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ORIGINAL ARTICLE

Outcome after liver re-transplantation in patients with recurrent chronic hepatitis C

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Summary

Long-term outcome after liver retransplantation for recurrent hepatitis C has been reported to be inferior to other indications. The identification of factors associated which improved long-term results may help identify hepatitis C positive patients who benefit from liver retransplantation. Outcome after liver retransplantation for recurrent hepatitis C was analyzed in 18 patients (group 1) and compared with hepatitis C positive patients undergoing liver retransplantation for initial nonfunction (group 2, $n = 11$) and patients with liver retransplantation for other indications (group 3, $n = 169$). Five-year patient survival following retransplantation for groups 1, 2 and 3 was 59% 84% and 60%. Increased alanine aminotransferase (ALT) and serum bilirubin, as well as white cell count and MELD score at day of retransplantation were associated with impaired patient outcome. Five-year survival after retransplantation in patients with recurrent hepatitis C is similar to that in patients undergoing liver retransplantation for other indications. Our analysis showed MELD score, bilirubin, ALT levels and white cell counts preorthotopic liver transplantation are important predictive factors for outcome. This observational study may help select patients and identify the optimal time-point of liver retransplantation in ''Hepatitis C'' virus positive patients in the future.

Introduction

Hepatitis C virus (HCV)-associated terminal liver disease has become the leading indication for orthotopic liver transplantation (OLT) now-a-days. Histological evidence of hepatitis C recurrence is almost universal [1]. The prevalence of HCV related graft failure increased during the last years as reported by Rosen *et al.* [2]. Retransplantation (re-OLT) is the only alternative for patients with severe graft hepatitis because of recurrent hepatitis C. However, repeated liver transplantation for hepatitis C is still a controversial issue. In several reports, HCV reinfection was associated with poor outcome after re-OLT compared with primary transplantation [3]. A study by Forman *et al.* showed an increased rate of deaths and allograft failure in HCV-positive compared to HCV-negative transplant recipients [4]. In contrast, in several small studies patient survival after re-OLT for HCV was similar to patient survival after re-OLT for all other causes [5,6]. In the past, several models predicting the outcome after repeated OLT were developed; however, none of these identified recurrent hepatitis C as a variable significant for patient survival [7–9]. Despite these findings, retransplantation for HCV recurrence is still a contraindication in a number of transplant centers, and we therefore investigated at our center the outcome of all patients undergoing retransplantation for severe graft hepatitis due to recurrent hepatitis C infection. As a control group we used all

Table 1. Indications for retransplantation in 169 HCV negative liver graft recipients.

Indication	*n* (%)
Primary non function	47 (28)
Hepatic artery thrombosis	35 (21)
Chronic rejection	26 (15)
Ischemic type biliary lesion	19 (11)
Vanishing bile duct syndrome	13 (8)
Recurrent hepatitis B	13 (8)
Portal vein thrombosis	3 (2)
Vena cava thrombosis	4 (2)
Others (recurrent Hepatitis B, PSC, AIH)	9 (5)

PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis.

hepatitis C positive graft recipients who underwent retransplantation for initial nonfunction (INF) as well as patients who underwent retransplantation for all other reasons (nonHCV). The aim of the study was to identify the factors associated with improved prognosis for hepatitis C positive liver transplant recipients who were listed for retransplantation. Additionally, the course of HCV recurrence after re-OLT and the significance of antiviral treatment strategies after repeated OLT were evaluated.

Patients and methods

Patient characteristics, demographics and clinical data

Between September 1988 and 2006, 1950 primary liver transplants were performed at our hospital. During this period, 198 patients underwent re-OLT. Survival and clinical course of these patients were assessed and subdivided into three groups: repeated OLT due to recurrent hepatitis C was performed in 18 patients (group 1). Eleven hepatitis C positive graft recipients underwent retransplantation because of INF postprimary OLT (group 2). One hundred and sixty-nine nonHCV positive patients underwent retransplantation for reasons other than recurrent hepatitis C (group 3). Indication for re-OLT because of recurrent hepatitis C was given when the following criteria were fulfilled: patients under 65 years with histologically proven recurrent hepatitis C infection and fibrosis (at least fibrosis stage 3) or HCV cirrhosis. Additionally, signs of progressive recurrent hepatitis such as elevated transaminases or chronic cholestasis in combination with reduced clinical condition and severe impaired liver synthesis (hypoalbuminemia, ascites) were mandatory. Indications for retransplantation in HCV negative graft recipients are shown in Table 1. The baseline characteristics of the three groups of patients are given in Table 2 and demographics of all HCV positive graft recipients are shown in Table 4. Long-term survival of all three groups was evaluated.

