Cancer After Heart Transplantation: A 25-year Single-center Perspective

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ABSTRACT

Background. Cancer is a major cause of morbidity and mortality after heart transplantation.

Methods. We studied 541 heart transplant patients from a single center over a period of 25 years, with a mean follow-up of 10.7 years. We determined incidence, type, risk factors, and prognosis for cancer after heart transplantation.

Results. Cancer was diagnosed in 181 patients, at a mean of 7.7 years after transplantation. Cumulative incidence of cancer at 5, 10, and 20 years was 14%, 29%, and 60%, respectively. The most frequent cancers were spinocellular skin cancer (22%), basocellular skin cancer (19%), lung cancer (16%), lymphoma (11%) and prostate cancer (10%). Age at transplantation $>$ 50 years (hazard ratio, 2.9; $P < .001$) and male recipient gender (hazard ratio, 1.7; $P = .038$) were significant risk factors for posttransplant malignancy on multivariate Cox proportional hazards analysis. Median patient survival after diagnosis of cancer was 2.9 years for patients with noncutaneous cancer, versus 13.1 years for patients with only skin cancer ($P < .001$).

POSTTRANSPLANT malignancies are a major cause of morbidity and mortality after heart transplantation. As short and midterm outcomes have improved, long-term complications after heart transplantation, such as transplant vasculopathy and posttransplant malignancy, gain importance. The risk of malignancy after heart transplantation is increased by 2- to 4-fold compared with the general population [1–5]. Notwithstanding its importance, there have been relatively few studies on the incidence of cancer post cardiac transplantation. Incidence of malignancy after heart transplantation ranged widely in previous studies, from 3% to 30% [6–8]. This large range mostly reflects the different length of follow-up. Another factor is the underreporting of skin cancer, the most frequent posttransplant malignancy, in many large registry-based studies. The current study provides a comprehensive retrospective analysis of incidence, risk factors, and prognosis of all malignancies after heart transplantation at our institution over the course of 25 years.

PATIENTS AND METHODS

Patient Population

A total of 563 patients underwent a first heart transplantation at the University Hospitals Leuven between September 1987 and December 2013. Consistent with previous studies, patients who died within the first month after transplantation were excluded from analysis; none of these patients were diagnosed with malignancy. The remaining 541 patients were followed to December 2014. After initial transplant hospitalization, patients were followed approximately monthly during the first year and every three months thereafter. Screening for posttransplant malignancy was an integral part of follow-up and consisted of clinical examination at every visit, yearly chest radiograph, dermatologic and (as applicable) gynecologic examination or prostate-specific antigen testing. Mammograms and colonoscopy were performed as routine care indicated. No patients were lost to follow-up.

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Immunosuppressive Regimen

Before 2000, standard triple immunosuppressive therapy consisted of cyclosporine, azathioprine, and methylprednisolone. After 2000, mycophenolate mofetil replaced azathioprine and tacrolimus replaced cyclosporine.

All patients received induction therapy with polyclonal rabbit antithymocyte globulin (Fresenius, Fresenius AG, Bad Homburg, Germany). Before 2000, rabbit antithymocyte globulin was given at a dose of 3 mg/kg once daily for 5 days. From 2000 on, rabbit antithymocyte globulin was given at the same dose for 3 days instead of 5 days. No patients received OKT3 or anti–interleukin-2 receptor antibodies.

Variables

The outcome data were the occurrence of de novo malignancies after heart transplantation. Malignancies were divided according to clinical and histologic type. Premalignant lesions such as carcinoma in situ were not counted as malignancy. For each patient, date of transplantation, diagnosis of malignancy, and date of death were recorded. Analyzed variables included gender, age at transplantation, smoking status before transplantation, era of transplantation (before or after 2000), retransplantation, presence of pretransplant malignancy, initial immunosuppressive regimen (tacrolimus vs cyclosporine and mycophenolate vs azathioprine), and rejection during the first month after transplantation.

Statistical Analysis

Continuous variables were reported as mean values ± standard deviation, and categorical variables as number and percentage. The incidence rates of the different types and subtypes of tumors were determined by dividing the number of malignancies of each type by the number of person-years at risk. Multiple tumors of the same histologic and clinical type (eg, recurrent spinocellular skin cancer) were counted as a single case. Incidence rates for prostate cancer and gynecologic cancer were determined for the appropriate gender only. Years at risk were counted from date of transplantation until death or the last available follow-up before the end of study on December 31, 2014. Kaplan–Meier curves were generated to estimate the cumulative incidence of cancer. Characteristics associated with the occurrence of malignancy were assessed by univariate and multivariate analysis according to a Cox proportional hazards model. Covariates found to be significant in the univariate analysis were tested in the multivariate analysis. Patients were censored at the time of death or at the last available follow-up. The patient was the unit of analysis. Retransplantation was assessed as a time-dependent covariate. Differences between groups were assessed by log-rank test. The criterion for statistical significance in all tests was $P < .05$.

RESULTS

Patient Characteristics

We included 541 patients in the study, with a mean follow-up of 10.7 ± 6.7 years, representing 5785 person-years of follow-up. Patients' characteristics are shown in Table 1. Mean recipient age at transplantation was 50 ± 14 years (range, 3–69); 80% were male. The most frequent indication for transplantation was ischemic heart disease.

Table 1. Patient Characteristics

	Mean ± Standard Deviation or n (%)
Age at transplant (y)	50 ± 14
Duration of follow-up after transplantation (y)	10.7 ± 6.7
Gender	
Male	431 (80)
Female	110 (20)
Positive smoking history	293 (54)
Era of transplantation	
Before 2000	252 (47)
After 2000	289 (53)
Etiology for transplantation	
Ischemic heart disease	244 (45)
Cardiomyopathy	233 (43)
Valvular	28 (5)
Congenital	24 (4)
Other	12 (2)
Immunosuppression	
Cyclosporine	272 (50)
Tacrolimus	269 (50)
Azathioprine	237 (44)
Mycophenolate	304 (56)

Incidence

There were 263 cancer diagnoses, corresponding to an incidence rate of 4511.7 per 100,000 person-years (Table 2). The total number of patients diagnosed with cancer was 181: some patients had multiple types of tumors. Age at diagnosis was 63 ± 11, which was 7.7 ± 5 years after transplantation. The cumulative incidence of cancer at 1, 5, 10, and 20 years after transplantation was 2% (95% confidence interval [CI], 0%–4%), 14% (95% CI, 10%–18%),

Table 2. Number, Type, and Incidence Rate of Cancers

Type of Cancer	No. of Cases	Proportion of All Cancers (%)	Incidence per 100,000 Person-years
Spinocellular skin cancer	58	22.1	1002.6
Basocellular skin cancer	51	19.4	881.6
Lung	41	15.6	708.7
Lymphoma	30	11.4	518.6
Prostate	25	9.5	541.2*
Colorectal	12	4.6	207.4
Hepatopancreatobiliary	8	3.0	138.3
Esophageal/gastric	7	2.7	121.0
Urothelial cell	6	2.3	103.7
Renal	5	1.9	86.4
Pharyngeal	5	1.9	86.4
Cervical/vaginal	3	1.1	257.5*
Chronic leukemia	3	1.1	51.9
Breast	2	0.8	171.7*
Malignant melanoma	2	0.8	34.6
Kaposi sarcoma	1	0.4	17.3
Testis	1	0.4	17.3
Unspecified	3	1.1	51.9
Total	263	100	4511.7

*Incidence rates determined for the appropriate gender (men, 4620 person-years; women. 1165 person-years).