

Risk factors and outcomes for the development of malignancy in lung and heart-lung transplant recipients

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MJ Metcalfe, DJ Kutsogiannis, K Jackson, et al. Risk factors and outcomes for the development of malignancy in lung and heart-lung transplant recipients. *Can Respir J* 2010;17(1):e7-e13.

BACKGROUND: Many factors may limit survival from lung and heart-lung transplantation, including malignancy.

OBJECTIVE: To investigate factors associated with the development of malignancy following transplantation and its effect on survival by retrospectively reviewing a population of lung transplant recipients.

METHODS: Data from 342 consecutive lung transplant patients were collected. Results were analyzed by fitting variables into a multivariate logistic regression model predicting the development of post-transplant malignancies. Covariates were selected based on crude associations that reached a level of significance at $P \leq 0.10$. Length of survival was analyzed using the Kaplan-Meier method.

RESULTS: Fifty-eight subjects developed post-transplant malignancies, which were the cause of death of 14 patients. Twenty-one patients had a pretransplant malignancy, of whom six developed a malignancy post-transplant – of these, two were fatal recurrences. No risk factors were significantly associated with all forms of post-transplant malignancy. When adjusted for age at transplantation and donor smoking history, Epstein-Barr virus seropositivity at the time of transplant was significantly associated with a reduced risk of a post-transplant lymphoproliferative disorder (OR 0.17; 95% CI 0.05 to 0.59). The median survival time in individuals without a post-transplant malignancy was significantly shorter than in those with a post-transplant malignancy ($P=0.018$ Wilcoxon [Breslow]). This may be secondary to the length of time required to develop malignancy and the fact that not all malignancies that developed were fatal. The median time to develop malignancy was greater than two years. In addition, the 14 patients who died as a result of their malignancy had a significantly shorter survival time than the 44 who died because of nonmalignant causes ($P<0.001$).

CONCLUSIONS: Malignancy was not associated with an overall decrease in survival time when compared with those who did not develop a malignancy. Risk factors specific for the development of malignancies remain difficult to specify.

Key Words: Heart and lung transplantation; Lung transplantation; Malignancy; Outcome; Risk factor; Thoracic transplantation

Lung and heart-lung transplantation have gained widespread acceptance as therapeutic options for patients with limited life expectancy due to advanced lung, or combined heart and lung disease. Transplantation can improve the quality of life and long-term patient survival can be attained (1-3). However, long-term survival remains limited and postoperative complications are frequent. Malignancy has been shown to be a frequent complication of solid organ transplantation and may be an important limitation to long-term survival. The most extensive data regarding post-transplantation malignancy is derived from the renal transplant literature, which indicates an increase

Les facteurs de risque et les issues de l'apparition d'une malignité chez des greffés du poumon et des greffés cœur-poumons

HISTORIQUE : De nombreux facteurs peuvent limiter la survie après une greffe du poumon ou cœur-poumons, y compris la malignité.

OBJECTIF : Explorer les facteurs associés à l'apparition d'une malignité après une greffe et leurs effets sur la survie grâce à l'analyse rétrospective d'une population de greffés du poumon.

MÉTHODOLOGIE : Les auteurs ont compilé les données de 342 greffés du poumon consécutifs. Ils ont analysé les résultats en insérant les variables dans un modèle de régression logistique multivariée afin de prédire l'apparition de malignités après la greffe. Ils ont sélectionné les covariables selon des associations brutes qui atteignaient un taux de signification à $P \leq 0,10$. Ils ont analysé la durée de survie au moyen de la méthode de Kaplan-Meier.

RÉSULTATS : Cinquante-huit sujets ont présenté une malignité après la greffe, laquelle a provoqué la mort de 14 d'entre eux. Vingt et un patients avaient une malignité avant la greffe; six d'entre eux en ont développé une après la greffe, dont deux se sont révélées fatales. Aucun facteur de risque ne s'associait de manière significative à toutes les formes de malignité après la greffe. Lorsque qu'on procédait aux ajustements compte tenu de l'âge au moment de la greffe et des antécédents de tabagisme, la séropositivité au virus d'Epstein-Barr au moment de la greffe s'associait de manière significative à une diminution du risque de trouble lymphoprolifératif après la greffe (RR 0,17; 95 % IC 0,05 à 0,59). La durée de survie médiane chez les individus sans malignité après la greffe était considérablement plus courte que chez ceux en présentant une ($P=0,018$ Wilcoxon [Breslow]). Ce peut être imputable à la période nécessaire pour développer une malignité et au fait que les malignités n'étaient pas toutes fatales. La durée médiane pour développer une malignité était de plus de deux ans. En outre, les 14 patients décédés en raison de leur malignité présentaient une durée de survie beaucoup plus courte que les 44 décédés de causes non malignes ($P<0,001$).

CONCLUSIONS : La malignité ne s'associait pas à une diminution globale de la durée de survie par rapport à l'absence de malignité. Les facteurs de risque propres à l'apparition de malignités demeurent difficiles à préciser.

in many types of tumours, particularly skin cancers and non-Hodgkin's lymphomas (4-6). However, there is concern that malignancy may be even more common in lung and heart-lung transplant recipients because of more aggressive immunosuppressive therapy (7,8). Furthermore, factors that predispose to postlung transplant malignancy remain unclear but could include a history of malignancy pretransplantation, smoking history, age at transplantation and pretransplant pulmonary diagnosis.

