# Outcome of Heart Transplants 15 to 20 Years Ago: Graft Survival, Post-transplant Morbidity, and Risk Factors for Mortality

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**Objectives:** The study was conducted to determine the long-term outcome of patients who underwent heart transplantation 15 to 20 years ago, in the cyclosporine era, and identify risk factors for death.

**Methods:** A retrospective analysis was done of 148 patients who had undergone heart transplantation between 1985 and 1991 at a single center. Operative technique and immunosuppressive treatment were comparable in all patients.

**Results:** Actuarial survival rates were 75% (n = 111), 58% (n = 86), and 42% (n = 62) at 5, 10, and 15 years, respectively. The mean follow-up period was 12.1 ± 5.6 years for patients who survived more than 3 months after transplantation (n = 131). The major causes of death were malignancy (35.8%) and cardiac allograft vasculopathy (24.7%). No death related to acute rejection was reported after the first month of transplantation. Graft coronary artery disease was detected on angiography in 66 (50.3%), and 7 (5.3%) had retransplantation. Malignancies developed in 131 patients (48.1%), including skin cancers in 31 (23.6%), solid tumors in 26 (19.8%), and hematologic malignancies in 14 (10.6%). Severe renal function requiring dialysis or renal transplantation developed in 27 patients (20.6%). By multivariable analysis, the only pre-transplant risk factor found to affect long-term survival was a history of cigarette use ($p < 0.0004$).

**Conclusions:** Long-term survival at 15 years after cardiac transplantation remains excellent in the cyclosporine era. Controlling acute allograft rejection can be achieved but seems to carry a high rate of cancers and renal dysfunction. History of cigarette use affects significantly long-term survival in our study. J Heart Lung Transplant 2008;27:486–93. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Cardiac transplantation has become the treatment of choice for the management of end-stage heart failure. Since the first heart transplant was performed more than 30 years ago, a further 73,000 cardiac transplants have been performed worldwide according to the registry of the International Society of Heart and Lung Transplantation (ISHLT).[1] The introduction of cyclosporin resulted in a marked prolongation of survival in these recipients. In 2006, approximately 50% of patients who underwent heart transplantation (HTx) survived for more than 10 years.[1]

This improved graft and patient survival, however, has led to an increase incidence of serious adverse effects related to the long-term use of immunosuppressants. This retrospective study was undertaken to:

- determine the long-term survival of patients who underwent HTx at our institution more than 15 years ago;
- describe the incidence of rejection, allograft vasculopathy, malignancy and renal dysfunctions; and
- identify risk factors adversely affecting survival.

## METHODS

### Study Population

From March 1985 to December 1991, 148 patients underwent orthotopic HTx at our institution. Data were collected until December 2006. This period was selected because the operative technique and immunosuppressive treatment were comparable in all patients and patients had the potential to survive between 15 and 20 years.

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Patients were excluded as initial candidates for transplantation according to generally accepted criteria of pulmonary hypertension with pulmonary vascular resistance higher than 6 Wood units (WU) and remaining higher than 3.5 WU after pharmacologic tests, neoplastic disease during the previous 5 years, recent uncontrolled infection, or other severe organ failure. A positive smoking history was defined as any tobacco use before the pre-transplant evaluation. Patients were defined according to the United Network for Organ Sharing (UNOS) status categories.[2]

### Operative Techniques

Grafts were harvested from beating-heart brain-dead donors and preserved using Bretschneider solution. Orthotopic HTx was performed with the biatrial technique.[3]

### Immunosuppressive Regimen

All recipients were treated with a similar immunosuppressive regimen. Patients were administered Thymoglobulin (Genzyme Transplant, Cambridge, MA) at a daily dose of 25 mg/10 kg during the first 5 post-operative days after HTx. Intravenous methylprednisolone was administered during the operation and continued in the post-operative period. Oral prednisone and azathioprine were started after the patient was extubated. Oral cyclosporine was initiated after normalization of the renal function or not sooner than Day 3 post-operatively. Patient regimens were modified during follow-up to include tacrolimus, mycophenolate, and/or sirolimus, or everolimus in lieu of or in addition to the primary agents started at initiation.

