

Liver retransplantation: indications and outcomes

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BACKGROUND: Liver transplantation is a life-saving therapeutic modality for patients with end-stage liver diseases. After liver transplantation, however, more than 10% patients may lose the grafts caused by a variety of reasons. This review covers the most frequent indications for liver retransplantation as well as the results and specific problems with each indication.

DATA RESOURCES: Searching MEDLINE (1997-2003) for articles on liver retransplantation.

RESULTS: The most frequent indications of liver retransplantation are primary non-function, hepatic artery thrombosis, graft rejection and recurrent diseases. The results after liver retransplantation remain inferior to those after first transplantation.

CONCLUSION: Liver retransplantation, which is the only means of prolonging survival in those patients whose initial graft has failed, makes an important contribution to overall survival.

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KEY WORDS: liver retransplantation;
primary non-function;
hepatic artery thrombosis; rejection;
recurrent diseases

Introduction

Since Starzl performed the first human orthotopic liver transplant in 1963, liver transplantation has become a life-saving therapeutic modality for thousands of patients with liver disease. Significant factors of this advancement include refinement of surgical techniques, improvement of perioperative management, advances in organ procurement and preservation, and ad-

vances in immunosuppression. After liver transplantation, however, graft loss caused by a variety of reasons still occurs in 10%-19.4% of adults^[1-4] and 13.3%-25.1% of children.^[5,6] The most frequent causes of irreversible graft damage are primary non-function, hepatic artery thrombosis, graft rejection and recurrent diseases. The common causes and rates of liver retransplantation in various reports are shown in Table. Liver retransplantation (re-LT) is the only therapy suitable for patients with loss of graft function after a primary liver transplantation (PLT). But re-LT carries a high morbidity and mortality compared with PLT. Azoulay et al reported that 1-, 5-, 10-year patient survival rates after retransplantation were 61%, 53.7%, and 50.1%, respectively. These percentages were significantly less than those after PLT during the same period (82.3%, 72.1%, and 66.9%).^[1] In some centers patients could receive three, four, or more than four transplants. The more the patients received transplants, the poorer the survival was.^[2] Although re-LT is inferior to initial transplantation, it is the only means of prolonging survival in the patients whose initial graft has failed, making an important contribution to overall survival.^[1,3,7] The outcomes after re-LT may be dependent on the cause of graft failure. The aim of this article is to analyze the common indications of re-LT and their results.

Primary non-function

Primary non-function (PNF) of a transplanted liver is a postoperative condition characterized by absence of hepatic recovery due to various insults during harvesting, preservation or revascularization, unappreciated diseases in the donor, or accelerated rejection. Moderate steatosis of donor liver (30% to 60%) is associated with an increased incidence of PNF and retransplantation rate.^[8] PNF, usually defined by the criteria of immediate graft failure with elevated level of liver enzymes, scarce bile output, encephalopathy, and coagulopathy, is the main indication for re-LT.^[2,9] According to the United Network for Organ Sharing (UNOS) data from 1988 to 2001, 761 patients underwent re-LT for PNF in the United States, accounting for 18.2% of all cases of re-LT.^[10] Based on 774 cases of liver retransplantation in

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Table. The common causes and rates in liver retransplantation (%)

Authors	Re-LT	HAT	PNF	Rejection	Recurrent diseases
Azoulay ¹	12	11.5	25.2	40.3	20.1
Jain ²	19.4	27.6	32.3	19.4	3.6
Bramhall ³	10	30	16	31	6
Jimenez ⁴	11.45	14.6	14.6	44	14.6
Deshpande ^{5*}	13.3	36	10	28	4
Jian ^{6*}	25.1	33.4	16.7	26.6	N/A

* : In children; Re-LT: liver retransplantation; HAT: hepatic artery thrombosis; PNF: primary non-function; N/A: not applicable.

Pittsburgh, Jain et al demonstrated that the causes for re-LT are first PNF (32.3%), then hepatic artery thrombosis (27.6%), graft rejection (19.4%), and recurrent diseases (3.6%).^[2] Despite the advances in surgical techniques and immunology, the incidence of re-LT caused by PNF did not appear to change appreciably in different eras. The incidence was 4.6%, 7%, and 6% from 1981 to 1985, 1986 to 1990, and 1991 to 1998, respectively.^[2] When PNF is suspected, it is first necessary to rule out other causes of multiple organ failure. If PNF is confirmed, the most definitive treatment is re-LT.