Immunosuppression and rejection treatment in patients who underwent re-OLT for recurrent hepatitis C

Standard immunosuppression refers either to cyclosporine A (CsA)- or tacrolimus (Tac)-based regimens. CsA-based protocols consisted of triple (CsA, azathioprine/mycophenolate mofetil, steroids) or quadruple drug induction regimens, including an antithymocyte globulin preparation (Fresenius AG, Bad Homburg, Germany), or monoclonal anti-interleukin 2-receptor antibodies [10,11]. Post-transplant protocol liver biopsies were routinely performed for each patient. Additional liver biopsies were performed because of elevated liver enzymes. Acute cellular rejection was scored based on the Banff rejection activity index [12]. Initial therapy of acute cellular rejection episodes consisted of 500 mg methylprednisolone for 3 days.

All HCV positive liver recipients on the waiting list for re-OLT showed histological evidence of hepatitis C recur-

Table 2. Baseline characteristics of patients undergoing retransplantation. Group I ($n = 18$), group II ($n = 11$) and group III ($n = 169$).

	Group I	Group II	Group III	*P*
Recipient age (years)	46 ± 12	51 ± 14	43 ± 14	NS
Donor age (years)	34 ± 10	45 ± 15	40 ± 16	NS
Time to re-OLT	32 ± 26 (month)	4.4 ± 1.9 (day)	34.1 ± 42 (month)	NS
MELD at re-OLT	24 ± 8	31 ± 7	22 ± 9	NS
Gender (*n*)				
Male	11	6	73	NS
Female	4	5	96	NS
HCV Genotype (*n*)				
1	4	2		NS
2	10	8		NS
3	–	1		NS
4	–	–		NS
5	1	–		NS
unknown	3	–		
Viral load at re-OLT (IU/ml)	832 375 ± 1 036 807	1 295 083 ± 1 779 739	–	NS

rence and severe graft hepatitis. Histological recurrence of HCV was based on histopathological findings such as necroinflammatory activity and fibrosis, inflammatory infiltrates (portal/periportal/lobular) and inflammatory cell types (lymphocytes/eosinophils/plasma cells).

Biochemical variables of patients who underwent re-OLT for recurrent hepatitis C ($n = 18$)

Biochemical and clinical variables at day of retransplantation and after re-OLT were analyzed including alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), white blood cell count, total serum bilirubin and serum creatinine at day of retransplantation. Furthermore, assessment of ALT on postoperative day 28 was carried out. Additionally, the module for end-stage liver disease scores (MELD) was collected if international ratio values were available.

HCV-RNA

The diagnosis of hepatitis C reinfection was defined by the detection of anti-HCV antibody (ELISA II; Chiron Corp., Emeryville, CA, USA). Direct evidence of hepatitis C was enforced using a competitive RT-PCR analysis (Amplicor; Roche Molecular Systems, Inc., Branchburg, NJ, USA). For genotyping of HCV, HCV-Aplicor products were employed in the Inno-LiPa assay (Innogenetics N.V., Zwynderecht, Antwerpen, Belgium).

Histological examination after retransplantation in patients who underwent re-OLT for recurrent hepatitis C

In all patients a liver biopsy was performed 1 year after retransplantation. All biopsy specimens were scored according to the amount of portal fibrosis, using a scale from 0 to 4 for the criterion 'portal fibrosis' (0: absent; 1: mild; 2: moderate without septa; 3: moderate with septa, 4: cirrhosis) according to the histological score proposed by Scheuer *et al.* [13].