### Follow-up

Patients were seen weekly at the outpatient clinic for the first several weeks after HTx and at least once every 3 months thereafter. We recorded post-operative infections, reoperations, number of episodes of treated acute rejection, and the incidences of cancer and graft coronary artery disease (GCAD). For the purpose of this study, the immunosuppression regimen and the blood level of cyclosporine was recorded every 3 months during the complete follow-up of each patient.

### Monitoring and Treatment of Rejection

Routine surveillance endomyocardial biopsies were performed weekly during the first month, biweekly until the third month, monthly in months 3 to 12, and then every 3 to 6 months thereafter. The frequency of biopsies was gradually reduced during the next several years, and most patients underwent biopsies once a year after the second year post-HTx. Nevertheless, additional endomyocardial biopsies were always performed when rejection was suspected on clinical grounds.

Rejections were graded according to the classification of the ISHLT,[4] and for the purpose of this study, acute rejection was defined as a rejection event with a biopsy ISHT grade of 2 or higher. Rejection episodes were treated with an intravenous daily bolus of methylprednisolone for 5 consecutive days. Rejection episodes refractory to corticosteroids were treated with either antithymocyte globulin or OKT3.

### Coronary Artery Disease

The angiographic diagnosis of GCAD was based on the presence of focal luminal narrowing of 50% or more, distal pruning, or progressive tapering of the epicardial coronary arteries. Coronary angiography was performed 2 years after HTx and annually thereafter.

### Statistical Analysis

For univariate analysis, continuous variables were analyzed using a Mann-Whitney test, and the chi-square or Fisher exact tests were used for categoric variables, as appropriate. A value of $p < 0.05$ was considered significant. For multivariate analysis, variables with a value of $p \leq 0.1$ were entered in a logistic model to determine significant independent predictors of the event studied. Calibration was assessed by a Hosmer-Lemeshow test and discrimination by a receiver-operating characteristic curve with an area that was determined. Significant independent continuous predictors of the event were entered in a classification tree model using the method of least squares to determine a cutoff value for discrimination. A Kaplan-Meier estimation model was used for survival analysis, combined with a Cox model to determine the effects of covariates on survival and to estimate change in hazard for an increase in the value of the covariate if continuous or for the presence of that covariable if categoric.

## RESULTS

### Patient Characteristics

The cause of end-stage heart failure and the indication for HTx was dilated cardiomyopathy in 67 patients (45.3%), ischemic cardiomyopathy in 60 (40.5%), valve-related disease in 3 (2%), and other causes in 18 (12.2%). Baseline demographic variables are summarized in Table 1. The UNOS classification was 1A for 34 patients (23%), and 4 (UNOS 1B) had long-term ventricular assistance with a Jarvik device (Jarvik Heart Inc, New York, NY). The mean follow-up period was 10.7 $\pm$ 6.5 years for the total cohort and 12.1 $\pm$ 5.6 years for the 131 patients who survived more than 3 months. One patient was lost to follow-up.

**Table 1.** Preoperative Characteristics

| Baseline characteristics | Mean ± SD or No. (%) (n = 148) |
|---|---|
| *Recipientrelated factors* | |
| Age at transplant, years | 49 ± 12.7 |
| Sex, M/F | 131/17 |
| Smoking history | 51 (34.4) |
| Diabetes | 9 (6) |
| Cancer | 9 (6) |
| Previous sternotomy | 21 (14.2) |
| Mean waiting time, days | 50.2 ± 51 |
| *Preoperative hemodynamic variables* | |
| Mean pulmonary artery pressure, mm Hg | 31.4 ± 10 |
| Pulmonary vascular resistance, WU | 2.4 ± 1.4 |
| Pulmonary capillary wedge pressure, mm Hg | 22.9 ± 9.5 |
| Cardiac index (Liter/min/m$^2$) | 2.2 ± 0.6 |
| *Donor-related factors* | |
| Donor age, years | 28.8 ± 9.3 |
| Donor sex, male | 123 (83.1) |
| Sex mismatch | 34 (23) |
| Ischemic time, min | 139.9 ± 38 |
| HLA mismatch | 4.5 ± 1 |

HLA, human leukocyte antigen; SD, standard deviation.

