

J. Odum, A. Banerji, S. Bahrami,
H. Laks

Is Third-time Heart Re-Transplantation Justifiable?

Since repeat heart transplantation traditionally carries higher risk than primary engraftment, we tested the hypothesis that third-time cardiac allograft transplantation is associated with prohibitive mortality and morbidity. The cohort of all third time cardiac retransplants performed at our institution (N=3) and reported to UNOS from 1987 to 2002 (N = 10) was reviewed. The primary endpoints were early and late mortality. Extending the study frame through 2003 captures a total of 5 and 15 third-time heart transplant recipients in UCLA and UNOS databases respectively.

Comparison of mortality outcome after 1st, 2nd, and 3rd cardiac transplants

Descriptor	1st Tx	2nd Tx	3rd Tx*
	UNOS 2000	UNOS 1987-1998	UNOS 1987-2002
Female	587/2198 (26.7%)	19%	2/10 (20%)
CHD	146/2198 (6.6%)		3/10 (30%)
Mean Age (y)	~58**	49	26.8
Interval b/w Tx		1st and 2nd Tx	2nd and 3rd Tx
≤6 m		171/597 (29%)	1/10 (10%)
>6 m		426/597 (71%)	9/10 (90%)
Mortality			
<30 d	2970/11346 (26%) ***	~33%	0
31 d-1 y	2827/11346 (25%) ***	~33%	2/10 (20%)
>1 y	5549/11346 (49%) ***	~33%	1/10 (10%)

Tx, transplant; CHD, congenital heart disease; b/w, between
Based on OPTN data as of July 11, 2002; ** median age; *** UNOS 1987-2001 data

Of the fifteen patients undergoing third-time retransplants, pre-operatively 1 was VAD dependent, 4 were on IV inotropes, and 2 had creatinine levels greater than 2.5. Additionally, 4 were male recipients of female donor hearts and the mean donor ischemic time was 2.6 hours. One patient was diagnosed with acute allograft rejection, thirteen with CAV/chronic rejection, and one with primary graft failure. At our institution, five patients underwent a third heart transplant. There was no early or hospital mortality. One patient died late from TCAD and another following a fourth allograft. The mortality rate for third-time heart allograft recipients is acceptable. These results are influenced by small sample size, younger age, case selection, and operations at select, high-volume institutions with significant experience.

Division of Cardiothoracic Surgery,
David Geffen School of Medicine at
UCLA, Los Angeles, CA, USA

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Kann eine Dritt-Herztransplantation gerechtfertigt werden?

Da bei einer erneuten Herztransplantation normalerweise größere Risiken bestehen als bei Ersttransplantation, haben wir die Hypothese untersucht, dass Dritt-Herztransplantationen mit einer inakzeptabel hohen Sterblichkeit und Morbidität einhergehen. Wir untersuchten alle Dritt-Herztransplantationen, die in unserer Einrichtung durchgeführt wurden (N=3), bzw. die von 1987 bis 2002 an UNOS berichtet wurden (N=10). Die primären Endpunkte waren frühe und späte Sterblichkeit. Wir haben den Studienzeitrahmen auf 2003 aufgedehnt und konnten damit insgesamt 5 bzw. 15 Dritt-Herztransplantationen aus den UCLA- bzw. UNOS-Daten einschließen.

Vergleich der Sterblichkeit nach 1., 2. und 3. Herztransplantat

Descriptor	1st Tx	2nd Tx	3rd Tx*
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Tx=Transplantat; CHD=kongenitale Herzerkrankung; b/w = zwischen

Nach den OPTN-Daten zum 11. Juli 2002; **mittleres Alter; ***UNOS-Daten 1987-2001