The outcomes after re-LT are worse than those after PLT. In addition, the UNOS data show that the 1-year graft survival of patients who underwent re-LT for PNF was 20% likely to lose their graft compared with those who underwent re-LT for other reasons.^[10]

Hepatic artery thrombosis

Hepatic artery thrombosis (HAT) after orthotopic liver transplantation can cause a significant morbidity or mortality and lead to liver failure or septic complications, and thus may require urgent retransplantation. The incidence of HAT is significantly higher in the pediatric population, especially, an increased risk in recipients younger than 3 years or weighing less than 15 kg as well as with livers obtained from donors weighing less than 15 kg. Allograft rejection is another possible reason of HAT. Acute rejection may result in endothelial cell injury and decrease vascular compliance because of graft edema. The data from Pittsburgh showed that HAT accounted for 27.6% of all re-LT cases in adults,^[2] and 33.4% of all re-LT cases in children.^[6] Using loupes and improved surgical techniques decreased the incidence of HAT. Jain et al^[2] demonstrated that the incidence of HAT was 8.1%, 6.7%, and 3.8% from 1981 to 1985, 1986 to 1990, and 1991 to 1998, respectively. Doppler ultrasonography is diagnostic in most patients. Nishida et al^[11] found that protocol Doppler ultrasonography of the liver (DUSL) detects early HAT and that urgent revascularization based on DUSL can significantly reduce

the incidence of biliary complication and graft loss requiring retransplantation in pediatric liver transplantation. In a consecutive series of 400 pediatric liver transplantations, 31 episodes of HAT were seen in 29 children.^[12] In patients with 13 episodes managed without retransplantation, 4 patients underwent early revascularization of the graft, which was successful in 2, and the remainders were conservatively treated. In those with 18 episodes resulting in retransplantation, 5 died and 2 experienced second episodes of HAT. It was shown that HAT may occur after retransplantation. Vivarelli et al^[13] reported that 24 patients underwent retransplantation for HAT. Four (16%) of these patients had recurrence of HAT in the second graft and 3 lost their first graft because of late HAT, whereas another one lost 4 consecutive grafts for early HAT. Recurrent HAT is linked to specific thrombophilic conditions. Hence careful screening of these disorders should be included in the pretransplant program, and adequate prophylaxis is advisable.

Rejection

In the 1980s, acute hepatic allograft rejection occurred in approximately 80% of patients undergoing liver transplantation. Chronic rejection is always preceded by one or more episodes of acute rejection, and usually refractory to immunosuppressive therapy. Chronic rejection is an important cause of late graft failure. Jain et al^[2] reported that from 1981 to 1985, 160 patients underwent re-LT at the Pittsburgh Medical Center. The major cause of re-LT was rejection, giving a rate of 38.8% (62/160). Over the past decades the deep understanding of rejection and improved immunosuppressive therapy have decreased the incidence of rejection. It is also related to the wide use of liver biopsy in evaluating liver allograft rejection, which allows for effective changes in immunosuppressive therapy. In recent years, the combined use of tacrolimus and sirolimus has lowered the rate of acute rejection to 14%.^[14] Meanwhile, chronic rejection has also been decreased from a peak of 15% to 18% by cyclosporine and prednisone regimen in the early 1980s to approximately 5% by tacrolimus-based immunosuppressive regimen.^[15] Therefore, the rate of re-LT caused by rejection is decreased significantly. From 1991 through 1998, 286 patients underwent re-LT at the Pittsburgh Medical Center; the major cause was PNF. The rate of rejection in these patients was 7.3% (21/286).^[2]

Recurrent diseases

Almost all liver diseases that necessitate liver transplantation may recur, and recurrent disease has the potential to

become a serious problem in transplantation.^[16] The common diseases that recur after liver transplantation are hepatitis C and hepatitis B.

