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ORIGINAL ARTICLE

Histological Recurrent Hepatitis C after Liver Transplantation: Outcome and Role of Retransplantation

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Impact of hepatitis C virus (HCV) recurrence on long-term outcome after orthotopic liver transplantation (OLT) is highly variable, and the role of retransplantation is still debated. From 1996 to 2003, 131 OLT with histologically proven HCV recurrence and 6 months of follow-up were retrospectively reviewed. One and 5-yr overall survivals were 90.7 and 81.3%, respectively. The mean time of HCV recurrence was 10.1 ± 6.2 months in patients whose donor's age was less than 70 yr old, and 6.6 ± 4.7 in patients whose donor's age was more than 70 ($P < 0.01$). The mean time between OLT and HCV recurrence was 10.7 ± 8.2 months among patients still alive, and 5 ± 4.2 among the 20 who died ($P = 0.02$). In 16 (12.2%) patients, retransplantation was required for severe HCV recurrence; 5 are still alive and 11 (68.7%) died. The mean survival time was 16.2 ± 6 months if re-OLT was performed within 12 months from first OLT, and it was 45.9 ± 10 months if re-OLT was performed later ($P < 0.01$). In conclusion, donors older than 70 yr are at high risk of early HCV recurrence; expectancy of life is significantly reduced in case of histologically proven recurrence within 6 months. Outcome is quite dismal in patients with early HCV recurrence requiring retransplantation within 1 yr of first OLT. ***Liver Transpl 12:1104-1111, 2006.***
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Hepatitis C virus (HCV)-related end-stage disease is nowadays the leading cause of liver failure requiring orthotopic liver transplantation (OLT), in both the United States and Europe.[1-3]

Unfortunately, HCV recurrence is almost universal after OLT.[3,4] Recent data showed that at least 20% of patients with HCV recurrence will develop allograft cirrhosis within 5 yr[2-5]; the outcome of HCV infection seems to be more aggressive and accelerated in transplanted patients than in immunocompetent patients.[5] During the 1990s, several reports showed no difference in long-term survival between HCV-positive and HCV-negative patients undergoing liver transplantation.[6,7] However, other recent studies seem to reveal a worse outcome of OLT in HCV-positive patients than in HCV-negative patients.[3,5,8]

With the increasing number of patients undergoing OLT for HCV-related end-stage disease, the number of patients with HCV recurrent allograft cirrhosis is expected to grow in the next few years, and consequently, the need for retransplantation (re-OLT) will become a common problem.

Re-OLT has been associated with a 20% reduction in survival in comparison to primary OLT[9,10]; several studies have attempted to identify prognostic factors associated with poor survival.[9-11]. The indication for re-OLT for recurrent HCV-related allograft cirrhosis is still questionable. Early and long-term results are discordant, depending on the reports analyzed.[12-14] No clear guidelines have been established to identify patients who could benefit from re-OLT.

In the present report, we evaluated the outcome and the possible factors affecting early HCV recurrence in patients with HCV re-infection proven by histology. We

Abbreviations: HCV, hepatitis C virus; OLT, orthotopic liver transplantation; MELD, Model for End-Stage Liver Disease; RNA, ribonucleic acid.

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analyzed the early and long-term results in patients undergoing re-OLT for HCV recurrence and which factors influenced prognosis in order to select which patients should be candidates for re-OLT.

PATIENTS AND METHODS

From 1986 to 2003, 830 OLTs were performed at the Department of Surgery and Transplantation, University of Bologna; among these, 446 were performed from 1996 to 2003 in which preoperative and postoperative data regarding recipients and donors are available in a homogeneous database. In 223 (50%), the reason for OLT was HCV-related cirrhosis; among the 205 patients with at least 6 months of follow-up, the HCV recurrence was histologically proven in 131 patients (63.9%), and this group represents our study population, which was retrospectively reviewed.

