list for liver transplantation better than the original does.

3. In patients with chronic cholestatic liver diseases the optimal time for liver transplantation is in a relatively early stage of the disease.

4. Patient groups at different risks of early acute rejection after liver transplantation can be identified by using a model containing a limited number of factors.

5. In patients prone to the development of malignancies this risk is increased after liver transplantation when a partial graft is used.

6. The use of the left liver lobe for heterotopic transplantation in the setting of a living related donor program reduces the risk for the donor as well as the recipient.

Two other hypotheses were tested, the first one being rejected and the second one not being confirmed as has already been described above:

1. In the treatment of patients with end-stage chronic liver failure heterotopic liver transplantation is superior to the conventional orthotopic procedure.

2. The survival of patients with acute liver failure is improved by orthotopic liver transplantation.

The achievements of the Rotterdam liver transplantation program are highlighted in chapter 7, and potential future goals or challenges are also pointed out here. These challenges lie in testing the yet untested hypotheses. The most important fields are the waiting list strategy and heterotopic transplantation of liver grafts from living donors. As usual, the analysis of our data has generated more questions than it has answered, but if we are to make real progress generating new hypotheses may well be more important than testing old ones.

CHAPTER 9

SUMMARY (IN DUTCH)

SAMENVATTING

Hoofdstuk 1 beschrijft kort de wetenschappelijke strategie die is gevolgd in de studies die het belangrijkste deel van dit proefschrift vormen, en plaatst deze studies in verschillende categorieën. Volgens deze indeling zijn er 3 descriptieve studies, 3 hypothesegenererende observationele studies en 2 observationele studies waarin hypothesen worden getest. Het is echter niet altijd makkelijk om een onderscheid te maken tussen de verschillende studiecategorieën. In feite bevatten bijna alle studies elementen die als hypothesegenererend kunnen worden beschouwd.

De eerste descriptieve studie staat in hoofdstuk 2. Het beschrijft het onderwerp van dit proefschrift, de groep patiënten die tussen 1986 en 2002 naar de afdeling Hepatologie van het Erasmus Medisch Centrum Rotterdam zijn verwezen voor levertransplantatie. Ook wordt aandacht geschonken aan de beslissingen met betrekking tot de behandeling en aan de uitkomsten in deze groep. Daarnaast worden de gebieden aangeduid die worden bestreken door de studies in de volgende hoofdstukken. Er wordt hier nog geen poging gedaan om hypothesen te ontwikkelen.

Drie uitzonderlijke patiënten die na heterotope levertransplantatie meer dan 10 jaar hebben geleefd worden beschreven in hoofdstuk 4b. Heterotope levertransplantatie is een chirurgische techniek die is ontwikkeld om een deel van de problemen te ondervangen van de meer gebruikelijke orthotope procedure, die ontstaan door de verwijdering van de eigen lever van de patiënt. Heterotope transplantatie heeft geen ingang gevonden als alternatief voor orthotope transplantatie, en is ook in Rotterdam in onbruik geraakt nadat er 23 waren gedaan in de 5 jaar tussen 1986 en 1990. In deze studie wordt de mogelijkheid besproken dat patiënten die met de heterotope techniek zijn getransplanteerd beschermd worden tegen ontwikkeling van hepatocellulair carcinoom in hun eigen lever door de vrijwel complete atrofie hiervan. Deze mogelijkheid kan

echter niet als een hypothese worden beschouwd, omdat er geen mogelijkheden zijn de juistheid ervan te testen.

Ook de studie in hoofdstuk 5b is voornamelijk descriptief van aard. Hierin wordt het beloop na transplantatie voor acuut leverfalen gedetailleerd beschreven. De belangrijkste bevinding is dat volledige rehabilitatie eerder regel dan uitzondering is voor patiënten die de operatie overleven. Er is echter een aantal veel voorkomende complicaties, die in toenemende mate optreden in de periode tot 10 jaar na transplantatie. Deze complicaties zijn overgewicht, dyslipidemie, hypertensie en matige nierinsufficiëntie. De hypothese die uit deze gegevens te destilleren valt is dat de toename van het aantal late complicaties na levertransplantatie met de tijd mogelijk omgebogen kan worden door modificatie of vermindering van de immunosuppressieve medicatie.