Treatment of HCV after retransplantation

Six patients after re-OLT with histological and biochemical proven recurrent hepatitis C after re-OLT received a combination therapy of peginterferon alfa-2b 1 μg/kg/BW weekly (Peg-Intron; Essex Pharma GmbH, Kenilworth, NJ, USA) and 400–1000 mg ribavirin depending on bodyweight (Essex Pharma GmbH). Sustained virologic response (SVR) at the end of 48 weeks of treatment with pegylated interferon was defined as undetectable HCV-RNA in serum. This was analyzed using Amplicor HCV version 2 (Roche Diagnostics, Branchburg, NJ, USA), which has a lower limit of detection (50 IU/ml).

Statistical analysis

All data were collected prospectively in a database (MICROSOFT ACCESS 2.0; Microsoft Cooperation, Redmont, USA). Statistical analysis was performed using SPSS for windows 10.0 (SPSS Inc., Chicago, IL, USA). Categorical data were compared using chi-squared test or Fisher's exact test. Continues variables were compared using the Wilcoxon signed-rank test and survival curves were calculated using the Kaplan–Meier method. Influence of possible risk factors on patient survival was analyzed by Cox multivariate regression. The effect of bilirubin, alanine aminotransferase (ALT), white blood cell count and MELD-score on day of re-OLT was evaluated by Receiver Operating Characteristic (ROC)-analysis. Statistical results were expressed as mean ± SE. A P-value of <0.05 was considered significant.

Results

Clinical data of HCV positive patients

Twenty-nine of 292 positive HCV positive liver transplant recipients underwent liver retransplantation (9.9%). Eleven of these 29 patients were transplanted because of INF after primary OLT for end-stage hepatitis C infection. Eighteen patients underwent retransplantation because of graft failure caused by severe recurrent graft hepatitis C. The patients characteristics, demographics and age at re-OLT, time interval between OLT and re-OLT and also the initial immunosuppression of each single patient are listed in Table 4. Seven of 18 (38.8%) patients showed at least one episode of acute rejection after retransplantation. All patients showed good response to pulse therapy of 500 mg methylprednisolone, which was administered for 3 days, with normalization of liver serum enzymes. None of the patients showed signs of chronic rejection.

Ten of the 18 (55.5%) patients are still alive after a median follow-up time of 44.2 ± 42 months. Two patients died of decompensated severe recurrent hepatitis C infection after re-OLT and another three died of graft failure ($n = 1$), gastrointestinal bleeding ($n = 1$) and sepsis ($n = 1$) during the course of severe cholestatic hepatitis C reinfection. Overall 5 of 18 patients died of recurrence of hepatitis C after retransplantation (27.7%).

During the follow-up period, one patient died of recurrent hepatocellular carcinoma, one patient died of *de-novo* malignant melanoma and one in an accident.

A univariate analysis of the time between primary liver transplantation and retransplantation showed no significant increase in survival for patients with prolonged waiting time for second transplantation ($P < 0.5$). Furthermore, we could not identify donor age

as an independent predictor of long-term survival ($P = 0.832$). The median age of liver donors for patients who underwent re-OLT caused by graft hepatitis was 34.6 ± 10.3 years.

Survival after Re-OLT: HCV-reinfection versus INF versus NonHCV

Kaplan–Meier analysis comparing the three groups of patients is shown in Fig. 1a. The 5-year survival of patients after re-OLT for recurrent hepatitis C was 59% (group 1; $n = 18$). Compared with nonHCV patients C (group 3; $n = 169$), no significant difference in survival was seen (60% 5-year survival, $P = 0.2$). The comparison between patients after re-OLT for recurrent hepatitis C (group 1) and hepatitis C positive patients after re-OLT for INF (group 2; $n = 11$) showed a significant longer survival of INF-patients (84% 5-year survival, $P = 0.04$).

The survival of patients not selected for retransplantation and the graft survival for the first liver transplantation is shown in Fig. 1b.