All of them were anti-HCV immunoglobulin G positive (by enzyme-linked immunosorbent assay) at the time of transplantation. In 8 cases (6.1%), a co-infection with hepatitis B virus was detected. In 3 patients (2.3%), alcohol abuse was also documented. In 33 cases (25.2%), the presence of a hepatocellular carcinoma was detected and was the reason for OLT in 7 Child A patients. Overall, there were 45 (34.4%) Child B patients and 79 (60.3%) Child C patients. There were 89 (67.9%) males and 42 (32.1%) females. The mean age was 55 ± 7.4 yr old (varying from 21 to 65 yr old). The Model for End-Stage Liver Disease (MELD) score, calculated as already reported, was routinely applied as the current allocation system in the last 2 yr[15] in this series, 24 (18.3%) patients had MELD scores superior to 20, and 107 (81.7%) less than 20. In all this group of transplanted patients with HCV-related cirrhosis, the preoperative diagnosis was confirmed by the final pathologic examination after OLT.

Study Period

Follow-up ended in June 2004. Mean follow-up was 39 ± 3 months (range, 6-88 months).

After discharge from the hospital, all patients were evaluated clinically and biochemically every 2 weeks, and then every month at the outpatient clinic or whenever necessary. No patients were lost to follow-up. Criteria applied for placement on the waiting list for retransplantation were similar to those for the first transplantation.

Different Regimens of Immunosuppression

The immunosuppressant therapy was based on calcineurin inhibitors. In the case of cyclosporine, the maintenance therapy included prednisone and azathioprine. Azathioprine was stopped at 6 months after OLT or as soon as alterations in biochemical test values, like anemia or neutropenia, required its discontinuation. In the case of tacrolimus, the maintenance therapy included prednisone. Prednisone was tapered off within 6 months of OLT, in both regimens.

HCV Recurrence

In transplanted patients for HCV-related end-stage disease, HCV recurrence was diagnosed by the persistent alterations of biochemical liver function tests in the absence of any other reason of hepatic damage, increase of HCV-ribonucleic acid (RNA) at the polymerase chain reaction evaluation, and confirmed by the pathologic examination of a liver biopsy where portal or lobular infiltration by mononuclear cells with piecemeal necrosis was found in the absence of any other specific disease (posttransplant liver biopsies were performed in the case of persistent increasing of serum transaminases, or when clinically indicated). The histological grade (activity) and stage of recurrent hepatitis was assessed using the Knodell score.[16] All liver biopsies were reviewed by the same group of pathologists.

Early HCV recurrence was defined when the abovementioned clinical and pathological characteristics appeared within 6 months of OLT.

HCV Recurrence after OLT and Outcome

Donor age, recipient age, donor hepatic macrovesicular steatosis, cold ischemia time, and postoperative acute rejection were analyzed to reveal which one was related to an early HCV recurrence after OLT. The preoperative recipient HCV-RNA level, which was available in 63 (48.1%) patients, was also analyzed if related to the time of HCV recurrence; 1.6 MEq was arbitrarily chosen as a cutoff level (quantitative HCV-RNA was determined by the branched deoxyribonucleic acid assay, Quantiplex HCV 2.0; Chiron Corp., Emeryville, CA).

The presence of histologically proven HCV recurrence within or after 6 months of OLT and the HCV-RNA level at the time of OLT were analyzed to evaluate whether it is related to long-term survival.

The outcome of the 2 patients (1.5%) who developed histologically proven HCV recurrence after receiving a graft from an HCV-positive donor was also reported.

Prognostic Factors after Retransplantation for HCV Recurrence

In 16 patients (12.2%), retransplantation was required for progressive liver failure due to severe HCV recurrence after the first OLT. In all these cases, the pathological final examination of the explanted liver confirmed the presence of end-stage disease due to HCV recurrence. Recipient age at the time of re-OLT, bilirubin level, MELD score, the interval between the first and second transplants, the interval between the first OLT and diagnosis of HCV recurrence, and the interval between diagnosis of HCV recurrence and the re-OLT were reviewed to evaluate which could affect the outcome after re-OLT.