Het hypothesegenerende deel van dit proefschrift begint met hoofdstuk 3a, waarin het "Model for End-stage Liver Disease" (MELD), ontwikkeld door de Mayo Clinics in de Verenigde Staten, wordt onderzocht. De hypothese die uit deze studie voortkomt is dat een vereenvoudigd model, dat slechts twee van de drie oorspronkelijke factoren bevat in de vorm van hun natuurlijke logaritmen, de mortaliteit op de wachtlijst voor levertransplantatie beter voorspelt dan MELD in zijn oorspronkelijke vorm. In dezelfde studie wordt een gedeeltelijke externe validering van dit nieuwe model gepresenteerd.

Onderwerp van studie in hoofdstuk 3b is de invloed van ziekte-ernst op de overleving van patiënten met Primaire Biliaire Cirrose en Primaire Scleroserende Cholangitis op de wachtlijst voor levertransplantatie en na de operatie. Deze studie laat zien dat het antwoord op de vraag wat het optimale moment voor transplantatie is afhangt van de keuze van het startpunt van de analyse en van de uitkomstmaat. De beste overleving in absolute zin wordt gevonden in de groep van laagrisicopatiënten, maar de grootste overlevingswinst wordt geboekt in de hoogrisicogroep. De hypothese die hieruit voorkomt is dat, althans vanuit het perspectief van de patiënt, transplantatie vóórdat het eindstadium van de leverziekte wordt bereikt de beste strategie is.

De studie in hoofdstuk 6, waarin wordt gezocht naar factoren die de kans op vroege acute afstoting na levertransplantatie beïnvloeden, is van hetzelfde type als die in hoofdstuk 3a. Ook hier wordt gebruik gemaakt van een "Cox proportional hazard rate model". De hypothese is ditmaal dat een risicoscore afgeleid van dit model gebruikt kan worden om een onderscheid te maken tussen patiënten met een lage en een hoge kans op acute afstoting, die baat zouden kunnen hebben bij een mate van postoperatieve immunosuppressie aangepast aan dit risico.

In de twee overblijvende studies worden hypothesen getest. In hoofdstuk 4a wordt de claim dat de resultaten van heterotope levertransplantatie voor chronische leverziekten beter zijn dan die van de conventionele orthotope procedure onder de loep genomen. Dit wordt gedaan in een observationele studie met een case-control opzet, die een relatief groot aantal patiëntjaren beslaat. Hoewel deze studie een aantal tekortkomingen heeft, levert zij het beste tot nu toe beschikbare bewijs dat deze hypothese verworpen moet worden, op zijn minst voor de specifieke aandoeningen die in deze studie zijn onderzocht. Achteraf had een minder ingewikkelde analyse op intention-to-treat basis, waarin geen rekening wordt gehouden met de verhuizing van één patiënt van de studiegroep naar de controlegroep ten tijde van retransplantatie, tot een meer definitief antwoord kunnen leiden. Daarnaast kunnen op grond van de observaties in deze studie nog twee nieuwe hypothesen worden geformuleerd. De eerste is dat gebruik van een transplantaat bestaand uit slechts een deel van de donorlever bij patiënten met een bovengemiddelde kans op maligniteiten dit risico verder vergroot. De tweede, expliciet verwoord in hoofdstuk 7, is dat in de setting van een living-related donorprogramma heterotope transplantatie toch beter zou kunnen zijn dan orthotope transplantatie.

Tenslotte wordt in hoofdstuk 3a de hypothese getest dat levertransplantatie de overleving van patiënten met acuut leverfalen verbetert, wederom in een observationele studie. Hoewel de alternatieve hypothese, dat er geen effect is, op statistische gronden niet verworpen kan worden, leveren onze gegevens sterke aanwijzingen op dat de oorspronkelijke hypothese correct is. Daarbij moet worden aangetekend dat, door het kleine aantal patiënten in onze single-center studie die zijn overleden voordat zij konden worden getransplanteerd, het niet makkelijk is statistische significantie te bereiken. Wel wordt hiermee aangegeven wat de optimale statistische methode is om de hypothese te testen zonder gebruik te maken van historische controles in een grotere studie.

Om de samenvatting samen te vatten, de studies in dit proefschrift hebben 7 min of meer nieuwe hypothesen opgeleverd, die hier nog eens worden weergegeven:

1. De toename van het aantal late complicaties na levertransplantatie voor acuut leverfalen hangt samen met de immunosuppressive medicatie, en kan mogelijk worden tegengegaan door verandering of vermindering daarvan.

