20-year survival post-liver transplant: much more is needed!

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Received: 9 December 2014 / Accepted: 17 February 2015 / Published online: 29 March 2015
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The manuscript entitled “Analysis of adult 20-year survivors after liver transplantation [1]” from a single centre in Barcelona, Spain, assessed the outcome and liver function of survivors 20 years after liver transplantation, together with the cause of death in those who did not survive to reach this milestone. There were 132 adult patients who received 151 liver transplants from deceased donors. During the first year, there were 41 recipients who died, with a further 41 deaths by 5 years and a further 22 who had succumbed by 20 years, leaving only 28 patients (21 %), approximately one in five of the recipients surviving to 20 years.

There are some discrepancies in the article which are difficult for the reader to reconcile. In the segment on patient and graft survival, the “overall actuarial 5, 10 and 20 year patient survival rates were 48, 38 and 22 % respectively.” According to the numbers presented in Table 5, the 1-, 5- and 20-year survivals were 69, 38 and 21 %, respectively, which are different from the aforementioned. In addition, in listing the causes of death in Table 5, the percentages listed at <1 year, 1–5 years and 5–20 years are values for 104 deaths and not percentage of deaths compared to the number of recipients, i.e. 41 (31 %) of 132 recipients during the first year, 41 (31 %) of 132 recipients during years 1–5, and 22 (17 %) of 132 recipients who died between 5 and 20 years.

In the discussion section—“On analysing the characteristics of our 20 year survivors, hepatitis C cirrhosis was the main indication in both groups (36 vs 34 % in non-20 year survivors)”—these percentages are related to the

number of HCV survivors and non-survivors compared with the total number of recipients in each group, rather than the % of HCV survivors and non-survivors at 20 years (22 vs 78 %, respectively). This certainly negates the statement “The younger age of donors in that period could explain the unexpected long-term survival from hepatitis C in 20 year survivors,” which was 22 and not 36 % as stated.

Among the conditions listed in Table 2, comparing donor and surgery characteristics of 20-year survivors and non-survivors, is portal thrombosis. As it is not defined, one has to assume that this is in the recipient and presumably pre-implantation, as it lists 20 such cases, while in the main postoperative complications in Table 3 only three cases of portal vein thrombosis are listed.

The study group comprised all adult patients transplanted between October 1988 and May 1993 during which 132 patients received 151 transplants. Twenty-eight patients (21 %) survived to 20 years. The main cause of death post-transplant was infections, which accounted for 57 % in the first 5 years, and the question of over-immunosuppression in the early period of transplant programs is raised. Maintenance immunosuppression in the present study group was cyclosporine and prednisone together with azathioprine, whereas tacrolimus was not initiated until 1993 and has had a significant impact in other studies where rates of acute or chronic rejection are significantly lower and graft loss from rejection has become relatively rare.

The main causes of death were infections in the first 5 years, with HCV recurrence, de novo malignancy and cardiovascular events in the later years of follow-up. Long-term complications in 20-year survivors included arterial hypertension, diabetes mellitus, dyslipidemia and renal dysfunction, together with de novo malignancy. All these parameters are similar to other studies [2].

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It would be fair to say that there should be some disappointment in viewing the results, with only 21 % of the recipients surviving to 20 years. However, consideration should be given to the era in which the transplants were performed. The learning curve in surgical techniques and postoperative management, together with evolution of preservation solutions, immunosuppression agents and regimes, etc., have had a significant impact on progressive improvement in results over the past several decades. Other than to demonstrate this improvement over time, comparison with present day results would be inappropriate. It would, however, be appropriate to outline results in other cohorts that occurred close to the same period as this Spanish study.

Jain et al. [2] reported on 4,000 patients transplanted in Pittsburgh from 1981 to 1998. In the 1,700 adult recipients transplanted from 1986 to 1990, the 1-, 5-, 10- and 18-year survival was 80, 67, 55 and 44 %, respectively. Tacrolimus was not introduced until the early 1990s, and while not used in the early transplant period, was available in subsequent years, if deemed appropriate. The early survival (0–5 years) was better in alcohol-related disease than with other indications, but after 5 years was less and did not appear to be related to recidivism. Most late deaths were due to de novo cancer, cardiorespiratory and cerebrovascular accidents and the risk was 2.3 times higher in the alcoholic group after 5 years. With regard to hepatitis C, patient survival was not different up to 5 years but recurrent hepatitis C saw a disproportionate decrease in survival after this.

In a subsequent publication, Jain et al. [3] reported on consecutive liver transplants under Tacrolimus immunosuppression. There were 630 adults from 18 to 60 years of age transplanted from 1989 to 1992. The survival at 1, 5, 10 and 20 years was 85, 70, 55 and 35 %, respectively. The causes of death were infection (16 %), cardiopulmonary (8.6 %), cancer-recurrent and de novo (7.4 %) and recurrent primary disease (5.4 %). Of the survivors, 54 % were on antihypertensive therapy, 24 % were diagnosed with diabetes mellitus, and 18 % suffered renal dysfunction. These results of causes of death and long-term complications are very similar to the present study.