Von den fünfzehn Patienten mit Dritt-Transplantation war 1 Patient präoperativ von einem VAD abhängig, 4 wurden intravenös mit Inotropen behandelt und 2 hatten Kreatininspiegel über 2,5. Darüber hinaus hatten 4 männliche Empfänger weibliche Spenderherzen erhalten und die mittlere Ischämiezeit betrug spenderseitig 2,6 Stunden. Bei 1 Patienten wurde eine akute Transplantatabstoßung diagnostiziert, 13 Pat. erlitten eine CAV/chronische Abstoßung und bei 1 Pat. kam es zu einem primären Transplantatversagen. In unserer Einrichtung erhielten fünf Patienten ein drittes Herztransplantat. Es gab keine frühe oder im Krankenhaus eintretende Mortalität. Ein Patient verstarb im späteren Verlauf an TCAD und ein anderer Pat nach einem 4. Transplantat. Die Sterblichkeitsrate für Dritt-Herztransplantatempfänger ist akzeptabel. Diese Ergebnisse sind durch die geringe Anzahl an untersuchten Pat. beeinflusst sowie durch das jüngere Alter, die Selektion der Patienten sowie durch Operationen an ausgewählten spezialisierten Zentren mit signifikanter Erfahrung.

Schlüsselwörter:

Herztransplantation, Re-Transplantation

Introduction

Orthotopic heart transplantation remains the gold therapeutic standard for end-stage heart failure. However, despite thirty-five years of refinement in surgical technique, donor and recipient management, immunosuppression protocols and rejection surveillance the conditional graft half-life is between 10 and 12 years pushing re-evaluation of options for retransplantation. In the vast majority of instances transplant coronary artery disease (TCAD) is the prime culprit for graft attrition and subsequent need for another allograft (1).

Justification of retransplantation procedures is further challenged by the glaring donor organ supply-demand imbalance making a cardiac allograft a scarce resource in face of recipients dying (15-20%) while awaiting the opportunity for even a first transplant. This predicament along with evidence that outcomes after retransplantation are slightly worse than after primary engraftment raises an ethical and moral specter and stokes the fire of conflict between self-interest and common good (2-10).

We hypothesized that third-time cardiac retransplantation would carry a prohibitive high risk for mortality and morbidity.

Methods

Patients

All recipients undergoing a third-time heart transplantation at UCLA since the inception of the program in 1984 were identified in retrospect. Their medical records were examined and key pre-, intra- and postoperative variables noted. The primary endpoint of the study was early and late mortality. Only five patients, in our database of over 1200 sole cardiac transplantation operations, underwent a third transplant. Multi-organ transplants involving heart were not included in this analysis though none of these patients have received a third cardiac allograft in our experience.

The UNOS international database was simultaneously queried for outcomes after second and third-time cardiac transplantation. The data of 10 third-time engraftments were kindly provided by UNOS for our analysis. Since

UCLA supports the national registry our patients formed part of the multi-institutional national registry. By the end 2003 the number of third-time heart recipients had risen to fifteen.

Immunosuppression

Since immunosuppression varied over the study time period at UCLA in general and across the nation in particular immune therapy was not recorded. Of note, however, is the lack of induction therapy with mono- or polyclonal antibody preparations at our institution. Similarly, variation in definition of rejection and it's surveillance was noted.

Statistical analysis

Crude mortality rates (proportions) are reported and Kaplan-Meier analyses were used to compute actuarial survival. Primary and first-time retransplantation data were obtained from historical controls reported in the literature in addition to data kindly provided by the UNOS.

Results

Single institution

Three patients with a mean age of 43 years (range, 19 to 62) received a third cardiac allograft at our institution during the study time frame (5 if extended to 4/30/04). There was neither early nor hospital death. Two out of three (66%) suffered late mortality; one from sepsis and multi-organ failure after 5 months and another required a fourth allograft 4 years later and expired 2 months later from multi-organ failure, sepsis, chronic hepatitis C and papillary carcinoma of the thyroid. Three out of five patients receiving a third allograft are alive today, 6 months, 1.5 and 6 years out from third cardiac engraftment (Table 2).