Statistical Analysis

The results were expressed as mean ± standard deviation. Regarding the analysis of prognostic factors, the survival curves were obtained by the Kaplan-Meier

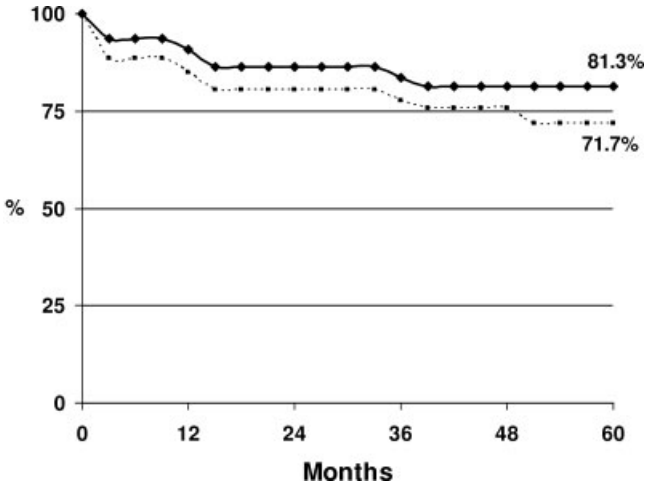


Figure 1. Overall patient (♦ continuous line) and graft (■ dotted line) survival curves in 131 OLTs with histologically proven HCV recurrence.

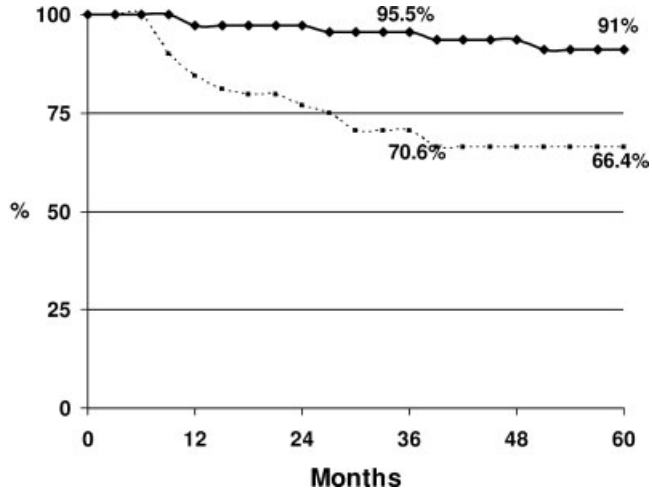


Figure 2. Overall survival curves in transplanted patients with HCV recurrence 6 months after OLT (♦ continuous line) and HCV recurrence within 6 months of OLT (■ dotted line).

method, and the differences in survival between the groups were compared by the log-rank test. Fisher's test was applied in the case of related variables.

Survival was considered from the day of first transplantation to the day of death or the most recent follow-up visit. Patient death or retransplantation was defined as graft failure.

The time to recurrence was computed from the day of transplantation to the time of liver biopsy that confirmed HCV recurrence. A multivariate analysis using Cox's proportional hazard model was used between the prognostic factors analyzed at the univariate analysis. A P value of <0.05 was considered statistically significant. Statistical analysis was carried out with SPSS version 10.0 (SPSS, Chicago, IL).

RESULTS

Time of HCV Recurrence, Knodell Score, Preoperative HCV-RNA Level, and Outcome

Among the 131 patients with histologically proven HCV recurrence, 20 (15.3%) died during the follow-up, 11 of them after re-OLT; 111 (84.7%) are still alive.

The 1-, 3-, and 5-yr overall survivals were 90.7, 83.4, and 81.3%, respectively. The 1-, 3-, and 5-yr graft survivals were 84.9, 77.7, and 71.7%, respectively (Fig. 1).