Hepatitis C

Cirrhosis in patients with chronic hepatitis C is one of the most common indications for liver transplantation in the United States. However, after liver transplantation the course of hepatitis C is accelerated, and no current therapy reliably prevents or arrests it.^[17] Histologic evidence of recurrence is apparent in approximately 50% of hepatitis C virus (HCV)-infected recipients in the first postoperative year. Approximately 20% or more of HCV-positive transplant recipients will develop allograft cirrhosis within 5 years after PLT, and 10% of HCV-infected recipients will die or lose their allografts secondary to hepatitis C-associated allograft failure.^[18] The only solution is retransplantation. But retransplantation for HCV-positive transplant recipients remains highly controversial since patients undergoing retransplantation for recurrent HCV have a significantly shorter median survival than those patients undergoing retransplantation for other reasons of graft loss.^[19-21] Most deaths occur in the first 6 months because of sepsis.^[22] Using Model for End-Stage Liver Disease (MELD) scores from the UNOS database from 1996 to 2002, McCashland^[23] has recently demonstrated that patient and graft survival rates of HCV-infected recipients who undergo retransplantation are similar to those of recipients undergoing retransplantation who are not HCV-infected.

Hepatitis B

In the 1990s the recurrence of hepatitis B virus (HBV) was noted histologically in 82% of patients 2 months after transplant and was implicated as a cause of death in 73% of patients beyond 2 months after operation.^[24] Because the 1-year survival rate is as low as 5% to 30%, re-LT due to graft damage caused by HBV reinfection is much controversial. Moreover, reinfection itself is a factor for increased mortality rate after retransplantation. The use of hepatitis B immunoglobulin and nucleoside analogues has diminished the risk of HBV recurrence and led to the improvement of patient and graft survivals, transplantation is now considered to be a standard treatment for patients with end-stage liver disease related to HBV.^[25] Current antiviral therapy (gancyclovir, lamivudine) before retransplantation may be a promising strategy.^[26]

Other liver diseases

Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis have a recurrence rate of 20% to 30% within 5 years after liver transplantation.^[15] In patients undergoing liver retransplantation among 447 transplant recipients with PBC and PSC at 3 transplantation centers, Kim et al found that

the patients had had retransplantation showed a 3.8-fold increase in the risk of death compared with those who had had no retransplantation.^[27]

Optimal timing for re-transplantation

During the first 6 months after the initial liver transplantation, re-LT was found to be associated with PNF or vascular complications and late re-LT was mainly indicated for cases of rejection or recurrent primary diseases.^[28] The outcomes of re-LT appear to be related not only to cause of graft failure but also to the timing of re-LT. Elective transplantation is safer than urgent retransplantation because of its lower mortality and complication rate. An estimated one-month survival rate of 73% after urgent retransplantation in contrast to that of 82% after elective one indicates that the period between PLT and re-LT is of considerable importance in patient survival.^[9] These results are probably dependent on the performance of procedures and the general conditions of the patient.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

- 1 Azoulay D, Linhares MM, Huguet E, Delvart V, Castaing D, Adam R, et al. Decision for retransplantation of the liver: an experience and cost-based analysis. *Ann Surg* 2002;236:713-721.
- 2 Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Rupert K, et al. Long-term survival after liver transplantation in 4000 consecutive patients at a single center. *Ann Surg* 2000;232:490-500.
- 3 Bramhall SR, Minford E, Gunson B, Buckels JA. Liver transplantation in the UK. *World J Gastroenterol* 2001;7:602-611.
- 4 Jimenez M, Turrion VS, Alvira LG, Lucena JL, Ardaiz J. Indications and results of retransplantation after a series of 406 consecutive liver transplantations. *Transplant Proc* 2002;34:262-263.
- 5 Deshpande RR, Rela M, Girlanda R, Bowles MJ, Muiesan P, Dhawan A, et al. Long-term outcome of liver retransplantation in children. *Transplantation* 2002;74:1124-1130.
- 6 Jain A, Mazariegos G, Kashyap R, Kosmach-Park B, Starzl TE, Fung JJ, et al. Pediatric liver transplantation in 808 consecutive children: 20-years experience from a single center. *Transplant Proc* 2002;34:1955-1957.
- 7 Adam R, McMaster P, O'grady JG, Castaing D, Klempnauer JL, Jamieson N, et al. European Liver Transplant Association. Evolution of liver transplantation in Europe: report of the European liver transplant registry. *Liver Transpl* 2003;9:1231-1243.
- 8 Rao AR, Chui AK, Shi LW, Tsai L, Leon CD, Sheil AG. Is donor obesity related to liver steatosis and liver graft dysfunction