2. Een vereenvoudigde versie van de MELD-score geeft een betere voorspelling van de mortaliteit op de wachtlijst voor levertransplantatie dan het origineel.

3. Voor patiënten met cholestatische leverziekten is een relatief vroeg stadium van de ziekte het optimale moment voor levertransplantatie.

4. Door gebruik te maken van een model met een beperkt aantal factoren kunnen groepen patiënten met een verschillende kans op vroege acute afstoting na levertransplantatie van elkaar worden onderscheiden.

5. Patiënten met een al verhoogde kans op maligniteiten lopen na levertransplantatie een extra risico als gebruik wordt gemaakt van een gedeeltelijk transplantaat.

6. Gebruik van de linker leverkwab voor heterotope transplantatie in de setting van een living-related donorprogramma verkleint het risico voor zowel de donor als de ontvanger.

Twee andere hypothesen werden getest, waarbij de eerste moest worden verworpen en de tweede niet geheel kon worden bevestigd, zoals hierboven reeds beschreven:

1. Als behandeling van patienten met chronische leverziekten geeft heterotope levertransplantatie betere resultaten dan de gebruikelijke orthotope procedure.

2. De overleving van patienten met acuut leverfalen wordt verbeterd door orthotope levertransplantatie.

De verworvenheden van het Rotterdamse levertransplantatieprogramma worden nog eens uitgelicht in hoofdstuk 7, en hier worden ook mogelijke doelen en uitdagingen voor de toekomst aangegeven. De uitdagingen liggen in het testen van de nieuwe hypothesen. De belangrijkste hiervan hebben betrekking op de wachtlijststrategie en heterotope transplantatie van gedeeltelijke levers van levende donoren. Zoals gebruikelijk heeft de analyse van onze gegevens meer vragen opgeroepen dan beantwoord, maar om werkelijk vooruitgang te maken zou het ontwikkelen van nieuwe hypothesen wel eens belangrijker kunnen zijn dan het testen van oude.

CHAPTER 10

ACKNOWLEDGMENTS (IN DUTCH)

DANKWOORD

Levertransplantatie is een "teamsport". Het is dan ook moeilijk een dankwoord te beginnen zonder te melden dat het ontstaan van dit proefschrift niet mogelijk was geweest zonder de inspanningen van allen die in de loop van de tijd hebben bijgedragen aan het Rotterdamse levertransplantatieprogramma en daarmee de gegevens hebben geproduceerd waarop dit proefschrift is gebaseerd. Daarbij denk ik aan medisch specialisten uit allerlei disciplines, maar ook aan verpleegkundigen en ondersteunde diensten. Het verzamelen, ordenen en analyseren van deze gegevens is echter een activiteit geweest van een beperkt aantal leden van het team. Dit vindt zijn weerslag in het auteurschap van de artikelen in dit proefschrift. Ook de verschillende medeauteurs wil ik hierbij bedanken. Een andere groep die onmisbaar is wordt gevormd door de patiënten, die evenals een deel van de teamleden geen aanspraak kunnen maken op medeauteurschap, maar zeker ook aparte vermelding verdienen.

Mijn promotor professor doctor Solko W. Schalm stond niet alleen aan de wieg van het Rotterdamse levertransplantatieprogramma, maar ook aan die van mijn carrière in de hepatologie. Daarnaast heeft hij dit proefschrift vanaf de conceptie begeleid, en is hij er steeds in blijven geloven, ondanks de extreem lange duur van de embryonale en foetale periode, met een aantal beslissingen over de ontwikkeling die in een latere fase moesten worden bijgesteld, en daarnaast de eigenwijsheid en een paar andere nukken van de promovendus. Beste Solko, mijn grote dank hiervoor! Ik hoop dat je me stelling 14 uit dit proefschrift niet al te kwalijk neemt, maar ook jij hebt een paar eigenaardigheden.