The mean time ± standard deviation of HCV recurrence was 9.5 ± 7.1 months (varying from 1-47 months).

The mean time ± standard deviation of HCV recurrence was 5 ± 4.2 months among the 20 patients who died during the follow-up, and it was 10.7 ± 8.2 months among the patients who survived ($P = 0.02$).

The long-term actuarial survival in patients with HCV recurrence within 6 months of OLT was significantly shorter than in patients with delayed HCV recurrence (Fig. 2; $P < 0.001$).

At the time of HCV recurrence, the median Knodell score was 6 (varying from 4-13). In all patients there were different degrees of hepatitis activity, while the median score of fibrosis was 1, varying from 0 to 3. There was no difference in graft and patient survival according to the Knodell score at the time of diagnosis of HCV recurrence.

Overall patient survival was not affected by preoperative HCV-RNA level; however, in patients with preoperative HCV-RNA level lower than 1.6 MEq, the 1-, 3-, and 5-yr graft survivals were 92, 81.5, and 81.5%, respectively; in patients with HCV-RNA levels higher than 1.6 MEq, the 1-, 3-, and 5-yr graft survivals were 77, 58, and 58%, respectively ($P < 0.05$).

Prognostic Factors Affecting HCV Recurrence

Recipient age, cold ischemia time, the presence or absence of graft steatosis, the preoperative HCV-RNA level, and postoperative acute rejection did not affect the time of HCV recurrence.

On the contrary, the mean time ± standard deviation of HCV recurrence was 10.1 ± 6.2 months in patients receiving grafts whose donor age was less than 70 yr old, and it was 6.6 ± 4.7 months if donor age was over 70 yr old ($P < 0.01$). A significant tendency to affect the time of HCV recurrence after OLT was also revealed depending on the presence of donor steatosis being less than 10% or more than 10%. These data are reported in Table 1.

Among the 2 patients receiving a graft from an HCV-positive donor, HCV recurrence was histologically proven 35 and 777 days after OLT. The 2 patients are still alive 37.3 and 53.6 months after surgery, respectively.

Re-OLT for Severe HCV Recurrence

Sixteen patients (12.2%) required retransplantation for graft dysfunction due to severe HCV recurrence. The mean time ± standard deviation from the diagnosis of

TABLE 1. Prognostic Factors Affecting HCV Recurrence After OLT

Prognostic factors		Mean HCV recurrence time	*P* value
Recipient age	<60 yr	9.9 months	n.s.
	>60 yr	8.4 months	
Cold ischemia time	<8 hours	8.1 months	n.s.
	>8 hours	10.8 months	
Graft steatosis	Absent	10.1 months	n.s.
	Present	7.8 months	
Donor age	<70 yr	10.1 months	<0.01
	>70 yr	6.6 months	
Graft steatosis	<10%	10.0 months	0.07
	>10%	6.0 months	
Preoperative HCV-RNA	<1.6 MEq	6.4 months	n.s.
	>1.6 MEq	4.1 months	
Acute rejection	Yes	7.0 months	n.s.
	No	8.5 months	

Abbreviation: n.s., not significant.

TABLE 2. Clinical Characteristics and Outcome of 16 Patients who Underwent Re-OLT for HCV Recurrence