Bilirubin, ALT and white blood cell count on day of re-OLT for HCV

Recipient parameters as serum bilirubin level, ALT level and white cell blood count were measured on day of re-OLT. Evaluation of recipients serum bilirubin on day of re-OLT showed a correlation with long-term survival. Bilirubin-levels ≥15 mg/dl correlated significantly with shorter survival after retransplantation by ROC-analysis ($P < 0.05$) (Fig. 2a). The same result was found for ALT levels on day of retransplantation. ALT levels ≥50 U/l showed a significant decreased survival compared with patients with levels below 50 U/l ($P = 0.019$) (Fig. 2b). ROC curve for ALT value on day of re-OLT showed a sensitivity of 90.0 and a specificity of 37.5 (Fig. 3).

On day of re-OLT, the white blood cell count was determined to evaluate the influence of graft hepatitis progression and portal hypertension on long-term follow-up. White blood cell count levels below 5/nl on day of retransplantation correlated significantly with shorter survival ($P < 0.01$).

Recipient laboratory data, MELD scores, gender of recipient, donor age, initial immunosuppression

Recipient laboratory data such as serum creatinine, GGT and alkaline phosphatase on day of retransplantation showed no correlation with survival in univariate analysis. Furthermore, gender, donor age and initial immunosuppression after re-OLT did not correlate with long-term survival. MELD scores were available for 16 of 18 patients. Univariate analysis of recipient's preoperative ROC-analysis for MELD scores showed a significant correlation with survival ($P = 0.001$). Preoperative MELD scores >25 were associated with poor outcome, as shown in Fig. 4.

ALT on POD 28 (initial graft function)

To determine the initial graft function after repeated liver transplantation, ALT serum levels were measured on post-operative day 28. Univariate Cox regression analysis

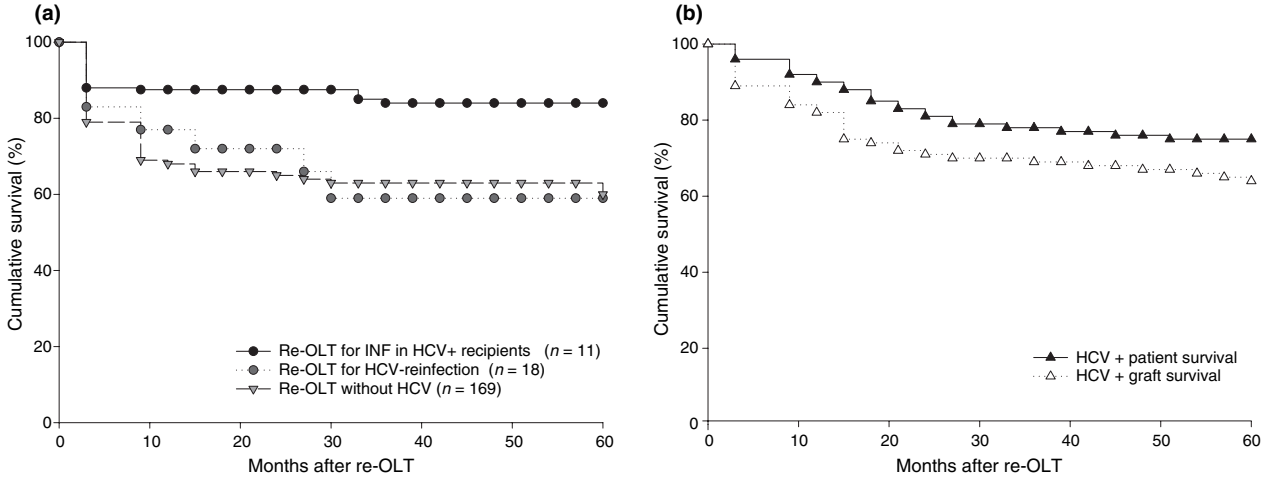

Figure 1 (a) Survival after re-orthotopic liver transplantation (re-OLT) for recurrent Hepatitis C virus (HCV) compared with patients who underwent re-OLT for initial nonfunction (INF) for reasons other than recurrent hepatitis C. Re-OLT for HCV recurrence versus re-OLT for INF in hepatitis C positive transplant recipients ($P = 0.041$). (b) Survival of HCV positive graft recipients not selected for liver transplantation ($n = 263$) and graft survival after first liver transplantation ($n = 279$).