## Survival

Actuarial survival rates were 75% (n = 111), 58% (n = 86), and 42% (n = 62) at 5, 10, and 15 years, respectively (Figure 1). Conditional half-time, defined as the time at which 50% of those transplanted remain alive, was 13.7 years for the entire cohort and 14.4 years for those surviving the first 3 months. The 30-day mortality was 8.1% (n =12). There were 81 deaths after the first month of transplantation. The main causes of death during the follow-up were cancer in 29 patients (35.8%) and GCAD in 20 (24.7%; Table 2). No death related to acute rejection was reported after the first month of transplantation.

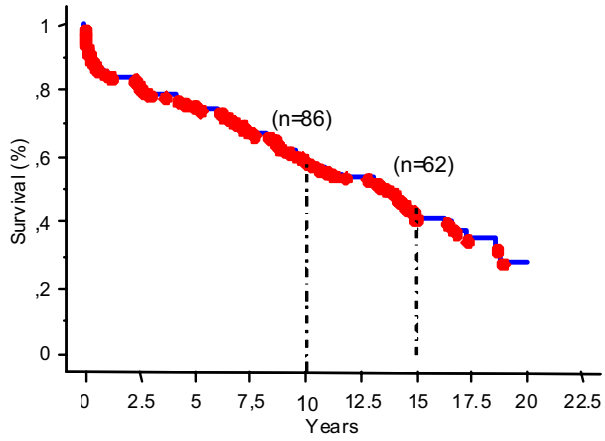


**Figure 1.** Actuarial survival of patients undergoing primacy heart transplantation between 1985 and 1991 in our institution.

**Table 2.** Causes of Late Death (> 1 Month)

| Causes of late death (> 1 month) | Total, % (No.) |
|---|---|
| Cancers | 35.8 (29) |
| Graft coronary artery disease | 24.7 (20) |
| Non-specific graft failure | 8.6 (7) |
| Infection | 6.2 (5) |
| Cerebrovascular | 4.9 (4) |
| Medication non-adherence | 3.7 (3) |
| Others* | 16 (13) |
| Total | 100 (81) |

*Pulmonary fibrosis, traumatic injury, renal failure, mesenteric ischemia, etc.

## Acute Rejections

The mean number of rejection episodes was 0.97 ± 0.8 during the first 3 months post-HTx and 1.5 ± 1.3 at 12 months. The total number of treated rejection episodes during the first year post-HTx was 201, and 38 after this initial period. After the first year of HTx, the mean number of acute rejection episodes per patient was 0.3 ± 0.6. Twenty-six patients (21%) were free from treatable rejection, and no death related to acute rejection was reported during the follow-up.

## Graft coronary artery disease

Chronic rejection was noted in 66 of 131 patients (50.3%). Freedom from GCAD at 5, 10, and 15 years was 81.8%, 49.9%, and 35.6 %, respectively. Ten patients had angioplasty with or without stenting at 12.5 ± 3.27 years after HTx. Target lesions included 5 in the left anterior descending artery, 4 in the left circumflex artery, and 4 in the right coronary artery. Seven patients (5.3%) required re-HTx because of severe GCAD, and 5 were still alive 15 years after HTx.

## Immunosuppression Regimens

Cyclosporine was the main immunosuppressor used during the time of this study, with 85% of patients still receiving cyclosporine after 15 years of transplantation, and only 8% converted to tacrolimus (Table 3). After 13 years, 5% to 10% of patients were maintained on low-dose monotherapy with cyclosporine (Figure 2). Four patients underwent withdrawal of calcineurin inhibitors and were treated with sirolimus or everolimus plus corticosteroids and mycophenolate. During the 15 years of follow-up, the mean cyclosporine dosage was decreased from 311 ± 98 to 124 ± 41 mg/day, and a 45% decrease of cyclosporine blood level was reached, from 240 to 108 ng/ml.