OLT (n)	Age (yr)	Time of recurrence (months)	Time of re-OLT (months)	Global survival (months)	Status	Cause of death	Survival after re-OLT (months)	HCV recurrence after re-OLT
299	61	3.5	4.9	6.2	Dead	Sepsis	1.3	–
326	57	3	13.5	14.1	Dead	Sepsis	0.6	–
352	53	29.4	37.7	71.6	Alive	–	33.9	Yes
358	59	6.8	26.1	28.4	Dead	Sepsis	2.3	–
375	50	4	7.5	67.1	Alive	–	59.6	Yes
409	59	3.6	6	11.9	Dead	Neurologic*	5.9	Yes
413	58	12.6	19.1	60.7	Alive	–	41.6	Yes
465	57	2	11.1	11.3	Dead	MOF	0.2	–
494	56	6.1	35	37.4	Dead	Sepsis	2.4	Yes
626	66	8.2	10.5	10.8	Dead	MOF	0.3	–
666	53	2.1	6.2	6.8	Dead	Sepsis	0.6	–
678	35	2.4	15.4	23.9	Alive	–	8.5	Yes
703	52	36	60	84	Alive	–	24	Yes
726	58	1.2	4.9	15.3	Dead	HCV recurrence	10.4	Yes
768	22	1.4	4.5	6.8	Dead	Sepsis	2.3	–
796	57	2	10	10.1	Dead	MOF	0.1	–

*Intracranial hemorrhage.
Abbreviation: MOF, multiple organ failure.

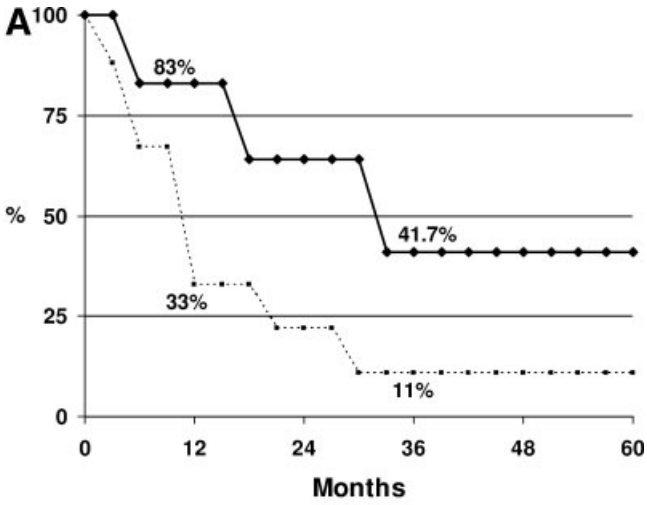
HCV recurrence to re-OLT was 8.2 ± 6.1 months (varying from 2-24 months).

The 1-, 3-, and 5-yr overall survivals after re-OLT were 43.8, 37.5, and 30.0%, respectively. Eleven patients (68.7%) died after re-OLT, 7 of them within 3 months of re-OLT, and only 5 (31.3%) are alive. The cause of death was sepsis in 6 cases, multiorgan failure in 3, HCV recurrence in 1, and intracranial hemorrhage in the last one. Survival and outcome of these patients are reported in Table 2.

In the 5 patients who are still alive, HCV recurrence appeared 1, 2, 4, 11, and 8 months after re-OLT, respectively; similarly, HCV recurrence was diagnosed in all patients surviving more than 3 months after reOLT (see Table 2).

Nine (56.2%) patients received re-OLT within 12 months of the first OLT, and the mean survival time was 16.2 ± 6 months; 7 (43.8%) patients received re-OLT 12 months after the first OLT, and the mean survival time was 45.9 ± 10 months ($P < 0.01$; Fig. 3A). Considering the outcome from the time of re-OLT, the mean survival times were 9.6 ± 3.3 and 24.5 ± 7.5 months in the 2 groups, respectively ($P = 0.05$; Fig. 3B).