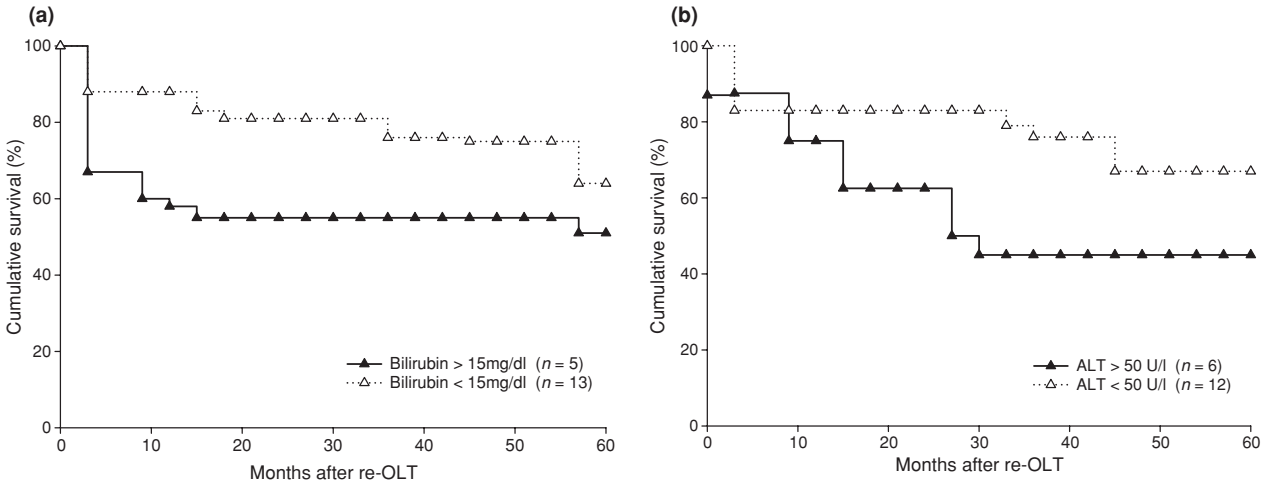

Figure 2 (a) and (b) Survival of patients undergoing retransplantation for recurrent hepatitis C. Bilirubin ($P = 0.05$) and alanine aminotransferase ($P = 0.019$) on day of re-orthotopic liver transplantation.

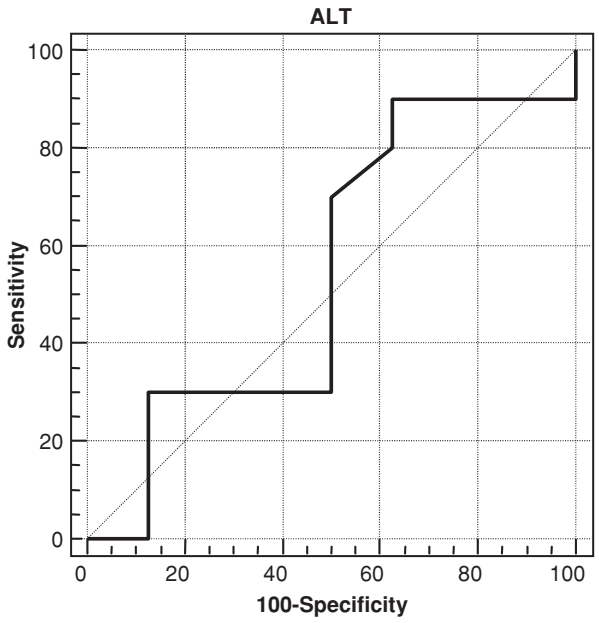

Figure 3 ROC curve for alanine aminotransferase value on day of re-OLT. Sensitivity 90.0 (95% CI 55.5–98.3), specificity 37.5 (95% CI 9.0–75.3).