Multi-institutional

Ten patients with a mean age of 26.8 years (range, 6 to 54) received a third cardiac allograft between 1987 and 2002 (total of 15 recipients out to

Tab. 1: Heart transplant patient survival rates – January 1, 1987 through December 31, 2002*

Transplant No.	No. receiving transplants	1-m survival (%)	1-y survival (%)	5-y survival (%)	10-y survival (%)
Transplants					
1	32,176	92.6	84.3	70.0	47.0
2	681	82.1	69.2	50.6	32.4
3	11	100	80.0	n/a	n/a

*Data from Katarina Anderson, SAS analyst, United Network for Organ Sharing

Tab. 2: UCLA Heart transplant patient survival rates – January 1, 1987 through April 30, 2004

Transplant No.	No. receiving transplants	1-m survival (%)	1-y survival (%)	5-y survival (%)	10-y survival (%)
Transplants					
1	1,188	94.5	85.0	72.5	59.9
2	51	94.1	86.3	67.6	45.8
3	5	100.0	80	60	n/a
4	1	100.0	0.0	n/a	n/a

2004). Twenty percent (2/10) were female and thirty percent (3/10) had an original diagnosis of congenital heart disease. The indication for regrafting was transplant coronary artery disease (TCAD) in the vast majority of instances (9/10). One recipient had early graft failure from acute cellular rejection. Ninety percent of the cohort had a greater than 6 month interval between the second and third allograft. Pre-operatively, one patient was ventricular assist device (VAD) dependent, four were on intravenous inotropic support and two had important renal insufficiency with serum creatinine levels above 2.5. Gender mismatch was present in 40 % of the group with 4 male recipients receiving female donor allografts. The mean donor graft ischemia time for this cohort was 2.6 hours. No patient died within 30 days, two patients died in the first year and one patient died beyond a year after transplantation (Table 1).

Discussion

The unremitting donor organ scarcity and diverging supply-demand curves for heart transplantation over the last decade and graft attrition, mandates revisiting the indications for multiple retransplantation. Historically, primary transplant recipients have enjoyed a survival advantage over retransplant patients across all solid organs (Figure 1). Though, on-going refinements in patient selection and management is closing the efficacy gap for certain patient subsets undergoing retransplantation. In the presence of scarce vital organs the potential poorer outcome after retransplantation spurred discussions over the organ allocation (rationing) system and the existence of a moral obligation to distribute scarce resources to those most likely to benefit from them (10). Is it fair for some patients to receive a third heart transplant while others die