In patients with HCV recurrence within 6 months of the first OLT, the mean survival time was 21.6 ± 7.2 months; in patients with HCV recurrence 6 months



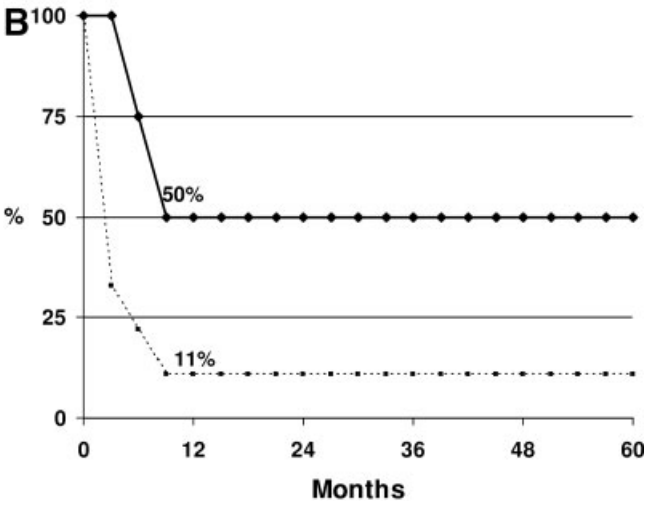
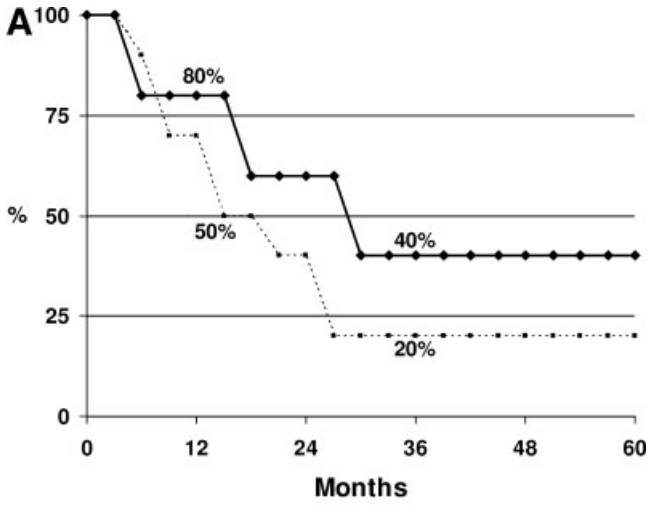


Figure 3. (A) Overall survival curves in 16 patients requiring retransplantation for HCV recurrence depending on time of re-OLT (♦ continuous line, patients receiving re-OLT 1 yr after OLT; ■ dotted line, patients receiving re-OLT within 1 yr of OLT). (B) Survival curves from the date of retransplantation (♦ continuous line, patients receiving re-OLT 1 yr after OLT; ■ dotted line, patients receiving re-OLT within 1 yr of OLT).



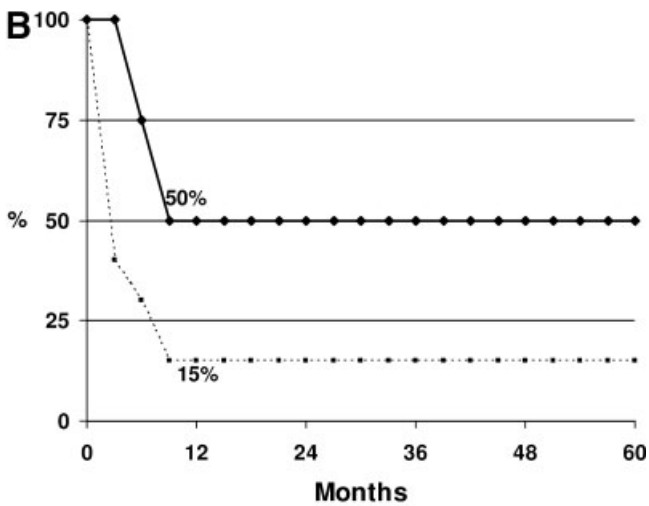


Figure 4. (A) Overall survival curves of 16 patients requiring retransplantation for HCV recurrence depending on time of HCV recurrence: (♦ continuous line, patients with HCV recurrence 6 months after re-OLT; ■ dotted line, patients with HCV recurrence within 6 months of OLT). (B) Survival curves from the date of retransplantation: (♦ continuous line, patients with HCV recurrence 6 months after OLT; ■ dotted line, patients with HCV recurrence within 6 months of OLT).

after the first OLT, the mean survival time was 43.9 ± 10.6 months ($P = 0.05$; Fig. 4A). Similar results were obtained considering only the survival time after re-OLT (Fig. 4B).