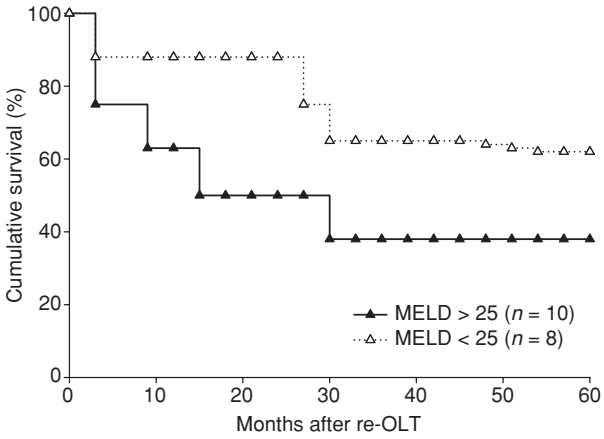

Figure 4 Survival of patients undergoing retransplantation for recurrent hepatitis C. MELD scores showed a significant correlation with survival ($P = 0.001$). Preoperative MELD scores >25 were associated with poor outcome.

showed that ALT levels below 50 U/l on day 28 were associated with a significant increased survival compared with patients with ALT levels above 50 U/l ($P < 0.041$) (Fig. 5).

Fibrosis score first year after re-OLT (Scheuer-index) and course of HCV after re-OLT

The fibrosis scores within the first and third postre-OLT year for group I and II are given in Table 3. Fibrosis progression was lower in HCV positive graft recipients who underwent retransplantation because of INF postprimary OLT.

Six patients received pegylated interferon alpha 2b (1 μg/kg/weekly) and ribavirin (600 mg) for 48 weeks after re-OLT for recurrent hepatitis C. Patients with recurrent hepatitis C more than 1 year after re-OLT were selected if the following criteria were fulfilled: a positive test for anti-HCV (second-generation enzyme immunoassay) and HCV-RNA by reverse transcription-polymerase chain reaction, 2–3 times elevated serum ALT levels before the initiation of treatment, and a liver biopsy showing recurrent hepatitis. Patients with decompensated liver diseases, hemoglobin values <10 g/dl, white blood cell count <2.5/nl, thrombocytopenia <60/nl, and other

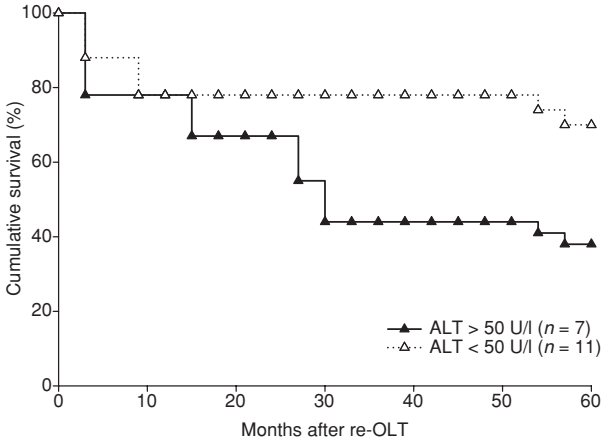

Figure 5 Survival of patients undergoing retransplantation for recurrent hepatitis C. Alanine aminotransferase on postoperative day 28 (initial graft function) ($P = 0.041$).

Table 3. The fibrosis scores within the first and third postre-OLT year for group I and II (Scheuer-Index).

Group	1 year	3 year
I	1.5 (0–3)	2.6 (0–4)
II	0.6 (0–1)	1.2 (0–3)

severe concurrent disease were not selected for antiviral treatment. A complete viral response (SVR) at the end of follow-up was defined by negative serum HCV-RNA, which has a lower limit of detection (50 IU/l) and was achieved by 3/6 patients (50%).

One patient after re-OLT because of severe cholestatic recurrence of hepatitis C showed a spontaneous elimination of HCV virus 10 months after second liver transplantation and has become HCV-RNA negative [14] (Table 4).