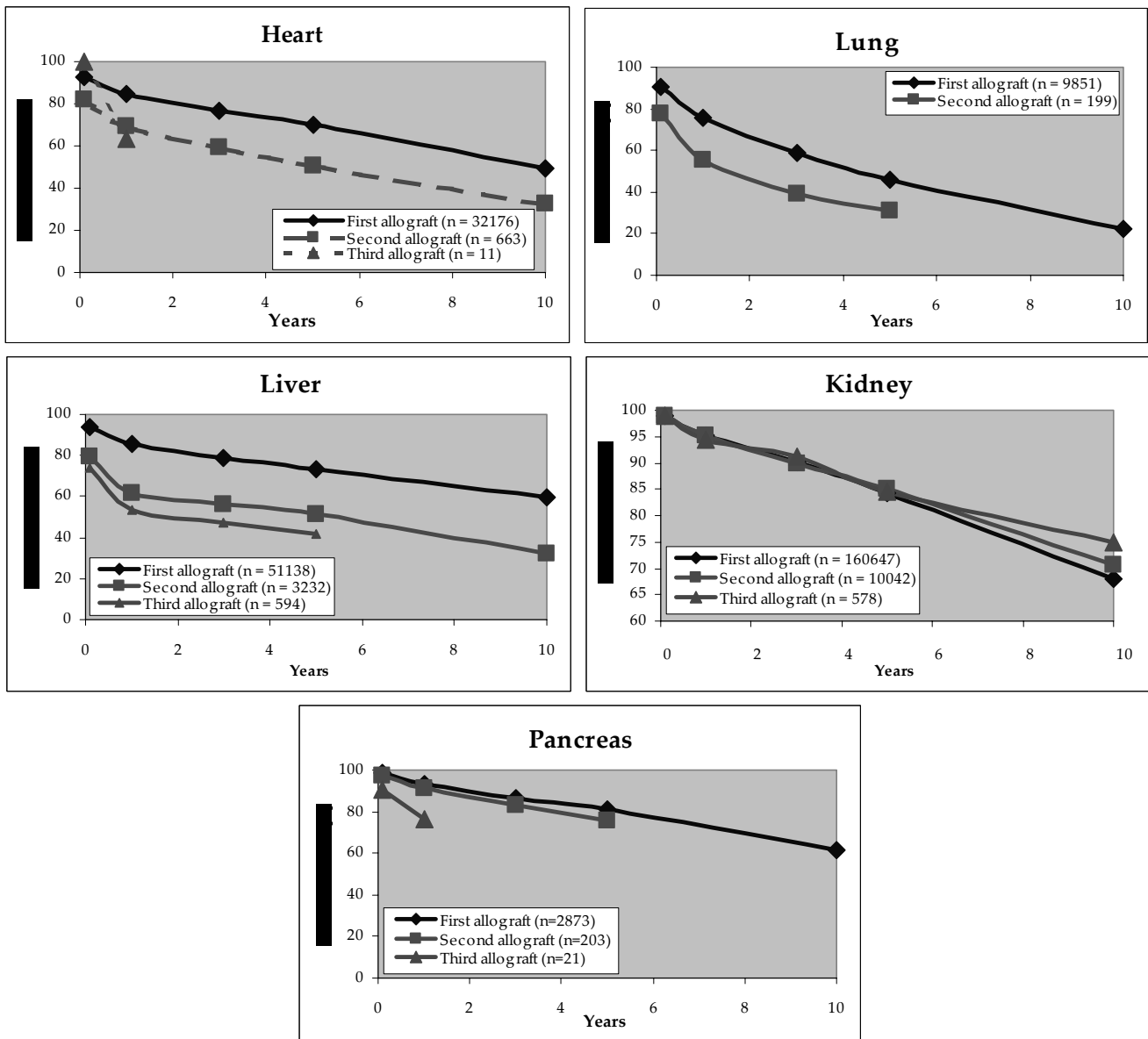


Fig. 1: Actuarial survival curves for all solid organ transplants and retransplants in UNOS database

waiting for their second...indeed 15 – 20% die waiting for their first organ? Second-time cardiac transplants account for 4 % of our heart transplant procedures compared to 0.4% for third-time allografts. Our institutional outcomes and efficacy for third-time cardiac allografts demonstrate no worse outcome than second-time retransplants with only a 5% and 13% disadvantage in 1- and 5-year actuarial survival rates when compared with primary allograft recipients. In fact the 1-month survival rate was 100 % and superior to first and second heart transplant recipients confirming that the re-operation can certainly be performed safely. Caution against making sweeping inferences is advisable given the small sample size.

An explanation for this unanticipated yet comparable outcome may lie in the younger age of the third-time transplant group, a predominant diagnosis of TCAD, and a greater than 6 month interval between the second and third grafts. The Cardiac Transplant Research Database Group and the University of Alabama recently performed a 10-year multi-institutional evaluation of retransplantation in 7,290 primary cardiac transplant patients between 1990 and 1999 demonstrates worse survival in the 106 patients later undergoing a second transplant. Risk factors associated with death after retransplantation included regrafting for acute rejection, early graft failure and the use of a female donor allograft (4). Survival for

the subset with TCAD was significantly better than the other aforementioned indications, however, overall survival after a second cardiac transplant procedure was significantly inferior to that after the primary transplant procedure (1-year survival: 54% vs. 85%). Survival was poorer in recipients who underwent cardiac retransplantation < 6 months after the initial transplant procedure. It is likely that predictors of worse survival outcome after second transplants apply to subsequent third-time retransplants and our findings in this series reflect a highly select subgroup of third-time recipients. While the focus of this study did not look at rejection the incidence of a first episode of acute cardiac rejection was no differ-

ent than after primary transplantation in the multi-institutional study (4). The second and third retransplantation rate was a considerably less proportion of all transplants in the multi-institutional UNOS database analyzed for this report. But the survival outcome of third graft was comparable to survival after a second heart transplantation at least at a year. As in the single institutional experience reported the majority of this cohort had favorable predictors for better outcome including diagnosis of TCAD, non-emergent status, and an interval > 6 months between the second and third allografts.