After 4 years of transplantation, more than 53% patients received a bitherapy with cyclosporine and corticosteroids. With the introduction of mycophenolate mofetil in the late 1990s, the proportion of patients receiving 3 drugs rose from 17% at 7 years to 37% at 15 years of follow-up. Corticosteroid withdrawal was

**Table 3.** Evolution of Immunosuppression After Heart Transplantation over 15-Year Follow-up

| Years post-HTx | 1 year | 3 years | 5 years | 7 years | 10 years | 11 years | 12 years | 13 years | 14 years | 15 years |
|---|---|---|---|---|---|---|---|---|---|---|
| CyA blood level, ng/ml | 240 | 178 | 169 | 172 | 138 | 125 | 116 | 115 | 112 | 108 |
| SD | 81 | 56 | 50 | 61 | 39 | 46 | 42 | 54 | 39 | 33 |
| No. | 118 | 111 | 105 | 96 | 76 | 73 | 70 | 66 | 61 | 53 |
| CyA posology mg/day | 311 | 259 | 233 | 199 | 170 | 157 | 145 | 135 | 131 | 122 |
| SD | 98 | 83 | 83 | 71 | 65 | 55 | 50 | 49 | 46 | 44 |
| No. | 118 | 111 | 105 | 96 | 76 | 73 | 70 | 66 | 61 | 53 |
| Corticoid posology, mg/day | 11.7 | 8.7 | 7.9 | 7.6 | 7 | 7 | 7.4 | 6.2 | 6 | 6 |
| SD | 3.7 | 3.3 | 3.3 | 3.1 | 2.8 | 2.7 | 2.5 | 2.3 | 2.1 | 1.7 |
| No. | 117 | 106 | 91 | 87 | 69 | 69 | 67 | 61 | 55 | 51 |
| Aza posology mg/day | 70 | 71 | 70 | 69 | 51 | 48 | 42.5 | 43.7 | 45 | 50 |
| SD | 37 | 35 | 38 | 31 | 17 | 13 | 12 | 11 | 10 | 0 |
| No. | 79 | 69 | 54 | 26 | 15 | 12 | 10 | 8 | 6 | 6 |
| Patients on tacrolimus, No. | 0 | 0 | 0 | 0 | 3 | 4 | 5 | 5 | 5 | 5 |
| Patients on MMF No. | 0 | 0 | 0 | 0 | 10 | 21 | 23 | 23 | 25 | 25 |
| Patients on everolimus or sirolimus No. | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 4 | 1 | 4 |
| Total population | 118 | 111 | 105 | 96 | 79 | 77 | 75 | 73 | 68 | 62 |

AZA, azathioprine; CyA, cyclosporine A; HTx, heart transplantation; MMF, mycophenolate mofetil.

achieved in approximately 15% of patients. Mean doses of corticosteroid decreased from 11.7 ± 3.7 to 6 ± 1.8 mg/day during the 15 years.

### Complications Related to Immunosuppression

**Peripheral vascular disease.** Significant vascular lesions were detected in 12.2% (16 of 131) of patients. The distribution of lesions included aortic aneurysm in 12%, aortoiliac occlusive disease in 32%, femoropopliteal occlusive disease in 48%, and multiple stenosis in 8%. Revascularization procedures were performed in 6 patients.

**Malignancy.** After HTx, 63 of the 131 patients (48.1%) had some kind of malignancy (Table 4), and 29 patients died.

**Skin cancer.** Skin cancers were the most frequent malignancies, accounting for 43.6% of all neoplastic diseases after transplantation. A total of 82 tumors were diagnosed in 31 patients (23.6%) at a mean time of 6.6 ± 4 years after HTx and at the age of 63.9 ± 8.2 years. The most common lesions were squamous cell carcinoma in 19 patients and basal cell carcinoma in 10; 3 patients had both tumors, and Bowen disease was diagnosed in 15 patients.

**Solid-organ cancers.** At 8.1 ± 4.5 years after HTx, 26 patients (19.8%) had non-lymphoid solid-organ cancer. Gastrointestinal malignancies were the most frequent solid tumors, followed by bronchogenic carcinoma (Table 5).