A statistically significant relationship was found between the time of HCV recurrence, early vs. delayed, and the time of re-OLT, less or more than 1 yr after the first OLT ($P < 0.05$).

The mean survival time in patients with serum bilirubin levels less than 10 mg/dL at the time of re-OLT was 45.3 ± 12.4 months, and it was 7 ± 4.2 months if bilirubin levels were greater than 10 mg/dL ($P < 0.05$).

A slight difference in survival time was present between patients with a MELD score of less than 20 at the time of re-OLT and patients with a MELD score over 20; however, it does not reach a statistically significant difference ($P = 0.08$).

Only 2 patients underwent re-OLT with a preoperative serum creatinine level over 2 mg/dL; both of them died due to multiorgan failure 1 and 10 days after the operation, respectively.

Recipient age at the time of re-OLT and the interval between HCV recurrence and the second transplant did not affect outcome after re-OLT. They are reported in Table 3.

At the multivariate analysis, only the time between the first and second OLTs less or more than 1 yr showed a significant correlation with survival time ($P < 0.05$).

DISCUSSION

We have shown that medium-term survival in transplanted patients with histologically proven HCV recurrence can be satisfying, with an overall 5-yr survival close to 80% and a graft survival of 71%. However, the

TABLE 3. Prognostic Factors Affecting Survival After Re-OLT for HCV Recurrence

Prognostic factors		Mean survival time	*P* value
Recipient age	<60 yr	19.3 months	n.s.
	>60 yr	8.5 months	
Bilirubin level	<10 mg/dL	45.3 months	<0.05
	>10 mg/dL	7.0 months	
MELD score	<20	20.8 months	0.08
	>20	12.2 months	
HCV recurrence	<6 months	21.6 months	0.05
	>6 months	43.9 months	
HCV recurrence/re-OLT	<6 months	17.5 months	n.s.
	>6 months	15.2 months	
OLT/re-OLT	<12 months	16.2 months	<0.05
	>12 months	45.9 months	

Abbreviation: n.s., not significant.

expectancy of life is quite dismal in patients with early HCV recurrence, and significantly lower compared to patients with late recurrence. In all patients who died in the present series, the mean time of disease recurrence was within 6 months of OLT.

Early HCV recurrence was significantly related to the use of old donor; and we found that there was a correlation between early HCV recurrence and the presence of mild macrovesicular steatosis in the hepatic graft. Worse outcomes in HCV-positive compared to HCV-negative patients have been reported in recent studies.[2,3,5,8] Several factors have been investigated, and there are consistent data regarding a negative effect of donor age on the outcome of OLT in HCV-positive patients.[14,17,18] There is evidence that genetic, biochemical, and bioenergetic functions of mitochondria deteriorate during normal aging; the mitochondrial mutations accumulate with aging and increase the susceptibility to oxidative stress, a hallmark of chronic HCV infection.[19,20] A limit to the use of old donors for HCV-positive patients is still lacking. We have reported that early and long-term results using old donors are similar to those using younger donors[21,22]; however, donors over 70 yr old and with mild to moderate steatosis show a high risk of early recurrent disease in HCV-positive patients and might not be used in this situation.