Discussion

Hepatitis C virus recurrence after liver transplantation is nearly universal and about 20–40% of liver recipients develop allograft cirrhosis after 5 years [15]. For these patients suffering from graft failure due to recurrent hepatitis, liver retransplantation is the only option of treatment. Although the discussion regarding the outcome of hepatitis C positive patients after retransplantation is still a controversial issue, repeated liver transplantation is still a common therapy for patients with hepatitis C graft hepatitis [16,17]. Lack of data concerning risk factors after retransplantation for hepatitis C and the critical-organ shortage make it difficult for transplant surgeons to deal with the question 'should we or shouldn't we'.

Rosen *et al.* reported on significantly shorter survival in patients after re-OLT for recurrent hepatitis C compared with patients who underwent repeated liver grafting for reasons other than recurrence of HCV [18]. However, our results comparing three groups of patients (group 1: re-OLT for HCV graft hepatitis; group 2: re-OLT for

Table 4. Patients characteristics and demographics prior to re-OLT: age at re-OLT, time interval from primary transplant to re-OLT, immunosuppressive regimen prior re-OLT, course of hepatitis C and cause of death.

Patient no.	Age at re-transplantation (years)	Interval from first OLT (months)	Initial immunosuppression regimen	MELD score on day of re-OLT	Cause of death	Survival (days)	Course of HCV
1	48	3	CyA/Pred/Aza	12	Alive	4053	HCV-RNA negative
2	42	9	CyA/Pred/Aza	18	HCC	3305	
3	44	12	CyA/Pred	23	Alive	3363	HCV-RNA negative
4	41	72	Prograf/Pred	15	Alive	2534	HCV-RNA negative
5	16	12	Prograf/Pred/Aza/ATG	20	Alive	2036	HCV recurrence
6	58	4	CyA/Pred/Aza	30	*De-novo* melanoma	1711	
7	51	9	Progaf/MMF	16	Alive	1359	HCV recurrence
8	66	79	Prograf/Pred	18	Alive	1224	HCV recurrence
9	47	57	Prograf/MMF	38	Alive	1178	HCV-RNA negative
10	43	7	Prograft/Pred	20	Alive	792	HCV recurrence
11	55	30	Prograf/Pred/ATG	23	Accident	720	
12	38	25	Prograf/Pred	43	Recurrent HCV	700	Death due to HCV
13	49	47	Prograf/Pred/MMF	25	Alive	600	HCV recurrence
14	65	64	Prograf/Pred/Simulect	19	Alive	320	HCV recurrence
15	57	11	Prog/Pred	25	Recurrent HCV	315	Death due to HCV
16	52	12	Prograf/Pred	40	Recurrent HCV	133	Death due to HCV
17	52	55	Prograf/Pred/ATG	25	Recurrent HCV	68	Death due to HCV
18	52	63	Prograf/Prednisolon/MMF	28	Recurrent HCV	60	Death due to HCV

initial non function (INF) in hepatitis positive graft recipients; group 3: re-OLT for all other reasons than hepatitis C recurrence) showed no significant difference in long-term survival for group 1 and group 3. In our results, only patients with INF showed a significant increased long-term survival compared with all other patients who underwent repeated OLT due to chronic graft failure including recurrent hepatitis C.

Analysis of specific risk factors for graft failure in HCV positive graft recipients reflected inhomogeneous results. Mc Cashland *et al.* identified the MELD score as a predictive parameter for survival after re-OLT; however, a study by Neff *et al.* could not confirm these findings [19]. To define high-risk patients in the light of organ shortage, some other authors developed mathematical models to predict survival in patients undergoing liver retransplantation [8]. As none of these such models identified hepatitis C recurrence as a significant variable for patient survival, we decided to look for potential risk factors associated with poor outcome after re-OLT. We evaluated parameters such as ALT, GGT, white blood cell count, total serum bilirubin and serum creatinine on day of retransplantation. To define initial graft function, an assessment of ALT on postoperative day 28 was carried out. It is well known that bilirubin and ALT seem to reflect the stage of progression of HCV infection. For that, long-term elevation of ALT may reflect the severity of viral activation after reinfection whereas high bilirubin levels reflect the status of the recipients condition.