**Hematologic malignancies.** Eleven patients (8.3%) had post-transplant lymphoproliferative disease, and 3 patients (2.3%) had myelodysplastic syndromes or acute myeloid leukemia.

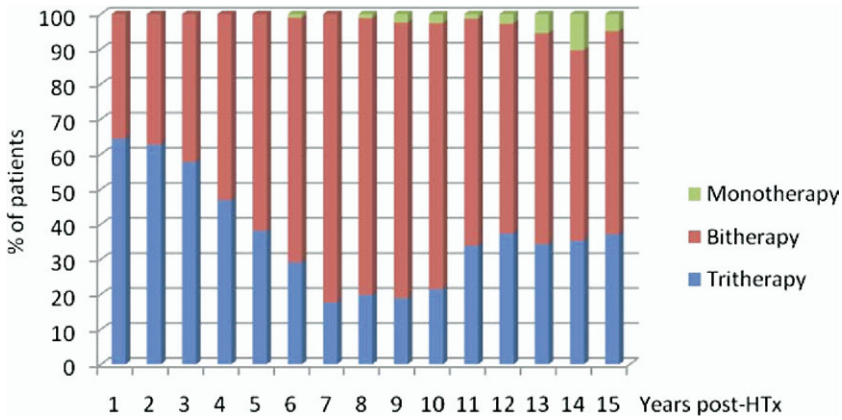


**Figure 2.** Immunosuppressive regimen evolution after heart transplantation (HTx) over 15 years. Light blue, monotherapy; red, bitherapy; dark blue, tritherapy.

**Table 4.** Case Distribution, Frequency and Incidence of Malignancies After Heart Transplantation

| | Number of Patients | Percentage | Incidence (n = 131), % |
|---|---|---|---|
| Skin cancer | 31 | 43.6 | 23.6 |
| Solid-organ cancers | 26 | 36.6 | 19.8 |
| Hematologic malignancies | 14 | 19.7 | 10.6 |
| Total | 71 | 100 | |

**Table 5.** Case Distribution of Solid Malignancy After Cardiac Transplantation

| Solid-organ Cancers | Patients, No. | Percentage | Incidence, % |
|---|---|---|---|
| Gastrointestinal | 8 | 30.7 | 6.1 |
| Lung cancer | 6 | 23 | 4.5 |
| Oral cavity/oropharyngeal | 5 | 19.3 | 3.8 |
| Urologic | 7 | 27 | 5.3 |
| Total | 26 | 100 | |

**Diabetes mellitus.** Seventeen patients (12.9%) were receiving treatment for diabetes during the follow-up, and 9 of these had diabetes before HTx.

**Chronic renal insufficiency.** In 15 years of immunosuppressive treatment, we could observe a 2-fold increase of creatinine level. Nevertheless, creatinine clearance only decreased from 58 to 48 ml/mn (Table 6). Twenty-seven patients (20.6%) required hemodialysis at a mean of 10.1 ± 4.1 years after HTx and at the age of 60.3 ±15 years. Six underwent kidney transplantation.

### Tricuspid regurgitation

During the follow-up, a moderate or severe tricuspid regurgitation was diagnosed in 29 patients (22%), and 2 underwent tricuspid valve replacement.

### Univariate and Multivariate Analysis for Late Mortality (>1 Month)

Univariate analysis of pre-transplant risk factors revealed that only a history of tobacco use had a significant effect on survival ($p < 0.004$). Three other risk factors showed a trend toward significance: donor age ($p = 0.06$), pulmonary vascular resistance ($p = 0.06$), and cardiac index ($p = 0.06$). Other variables were not statistically significant (Table 7). Univariate analysis of post-HTx risk factors revealed that solid-organ cancers ($p = 0.002$) and hematologic malignancies ($p = 0.042$) had a significant effect on survival (Table 8).