Taking into consideration that 1) HCV-related end-stage liver disease is nowadays the leading cause of OLT in Western countries,[1–3] 2) HCV re-infection is almost universal after OLT, and by the fifth postoperative year 30% of HCV-infected recipients will develop cirrhosis and a full 10% will die or lose their grafts,[2,23] and 3) the use of old donors is universally accepted to reduce the problem of donor shortage, we will probably be exposed in the near future to an increased request of relisting for patients with HCV-re-infected allograft cirrhosis. The indication to retransplantation for these patients is still controversial. In the present series, 1-yr survival after re-OLT for HCV recurrence was less than 50%, and long-term outcome was quite different depending on the time of HCV recurrence. The mean survival time in patients with HCV recurrence within 6 months of the first OLT was less than half compared to the mean survival time of patients with a late HCV re-infection. Similar results were obtained if re-OLT was performed within 12 months of the first OLT or later, and 4 of 5 survivors underwent re-OLT 1 yr after the first OLT. The 1-yr survival rate in re-OLT patients within 12 months of the first OLT was 22%. The main cause of death was septic complications, consistent with other reports.[4,14] It can be speculated that patients with early HCV recurrence requiring re-OLT within 12 months are usually in poor general condition since they did not recover completely from the first OLT. Furthermore, they are in the period of the highest immunosuppressant regimen. They are quite exposed to septic complications, particularly if they underwent a retransplantation. On the contrary, in the case of late HCV re-infection requiring a late re-OLT, patients have completely recovered from the first OLT and the immunosuppressant regimen is usually the minimum possible; therefore, the possibility of septic complications is almost similar to that for those undergoing primary OLT.

We found that total serum bilirubin levels significantly affect outcome after re-OLT, and 4 of the 5 patients who are still alive showed a preoperative bilirubinemia of less than 10 mg/dL; both patients with preoperative renal impairment died due to multiorgan failure. Recently, several reports have been focused on the impact of the MELD score and physical conditions on long-term outcome in patients undergoing re-OLT, underlining the importance of timing in order to achieve satisfactory results.[9,11,14,24] Currently, we will not consider as candidates for re-OLT those patients with early recurrent HCV graft failure with progressive jaundice and requiring hospitalization.

If sepsis is the main immediate problem after re-OLT, HCV re-infection of the second graft is the major late problem. In the present series, 1 patient died of HCV relapse, and in all 5 survivors, histologically proven HCV recurrence was diagnosed between 1 and 11 months after re-OLT. Berenguer et al. reported an extremely aggressive hepatitis C recurrence after retrans-

plantation, because more than two-thirds of patients developed severe HCV-related graft dysfunction in less than 2 yr.[4] Safe and effective antiviral treatments are still lacking, and recurrent hepatitis C remains a significant source of mortality after re-OLT.[14–24] Only 30 to 50% of treated patients have a maintained viral response, and the efficacy of prophylactic antiviral therapy is anecdotal.[25]

Donor shortage remains the main problem for the indication for OLT, and the allocation of a scarce resource involves a careful balancing of competing ethical principles. On the one hand, there are patients waiting for their first chance who may have a good outcome after OLT, like those suffering from HCC on cirrhosis, or those suffering from cholestatic or metabolic diseases. On the other hand, we have patients with HCV recurrence after OLT who will probably have a dismal prognosis after re-OLT and who will develop disease recurrence whatever we do; these patients should be retransplanted with a low MELD score in order to improve long-term results, receiving some kind of priority. The increase in the MELD score up to 25,[26] the presence of severe liver and renal dysfunction,[11,14,27] and the need for bed rest with little or no activity and dependence on another person for daily activities[24] seem to greatly reduce the survival after re-OLT. Practical guidelines should therefore be considered to exclude from the waiting list those patients (with HCV recurrent graft failure) who show a progressive increase in the MELD score over 25 while waiting for the organ and who require hospitalization for functional organ impairment.

In conclusion, in the next few years more patients with HCV re-infection after OLT will ask for re-OLT. Patient selection will remain the key point in achieving good long-term results: re-OLT should be considered in young patients with late HCV re-infection who may reasonably have a chance of long-term survival; those with histologically proven early HCV re-infection, requiring re-OLT within 1 yr of the first OLT, and in poor clinical condition should be excluded from evaluation for retransplantation.

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