In summary, the results of cardiac retransplantation a third time for TCAD are comparable to those following a second transplant and continue to improve and thus remain an appropriate indication for retransplantation. Third-time retransplantation in the emergent setting and for acute cardiac rejection and early graft failure probably remains a relative contraindication given reported experience after second-time engraftment and poorer outcomes. The policy of allocating marginal donor allografts (organs not traditionally used for transplantation) to patients waiting for retransplantation expands the donor organ pool and does not deprive first timers awaiting a regular cardiac allograft. This strategy leans towards the utilitarian view that goods should be allocated in ways that maximize total happiness or utility (11).

Limitations of this study

In this retrospective study, the small number of patients having undergone a third-time heart transplantation represents a highly select group of recipients, donor allografts and transplant teams and thus these findings may not be generalisable.

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Jonah Odum, M.D.

Division of Cardiothoracic Surgery
David Geffen School of Medicine at
UCLA

10833 Le Conte Avenue
Los Angeles, California 90095-1741
USA

E-mail: jodim@mednet.ucla.edu

Outcome of a third Kidney Transplant: Is it Worth it?

A. H. Reboux, O. Cointault, N. Kamar, B. Malavaud, M. Fort, D. Durand, P. Rischmann, L. Rostaing
Nephrology, Dialysis, and Transplantation, CHU Rangueil, Toulouse, France

Many patients on waiting lists are potential recipients for a second or third graft. In this retrospective study we assessed the outcome of recipients who received a third kidney transplant (KT). From 1989 to 2004, 1265 KTs have been performed at our center. Of these, 35 were recipients of a third KT: there were 28 men and 7 women, with a median age of 43 years (23-60). Their median time on dialysis was 148 months (24-308). HLA ABDR mismatches (MM) were ≤ 1 in six cases (17%), 2 to 3 in 21 cases (60%), and 4 in 8 cases (23%). Twelve patients had no HLA DR MM, 20 had one HLA DR MM; and three had no DR matching. Peak panel-reactive antibodies (PRA) were >60% in 26 patients. In all the cases but two immunosuppression was quadruple and was sequential with induction therapy (antithymocyte globulins: n = 26; OKT3: n = 6, anti CD-25 MoAb: n = 1), steroids, azathioprine or mycophenolate mofetil and either ciclosporine A (n = 16) or tacrolimus (n = 19).

Results: The median follow-up is 5 years (0.5-7). Current patient survival is 94%, two patients died from cardiovascular complications.

The current graft survival is 89%. Delayed graft function defined by the need for at least one post-KT dialysis session was present in 14 patients (40%).

Ten patients presented with acute rejection -AR-(28.5%); of these five were steroid-resistant. The median time to AR was 30 days (12-150). Renal function was excellent with a mean creatinine clearance (\pm SD) of 58 (16.7) ml/mn at day 90, 62 (20) ml/mn at day 180, and 60 (21), 57 (24.5) and 57 (23) ml/mn at 1,3 and 5 years, respectively. Fifteen patients presented with technical complications, including lymphocele (4), perirenal hematoma (2), ureteral stenosis (2), renal artery stenosis (2), and others reasons (5).

17 patients experienced infection episodes leading to re-hospitalization: of these, 7 had pyelonephritis, 4 had CMV diseases, 3 had peritransplant infections.

Conclusion: A third KT is associated, overall, with good results as far as patient and graft survivals are concerned. Complications, such as AR, technical problems, or infection are within the average range. Therefore, contemplating a third KT is worth it!