Multivariate analysis identified a history of tobacco, with an odds ratio (OR) of 6.47 (95% confidence limits [CL] 2.3, 17.8; $p < 0.0004$), and solid-organ cancers, OR of 4.9 (95% CL, 1.4, 16.5; $p = 0.011$), as statistically significant risk factors to adversely affect survival after HTx. Among recipients with a history of smoking, only 16.2% survived more than 15 years compared with 54.1% who had never used tobacco (Figure 3).

## DISCUSSION

Due to the increasing lack of donors and improved management of heart failure, including angiotensin-converting enzyme inhibitors, β-blockers, and multisite stimulation, the number of HTxs and patients enrolled on a waiting list has been progressively decreasing during the last decade.[1] However, HTx remains the therapy of choice for end-stage cardiopathies, as demonstrated by this study with long-term survivals unequalled by other treatments. Indeed, the follow-up reached by several international transplantation centers allows them to publish very satisfactory survival rates at 10 years,[5–7] but few teams have assessed their patients' survival for longer than 15 years of follow-up. The ISHLT registry estimates that about 30% of HTx patients are still alive at this stage of transplantation, whereas in our series we report a survival rate of 42% at 15 years.

Several reasons may explain these results. First, only single-center studies such as ours allow an exhaustive follow-up of a small cohort of patients who received transplants more than 15 years ago, with a very low number of patients lost to follow-up compared with large multicenter studies. Thus, the long-term results obtained with a series of 325 HTx patients that was published by The Cleveland Clinic compare with our survival rate.[7]

Second, quality criteria of the grafts were excellent 15 years ago, with young donors and short ischemia duration. Furthermore, recipients' hemodynamic picture allowed them to wait for HTx in acceptable conditions: only 25% of the HTx patients had required pre-operative inotropic support or circulatory assistance.

**Table 6.** Evolution of Creatinine Blood Level and Estimated Creatinine Clearance (using the Cockcroft-Gault formula) During 15 Years of Heart Transplantation

| Years post-HTx | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Creatinine level, μmol/Liter | 98 | 153 | 158 | 158 | 157 | 159 | 174 | 187 | 176 | 171 | 178 | 169 | 180 | 193 | 163 |
| SD | 56 | 43 | 64 | 66 | 60 | 70 | 105 | 135 | 113 | 95 | 120 | 102 | 122 | 153 | 97 |
| Creatinine clearance, ml/mn | 58 | 55 | 54 | 53 | 54 | 53 | 53 | 51 | 50 | 52 | 51 | 51 | 51 | 49 | 48 |
| SD | 19 | 19 | 19 | 19 | 20 | 20 | 20 | 22 | 20 | 23 | 22 | 22 | 22 | 23 | 26 |
| No. | 124 | 119 | 116 | 109 | 107 | 103 | 103 | 97 | 94 | 86 | 81 | 73 | 73 | 68 | 61 |

HTx, heart transplantation; SD, standard deviation

**Table 7.** Univariate Analysis of Pre-transplant Risk Factors for Late Mortality (>1 month) After Heart Transplantation

| Pre-transplant risk factor | *p*-value |
|---|---|
| *Demographic variables* | |
| Recipient age at transplantation | 0.53 |
| Recipient sex | 0.40 |
| Smoking history | 0.0004 |
| Diabetes | 0.70 |
| Previous sternotomy | 0.60 |
| Creatinine | 0.32 |
| CMV serostatus | 0.99 |
| UNOS IA or IB | 0.08 |
| *Preoperative hemodynamic variables* | |
| Mean pulmonary artery pressure | 0.08 |
| Pulmonary vascular resistance | 0.06 |
| Pulmonary capillary wedge pressure | 0.19 |
| Cardiac index, Liter/min/$m^2$ | 0.06 |
| *Donor-related factors* | |
| Donor age | 0.06 |
| Donor sex | 0.99 |
| Sex mismatch | 0.83 |
| Ischemic time | 0.12 |
| HLA mismatch | 0.79 |
| CMV serostatus | 0.83 |

CMV, cytomegalovirus; HLA, human leukocyte antigen; UNOS, United network organ sharing.