Our findings showed a bilirubin level ≥15 mg/dl a significant risk factor for short survival (ROC-analysis). Furthermore, ALT levels above 50 U/l showed a significant decreased survival when compared with patients with ALT levels below 50 U/I. Additionally, measurement of white blood cell count on day of re-OLT correlated with shorter survival in patients with white blood cell count levels below 5/nl. One reason for that may be the occurrence of portal hypertension because of progressive hepatitis.

Anemia and neutropenia are common side effects of currently available HCV therapies. However, several studies suggest that HCV infection itself can also induce neutropenia [20,21]. Therefore, white blood cell count in HCV positive patients may also reflect the severity of hepatitis activation due to replication of HCV in the bone marrow leading to peripheral blood count abnormalities [22]. Data from this study suggest that liver recipients with advanced stages of hepatitis C combined with portal hypertension and distinct neutropenia after primary transplantation are more susceptible to poorer outcome compared with patients with earlier stages of recurrent hepatitis C after OLT. Our results regarding the MELD-scores emphasize this argument, as we saw a strong correlation between MELD-scores and survival. Therefore, patients with recurrent hepatitis C after OLT should be evaluated as soon as signs of advanced graft hepatitis become apparent. Neither the time between primary transplantation and second transplantation nor the time between re-evaluation and second transplantation seems be an important factor. Important is defining the right moment of re-evaluation for re-OLT. To realize this, an extensive post-transplant aftercare is indispensable to determine the clinical course after OLT and to identify patients for a possible re-OLT.

The role of donor age in patient survival after OLT is well known now-a-days [23]. Interestingly, we could not confirm this in our patients with a median donor age of 34 years for re-OLT. In the past, our center's policy implied to provide, if possible, only excellent organs to HCV-positive patients who are listed for re-transplantation. Today the mean donor age is increasing. Because of that, it is not possible to allocate young donor grafts for every HCV positive liver graft recipient.

Several authors reported that HCV positive patients after liver transplantation are especially susceptible to postoperative sepsis [13]. In our series only one patient died due to an infection leading to septic heart failure.

Recurrent hepatitis C as a source of mortality after repeated liver transplantation was seen in five patients. Two of eight patients died of severe graft hepatitis during long-term follow-up. Three patients died in hospital for reasons of gastrointestinal bleeding, graft failure or sepsis due to fulminant recurrent hepatitis C infection.

One patient died in an accident and two further patients died of malignancies, one from recurrent hepatocellular carcinoma, and the other patient from *de-novo* melanoma. These results clearly demonstrate that five of the eight deaths were directly associated with hepatitis C recurrence after repeated OLT. Strategies for prevention of severe fulminant or chronic recurrent hepatitis C infection are needed. The use of pegylated interferon alpha 2b after re-OLT for recurrent hepatitis C showed in our patients acceptable results with a SVR of 50%. It is important to note, that such therapies are associated with a number of severe side-effects, which limited the number of patients available for treatment [24].

However, these results are promising that antiviral treatment after retransplantation for hepatitis C is feasible and patients after retransplantation for hepatitis C can benefit from the present day new antiviral strategies.

In conclusion, hepatitis C recurrence has been identified as a significant cause of morbidity and death in our cohort whereas the long-term survival are not inferior to patients undergoing liver retransplantation for other indications.

The stage of recurrent graft hepatitis seems to play a major role in long-term survival after re-OLT for recurrent hepatitis C. Roche *et al.* postulate an improved outcome if patients undergo retransplantation before infections and renal complication develop [25]. As a consequence, post-transplant aftercare should be accomplished thoroughly for patients with hepatitis C recurrence to find the best moment for re-evaluation. By defining the 'when', more advanced stages of graft hepatitis might be avoided and for that outcome of patients after repeated liver transplantation might be increased. Prevention of severe courses of reinfection in these patients will be another important goal for the future.

Authorship

MB, designed research/study, performed research/study, analyzed data wrote the paper; UPN, designed research/study, analyzed data; DJ, RN, collected data; TB, contributed important reagents; JML, PN, designed research/study.

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