- in liver transplantation? *Transplant Proc* 2000;32:2103.
- 9 Dudek K, Nyckowski P, Zieniewicz K, Michalowicz B, Pawlak J, Malkowski P, et al. Liver retransplantation: indications and results. *Transplant Proc* 2002;34:638-639.
 - 10 Yoo HY, Maheshwari A, Thuluvath PJ. Retransplantation of liver: primary graft nonfunction and hepatitis C virus are associated with worse outcome. *Liver Transpl* 2003;9:897-904.
 - 11 Nishida S, Kato T, Levi D, Naveen M, Thierry B, Vianna R, et al. Effect of protocol Doppler ultrasonography and urgent revascularization on early hepatic artery thrombosis after pediatric liver transplantation. *Arch Surg* 2002; 137: 1279-1283.
 - 12 Stringer MD, Marshall MM, Muiesan P, Karani JB, Kane PA, Mieli-Vergani G, et al. Survival and outcome after hepatic artery thrombosis complicating pediatric liver transplantation. *J Pediatr Surg* 2001;36:888-891.
 - 13 Vivarelli M, La Barba G, Legnani C, Cucchetti A, Bellusci R, Palareti G, et al. Repeated graft loss caused by recurrent hepatic artery thrombosis after liver transplantation. *Liver Transpl* 2003;9:629-631.
 - 14 McAlister VC, Peltekian KM, Malatjalian DA, Colohan S, MacDonald S, Bitter-Suermann H, et al. Orthotopic liver transplantation using low-dose tacrolimus and sirolimus. *Liver Transpl* 2001;7:701-708.
 - 15 Wiesner RH, Rakela J, Ishitani MB, Mulligan DC, Spivey JR, Steers JL, et al. Recent advances in liver transplantation. *Mayo Clin Proc* 2003;78:197-210.
 - 16 Rosen HR. Disease recurrence following liver transplantation. *Clin Liver Dis* 2000;4:675-689.
 - 17 Wall WJ, Khakhar A. Retransplantation for recurrent hepatitis C: the argument against. *Liver Transpl* 2003;9:S73-78.
 - 18 Charlton M. Natural history of hepatitis C and outcomes following liver transplantation. *Clin Liver Dis* 2003;7:585-602.
 - 19 Chan SE, Rosen HR. Outcome and management of hepatitis C in liver transplant recipients. *Clin Infect Dis* 2003;37:807-812.
 - 20 Biggins SW, Terrault NA. Should HCV-related cirrhosis be a contraindication for retransplantation? *Liver Transpl* 2003;9: 236-238.
 - 21 Berenguer M, Prieto M, Palau A, Rayon JM, Carrasco D, Juan FS, et al. Severe recurrent hepatitis C after liver retransplantation for hepatitis C virus-related graft cirrhosis. *Liver Transpl* 2003;9:228-235.
 - 22 Roayaie S, Schiano TD, Thung SN, Emre SH, Fishbein TM, Miller CM, et al. Results of retransplantation for recurrent hepatitis C. *Hepatology* 2003;38:1428-1436.
 - 23 McCashland TM. Retransplantation for recurrent hepatitis C: positive aspects. *Liver Transpl* 2003;9:S67-72.
 - 24 Todo S, Demetris AJ, van Thiel D, Teperman L, Fung JJ, Starzl TE. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *Hepatology* 1991; 13: 619-626.
 - 25 Sponseller CA, Ramrakhiani S. Treatment of hepatitis B and C following liver transplantation. *Curr Gastroenterol Rep* 2002; 4:52-62.
 - 26 Cahlin C, Olausson M, Friman S. Severe clinical course of de novo hepatitis B infection after liver transplantation. *Transplant Proc* 2001;33:2467-2468.
 - 27 Kim WR, Wiesner RH, Poterucha JJ, Thorneau TM, Malinchoc M, Benson JT, et al. Hepatic retransplantation in cholestatic liver disease: impact of the interval to retransplantation on survival and resource utilization. *Hepatology* 1999; 30: 395-400.
 - 28 Jimenez M, Turrion VS, Lucena JL, Alvira LG, Ardaiz J. Late liver retransplantation versus early liver retransplantation: indications and results. *Transplant Proc* 2002;34:304-305.

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