Third, hospital mortality in our series is below the values published for this period.[8,9]

Fourth, the immunosuppressive protocol applied in our department seemed particularly well adapted to obtain optimal immune control because the main cause of death in our series was not related to acute or chronic rejections, as in other numerous series.[6,10]

In fact, no HTx patient died from late acute rejection, and chronic rejection progression seems to have been reduced, as confirmed by the 17% rate of GCAD observed

**Table 8.** Univariate Analysis of Post-transplant Risk Factors Affecting Long-term Survival After Cardiac Transplantation

| Post-transplant risk factor | *p*-value |
|---|---|
| Number of rejections at 3 months | 0.13 |
| Number of rejection at 12 months | 0.09 |
| Number of rejection after 12 months | 0.06 |
| Number of infections | 0.27 |
| Malignancies | 0.076 |
| Skin cancer | 0.14 |
| Solid-organ cancers | 0.002 |
| Hematologic malignancies | 0.042 |
| Graft coronary artery disease | 0.59 |
| Angioplasty | 0.12 |
| Retransplantation | 0.11 |
| Peripheral vascular disease | 0.60 |
| Hemodialysis | 0.12 |
| Mean cyclosporine blood level at 1 year | 0.68 |
| Mean cyclosporine blood level at 2 year | 0.96 |

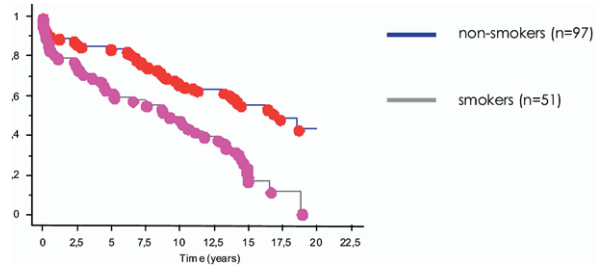


**Figure 3.** Kaplan-Meier analysis of the survival of 51 former smokers (lower line) vs 97 non-smokers (upper line) after heart transplantation.

at angiography examination 5 years after transplantation. Surprisingly in our study, chronic rejection is not a risk of late death; however, there are 2 statistical possible biases. The first is related to the excellent survival results obtained with patients who had re-Htx for GCAD, and the second is attributable to an inadequate classification due to lesions underestimated at coronarography.

Despite all this, our HTx patient population appears to have been protected from acute rejection-related death thanks to a higher immunosuppressant level than in other series. As a consequence, the HTtx patients' survival in our series comes with an increase in neoplastic and renal complications related to long-term immunosuppression. This evolution is also observed in the ISHLT registry[1] as well as in the Cardiac Transplant Research Data Base Group,[11] where neoplastic complications represent the main cause of death after 3-year or 5-year transplantation, respectively.

The pro-carcinogenic consequences of long-term immunosuppression in transplant recipients have been evaluated for many years,[12] especially in renal transplantation,[13] where the cancer incidence reaches 40% after 20 years of immunosuppressant use. The risk that a transplant recipient will develop a cancer is 100 times higher than the global population.[14] The incidence of neoplastic complications after transplantation also varies according to the type of transplanted organ; therefore, the lymphoma incidence is higher among HTx patients than for renal transplant recipients.[15] This is probably due to a much higher immunosuppression in HTx than in renal transplantation.

Nevertheless, the cancer incidence in our series is 3 to 4 times higher than in numerous published studies on HTx (Table 9).[16–20] This difference mainly comes from our high incidence of cutaneous neoplasia and solid tumors, which represent almost 80% of the pathology. These results are probably reflecting an intense immunosuppression that also manifested itself in a high incidence of renal dysfunctions. Immunosuppression levels and cancer risks appear to be directly correlated, because it has been proven that the higher cyclosporine doses are, the more important is the risk of skin cancer in renal transplant recipients.[21]

**Table 9.** Incidence of Malignancies After Heart Transplantation Reported in the Literature

| First authors | Mean follow-up, years | Incidence of malignancies, % | Cancer incidence, % | | |
|---|---|---|---|---|---|
| | | | Skin cancer | Solid-tumor | PTLD |
| I. El-Hamamsy[16] | 8.2 ± 4 | 21 | 8.2 | 11 | .01 |
| M. Rinaldi[17] | 4.7 ± 4 | 11.6 | 1 | 6.5 | 2.3 |
| Olivari[18] | 2 | 8 | 6.7 | 0 | 1.5 |
| Dresdale[19] | 3.4 | 8 | 4.4 | 3.5 | 0 |
| Pham et al.[20] | 4.3 | 15.3 | 2.6 | 3.5 | 9 |

PTLD, post-transplant lymphoproliferative disease.