In een laat stadium heeft Huug Tilanus zich bereid verklaard mijn eerste promotor te ontlasten door mede-promotor te worden en mij in het gareel te houden. Dat laatste is hem wonderwel gelukt, voor deze niet geringe prestatie ben ik hem uiterst dankbaar. De overige leden van de promotie-commissie ben ik erkentelijk voor hun bereidheid zich door dit boekje heen te werken en er hun kritiek op te leveren. In het bijzonder wil ik mijn eerste afdelingshoofd professor J.H.P. Wilson bedanken, die mij (als kersvers geregistreerd internist) in 1984 binnenhaalde in de afdeling Inwendige Geneeskunde 2 van het toenmalige Academisch Ziekenhuis Rotterdam – Dijkzigt, en die mij altijd heeft gesteund in mijn werk. Na het ontstaan van een zelfstandige afdeling Maag-, Darm- en Leverziekten is zijn rol overgenomen door professor doctor E.J. Kuipers, die mij in staat heeft gesteld dit proefschrift uiteindelijk af te ronden.

Bij zijn afscheid als hoogleraar in de leverziekten heeft mijn promotor het begrip "hepatologen van Hoboken" geïntroduceerd, waarvan hij als de pater familias kan worden beschouwd. Als we deze analogie doortrekken is Henk van Buuren de oudste zoon. Henk heeft deze rol met verve vervuld, en niet alleen vele anderen maar ook mij altijd met raad en daad terzijde gestaan. Ook de ongedwongen vrijdagmiddag-bijeenkomsten, als regel op zijn kamer, worden door mij node gemist. Ineke van der Ende is lange tijd een tweede steun en toeverlaat geweest. Zij was de baas van het Practicum Klinische Vaardigheden, waar ik ooit mijn academische loopbaan ben begonnen, en gedurende vele jaren mijn kamergenoot op de D-vleugel. Het besluit om een andere kamer te betrekken betreur ik nog steeds. Natuurlijk moet ik hier ook Marion Hoogendoorn noemen, die zich met nimmer aflatende blijmoedigheid steeds door de chaos die ik haar bezorgde heen werkte, en er altijd iets leesbaars van wist te maken.

Hoezeer ik ieders bijdrage ook waardeer, ik was nooit gekomen waar ik nu ben zonder mijn ouders en vooral mijn levensgezellin van de afgelopen 25 jaar, Jeltje Zeelenberg. Mijn vader, die in 1990 is overleden, heeft altijd stilzwijgend achter me gestaan. Voor mijn moeder geldt hetzelfde, zij het dat die wat meer vocaal is aangelegd. Beiden hebben mij altijd in al mijn ondernemingen gestimuleerd. Jeltje, je hebt mijn nukken nu al 25 jaar verdragen, en meer dan dat. Ondanks je eigen veeleisende werk heb je jarenlang méér dan je deel in het huishouden gedaan en niet alleen mij alle gelegenheid gegeven voor mijn eigen activiteiten, maar me daarin ook aangemoedigd. Ik vertel altijd graag dat ik zonder jou nooit de top van de Kilimanjaro zou hebben gehaald, maar zonder jou zou ik helemaal niets hebben bereikt. Van promoveren wordt gezegd dat het leuker is dan trouwen, omdat je het in je eentje doet: niet waar!

CHAPTER 11

CURRICULUM VITAE (IN DUTCH)

De schrijver dezes is geboren te Rotterdam op 23 januari 1953. In deze zelfde stad volgde hij van 1972 tot 1979 de studie Geneeskunde aan de Medische Faculteit van de Erasmus Universiteit. De opleiding tot internist vond in zijn geheel plaats in het St. Elisabeth Ziekenhuis in Tilburg, tussen 1979 en 1984, met dr. V.A.M. Terwindt en dr. J.H.M. Lockefeer als opleiders. Het jaar 1984 werd doorgebracht op de dienst Nierziekten van het Universitair Ziekenhuis Gasthuisberg te Leuven, België (hoofd: prof. dr. P. Michielsen). Dit was de eerste kennismaking met het transplantatie-vak, onder het toeziend oog van dr. Y. Vanrenterghem.

Het dienstverband met de Erasmus Universiteit Rotterdam begon eind 1984, eerst als medewerker van het Practicum Klinische Vaardigheden, later aangevuld met een aanstelling bij de afdeling Inwendige Geneeskunde 2. Daar werd vanaf 1986 deelgenomen aan de activiteiten rond het beginnende levertransplantatieprogramma. Vanaf dat moment vormde het verzamelen, ordenen en beheren van de gegevens over het programma een belangrijk deel van de werkzaamheden. Analyse van deze gegevens heeft uiteindelijk geleid tot dit proefschrift, in een proces dat bijna 20 jaar heeft gevergd.