In an analysis of 20-year survivors transplanted in Los Angeles between 1984 and 1988, 52 % of recipients survived 20 years [4]. However, 39 % were pediatric patients and, as in most series, the survival in these patients is superior to adult recipients. In their subsequent report on 3,752 adult liver transplants over three decades, the survival at 1, 5, 10 and 20 years was 82, 68, 60 and 47 %, respectively [5]. Again, one needs to be cognizant of the fact of the progress in many areas over time. The report did identify many of the same factors that have shown impaired long-term survival such as recipient factors

including age, etiology of liver disease, and retransplantation; donor factors such as age; and operative factors such as ischemia. In contradistinction to recipients retransplanted for chronic rejection who achieved a 53 % 10-year survival, retransplantation for recurrent HCV had only a 44 % 5-year survival and, as stated, “recurrent HCV remains one of the major challenges limiting liver transplantation.”

In 2013, Schoening et al. [6] reported on 313 adult recipients transplanted between 1988 and 1992 in a single center in Berlin and recorded a patient survival at 1, 10 and 20 years to be 88.4, 72.7 and 52.5 %, respectively. Retransplants were performed on 24 patients (7.7 %). The most common causes of death were recurrent disease (21.3 %), infection (20.6 %) and de novo malignancy (19.9 %) while the prevalence of hypertension, obesity and impaired renal function increased during the follow-up period.

In the European Liver Transplant Registry (ELTR), Adams et al. [7] reported in 2012 on the results of liver transplantation in Europe. In the period 1990–1994, patient survival in the 12,007 recipients at 1, 5 and 10 years was 81, 65 and 56 %, respectively, but included approximately 10 % being performed in paediatric patients less than 15 years of age.

The Australia and New Zealand Liver Transplant Registry [8] recorded that in the 411 adult recipients transplanted in three centres (Brisbane, Melbourne, Sydney) from 1990 to 1994, the 1-, 5-, 10- and 20-year patient survival was 83, 78, 64 and 44 %, respectively.

It is accepted that there is not an exact comparison between the various studies cited and the Barcelona group, but it is apparent that their numbers surviving to 20 years is well below those from other centers during the same time period. This was primarily related to the high mortality during the first 5 years, whereas most of the other parameters and complications are similar.

The upper limit of graft longevity is not known, although there are recipients alive and well with normal liver function more than 30 years after transplantation. However, some caution needs to be expressed in extrapolating this to pediatric recipients, in that histological examination of 5- and 10-year protocol biopsy samples have detected increased graft hepatitis and fibrosis even in those with normal liver function [9]. It was unclear whether these changes represented a form of chronic hepatitis or de novo autoimmune hepatitis, with long-term implications uncertain.

Series reports from small centres perhaps accentuate the problems that occur during the development of very complex medical procedures such as liver transplantation. It is more difficult to build experience and identify trends in outcomes with smaller number of patients. The relatively

low 20-year survival reported here is due in large part to attrition during the first 5 years post-transplant, not so much because of technical complications but instead because of what we now recognize as excessive immunosuppression. In the long-term survivors (more than 10 years) this series shows results comparable to other reports and again highlights a new series of problems that are only now emerging—such as de novo malignancy. This raises further questions in management such as whether patients transplanted for alcoholic liver disease should be subject for more intense surveillance for respiratory tract cancers.

References

1. Dopazo C, Bilbao I, Castells L, Sapisochin G, Moreiras C, Campos-Varela I, et al. Analysis of adult 20-year survivors after liver transplantation. *Hepatol Int* 2015. doi:[10.1007/s12072-014-9577-x](https://doi.org/10.1007/s12072-014-9577-x)
2. Jain A, Reyes J, Kashyap R, Dason F, Demetris J, Ruppert K, et al. Long term survival after liver transplantation in 4,000 consecutive patients at a single center. *Ann Surg* 2000;232:490–500
3. Jain A, Singhal A, Fontes P, Mazariegos G, DeVera M, Cacciarelli T, et al. One thousand consecutive primary liver transplants under tacrolimus immunosuppression: a 17–20 year longitudinal follow-up. *Transplantation*. 2011;91:1025–1030
4. Duffy J, Kao K, Ko C, Farmer D, McDiarmid S, Hing J, et al. Long-term patient outcome and quality of life after liver transplantation. *Ann Surg* 2010;252:652–661
5. Agopian V, Petrowsky H, Kaldas F, Zarringpar A, Farmer D, Yersig H, et al. The evolution of liver transplantation during 3 decades. *Ann Surg* 2013;258:33–45
6. Schoening W, Buescher N, Rademacher S, Andreou A, Kuehn S, Neuhaus R, et al. Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. *Am J Transpl* 2013;13:2384–2394
7. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. *J Hepatol* 2012;57:675–688
8. Australia & New Zealand Liver Transplant Registry—25th Annual Report, 2013. www.anzltr.org. Accessed 22 Feb 2015
9. Kelly D, Bucuvalas J, Alonso E, Karpen S, Allen U, Green M, et al. Long-term medical management of the pediatric patient after liver transplantation. *Liver Transpl* 2013;19:798–825