Other factors must also be considered, however, such as the important follow-up of the study. Indeed, the mean follow-up of patients having developed neoplastic complication in our series is more than 11.5 ± 5 years. Very few publications on the subject present such a follow-up because study follow-up is generally 2 to 5 years (Table 9). However, the incidence of neoplasia and especially skin cancer after transplantation is exponential to the immunosuppression duration.[22] It is therefore logical that the incidence of neoplastic complications in our series is higher than in other published studies with a shorter follow-up.

Skin cancers represent the most frequent neoplastic complication and affect more than 20% of HTx patients. Several of our patients living by the sea had a high level of sunshine that probably increased this neoplasia incidence.[23] Indeed, after 20 years of immunosuppressive treatment, 50% of the patents living in very sunny areas may be affected by cutaneous cancer.[24] Concerning solid tumors, Sheil et al[24] have also published a similar experience to ours after 20 years of renal transplantation. The incidence of post-transplant lymphoproliferative disease in our study is high but similar to data published by other teams with a long-term follow-up[25] and agrees that the risk for lymphoma is higher after HTx than for the global population.[26]

Renal dysfunction, the last complication related to immunosuppression, appears to be particularly important during a 15-year follow-up. It shows a 20% incidence of dialyzed end-stage renal insufficiency, whereas it is between 5% and 10% at 10 years for other series.[27,28] This high incidence of hemodialysis is probably due to an important exposure to cyclosporine. In our series, renal function impairment during transplantation was not associated with increased mortality, as observed by other authors.[28,29]

Our study demonstrated that the only pre-operative risk factor for poor survival is a history of cigarette smoking. Other pre-operative or peri-operative risk factors for death after transplantation identified from different studies[28,30] or from the registry of the ISHLT were not found to affect survival in our study. As reported by Baron et al,[32,32] UNOS status and age recipient did not affect survival.

Several studies have showed that the deleterious effects of smoking in transplantation were numerous as well as multidisciplinary. Concerning renal transplantation, history of smoking is associated with a risk of graft deficiency,[33] increased cardiovascular diseases,[34] and epidermoid-type cutaneous cancers[35]; and concerning HTX, smoking increases the incidence of chronic rejection.[36] In hepatic transplantation, smoking history is closely related to increased vascular complications of the graft[37] and to epidermoid carcinoma. Finally, in pulmonary transplantation, bronchopulmonary cancers[38] and skin neoplasia[39] are frequently observed among smoking patients.

In view of the wide spectrum of tobacco-related complications, it seems obvious that smoking globally affects the transplant patients' survival, with a specific risk for neoplastic complications. So, in a German series of HTx patients[40] in whom active smoking had been assessed by a systematic level of carboxyhemoglobin, mortality at 4 years was 100% for patients with a carboxyhemoglobin level exceeding 2.5%.

In conclusion, the long-term results of heart transplantation with standard immunosuppression show excellent survival at 15 years. A tritherapy associated with induction of immunosuppression with cytolytic antibodies allows optimal control of acute rejections. Nevertheless, a high level of immunosuppression seems to be associated with a high incidence of neoplastic complications and long-lasting renal insufficiencies. In our series, a history of smoking is the sole preoperative risk factor of late death. The high morbidity and mortality rate in smokers after heart transplantation would lead to a more adapted choice of immunosuppressive regimen associated with a more severe screening for cancers among this transplant patient subgroup. Smoking stoppage should be a pre-requisite to any enrollment onto a heart transplantation waiting list.[31]

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