In 1999 werd de overstap gemaakt van de Inwendige Geneeskunde naar de nieuw gevormde afdeling Maag-, Darm- en Leverziekten. Op 20 februari 2001 volgde registratie als gastroenteroloog. Eind 2004 werd Rotterdam op eigen initiatief min of meer verlaten, het dienstverband werd omgezet in een gastvrijheidovereenkomst, hetgeen mede de voltooiing van dit proefschrift mogelijk heeft gemaakt. Naast de stukken in dit proefschrift heeft de medische loopbaan 29 publicaties opgeleverd, waarvan 25 in internationale Engelstalige tijdschriften en 12 van deze 25 als eerste auteur.

In augustus 1980 werd de relatie met Jeltje Zeelenberg een feit, hetgeen op 28 november 1989 werd bezegeld met een huwelijk. De omzwervingen door Nederland en België zijn in 1991 geëindigd in Bennekom.

STELLINGEN behorende bij het proefschrift van S. de Rave:

HETEROTOPIC AND ORTHOTOPIC LIVER TRANSPLANTATION IN MAN

1) De vraag die aan potentiële orgaandonoren zou moeten worden gesteld is "wilt u indien nodig getransplanteerd worden?". Een opt-in-systeem van registratie voor transplantatie van postmortaal verkregen menselijke organen, waarin donorschap en ontvangerschap aan elkaar gekoppeld zijn, zou zeker bijdragen aan het oplossen van de wachtlijstproblematiek (dit proefschrift).

2) Naast de nu geldende criteria voor levertransplantatie bij patiënten met een hepatocellulair carcinoom verdient ook de vraag wat het effect van de wachttijd op de overleving is nader onderzoek (dit proefschrift).

3) Het uitgangspunt “de ziekste patiënt eerst”, waarop het huidige Nederlandse wachtlijstsysteem voor levertransplantatie berust, werkt uiteindelijk door de schaarste aan donororganen nadelig voor zowel de patiënten als voor de gemeenschap. Een regeling die het mogelijk maakt patiënten in een vroeger stadium van hun ziekte te transplanteren verlaagt voor alle partijen de kosten en verbetert de resultaten (dit proefschrift).

4) Met betrekking tot de praktische toepassing van statistische modellen in de kliniek is de vraag wat in deze modellen kan worden weggelaten minstens zo belangrijk als de vraag wat kan worden toegevoegd (dit proefschrift).

5) De bevinding dat acute afstoting na levertransplantatie niet de algehele mortaliteit maar wel de infectiegerelateerde mortaliteit verhoogt wijst erop dat ook het voorkómen van afstotingen mogelijk een nadelig effect heeft (dit proefschrift).

6) Er bestaat geen statistisch model dat met enige mate van nauwkeurigheid de overleving voorspelt voor de individuele patiënt (vrij naar dame Sheila Sherlock in “Diseases of the Liver and Biliary System”, 9^{e} uitgave, pg. 244, Blackwell Scientific Publications 1993).

7) Behandeling van chronische hepatitis C met PEG-Interferon en Ribavirin dient, ongeacht het genotype van het virus, niet langer te duren dan 6 maanden, en te worden herhaald bij terugkeer van de ziekte. Deze strategie is niet minder effectief dan behandeling gedurende 12 of 18 maanden, en veel goedkoper (De Rave S, Vrolijk JM, Schalm SW. Medical Hypotheses 2005;65:238-242.).

8) Primaire Scleroserende Cholangitis is geen infectieziekte (Boomkens SY, de Rave S, Pot RG, et al. FEMS Immunol Med Microbiol 2005;44:221-225.).

9) De aangewezen diagnostische ingreep bij een resectabele haard in een normale lever is, bij een sterke verdenking op maligniteit, niet een biopsie maar operatieve verwijdering.

10) Autoimmuun hepatitis is een ziekte die nog steeds wacht op een bruikbare definitie.

11) Vrije toegang tot alle wetenschappelijke publicaties kan door onderzoekers worden bevorderd door gebruik te maken van de werking van de vrije markt, en manuscripten uitsluitend aan te bieden aan tijdschriften waarvan de inhoud binnen een redelijke termijn in het publieke domein van het internet wordt geplaatst.