The aim of the present study was to analyze results from a single centre to determine the prevalence of malignancy and

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TABLE 1
Patient demographic data

Variable	All transplant patients (n=342)	Developed post-transplant malignancy	
		No (n=283)	Yes (n=58)
Female sex	143 (42)	116 (41)	27 (46)
Male sex	199 (58)	167 (59)	31 (54)
Indication for transplant			
Emphysema	118 (35)	99 (35)	19 (32)
Pulmonary fibrosis	56 (16)	41 (14)	15 (25)
Cystic fibrosis	52 (16)	44 (16)	8 (14)
Alpha 1 antitrypsin deficiency	40 (12)	34 (12)	6 (10)
Secondary pulmonary hypertension	14 (4)	13 (5)	1 (2)
Primary pulmonary hypertension	14 (4)	11 (4)	3 (5)
Talcosis	14 (4)	12 (4)	2 (3)
Other	34 (10)	29 (10)	5 (8.5)
Type of transplant			
Double lung	232 (68)	195 (69)	37 (63)
Left lung	44 (13)	37 (13)	7 (12)
Right lung	41 (12)	29 (10)	12 (20)
Heart lung	25 (7)	22 (8)	3 (5)
Living donor	5 (1)	4 (1)	1 (0)
Recipient history			
Smoking history, pack-years	234 (69)	194 (69)	40 (69)
0–10	18 (5.3)	14 (5)	4 (8)
11–20	34 (10)	27 (10)	7 (12)
>20	182 (53)	153 (54)	29 (49)
Diabetes	20 (6)	17 (6)	3/20 (15)
Body mass index >30 kg/m ²	197/311 (63.3)	169 (58)	28 (55)
Previous malignancy	21 (6)	16 (5)	6 (12)
Donor			
Male sex	151 (49)	144 (49)	24 (47)
Female sex	174 (51)	147 (51)	27 (51)
History of diabetes	10 /332 (2.9)	8 (3)	2 (2)
Smoking, pack-years	172 (50)	68 (24)	17 (29)
0–10	95 (29)	17 (29)	68 (24)
11–20	36 (11)	5 (8)	31 (11)
>20	182 (56)	11 (19)	40 (14)
History of cancer*	7 (2)	2 (3.3)	5 (1.8)
Serology			
Recipient Epstein-Barr virus seronegativity	30/327 (9.2)	21/270 (7.8)	4/49 (18)
Epstein-Barr virus mismatch	136 (40)	108 (38)	28 (47)
Herpes simplex virus mismatch	261/340 (76)	210/281 (75)	51/59 (86)
Cytomegalovirus mismatch	161 (47)	139 (49)	22 (37)

Data are presented as n (%). *Donor history of cancer included only benign lesions in the central nervous system and squamous cell carcinoma or basal cell carcinoma

types of tumours in a post-transplant population of lung and heart-lung recipients, the effect of malignancy on survival and the risk factors that may predispose to its development.

METHODS

The present study was a retrospective review of all lung and heart-lung transplant recipients at the University of Alberta (Edmonton, Alberta) from 1986 to May 2007. Ethics approval was obtained from the University of Alberta Health Research Ethics Board. All patients and all forms of malignancy were included in the present study. Patient follow-up was until either death or May 2007. Follow-up was performed by chart

review at the University of Alberta Lung Transplant Program along with analysis of the Alberta Cancer Registry. If a patient's follow-up was not complete at this point, his or her individual family doctor and/or provincial cancer registry was contacted.

The primary outcome measures included the morphology and location of any malignancies, survival postlung transplantation and cause of death. Donor and recipient variables collected included the indication for lung transplantation, the morphology and site of any previous cancer, smoking history, Epstein-Barr virus (EBV), herpes simplex virus and cytomegalovirus serological status, comorbidities of cardiovascular

disease, diabetes as well as demographic data. Treatment variables collected included the type of transplant received and the form of post-transplant immunosuppression.

Induction immunosuppression with a polyclonal anti-lymphocyte globulin is routinely used in the program. All patients received standard maintenance immunosuppression with a triple drug regimen that included a calcineurin inhibitor, a corticosteroid and an antimetabolite. The calcineurin inhibitor used was either cyclosporine A or tacrolimus. The antimetabolite used was either azathioprine or mycophenolate mofetil. Data regarding which therapy patients were receiving at three months, one year, three years and five years, were collected. Patients' cumulative length of time on each drug was calculated based on the assumption that the patient remained on the same form of immunosuppression between the measured time intervals.

Statistical analysis

Descriptive statistics included the use of means, medians and SDs. Univariate associations between risk factors and outcomes were analyzed using Fisher's exact tests, χ^2 tests and logistic regression. Risk factors that were found to be associated with the development of post-transplant malignancy at $P \leq 0.10$ were included as covariates in a multivariable logistic regression model predicting the development of post-transplant malignancy and post-transplant lymphoproliferative disorders (PTLDs). Predictors of the development of post-transplant malignancy were maintained in the final logistic regression model if their association reached a level of significance of $P \leq 0.05$. Survival analysis was performed using the Kaplan-Meier method. Comparisons of the survival distributions in subjects developing post-transplant malignancy with those not developing post-transplant malignancy was performed using the Wilcoxon (Breslow) test, given that survival curves crossed at nine months.

RESULTS

Prevalence and risk factors

The study population included 342 patients. The mean (\pm SD) age of the transplant recipients was 48.6 ± 13.3 years. A summary of all the variables and their association with the development of malignancy is presented in Table 1. Variables examined included sex, diagnosis, type of transplant, donor and recipient history, and donor and recipient serology. The only association that was statistically significant for the development of malignancy was that of EBV serology, which is discussed in more detail below.

A total of 58 patients (17%) developed a post-transplant malignancy. Eleven patients had two independent post-transplant malignancies and one patient developed four. In total, 73 neoplasms developed in 342 patients. In cases of multiple malignancies, either a squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) was involved at least once. The median time to diagnosis was less than 2.5 years (Figure 1). This delayed onset is an important factor in considering the effect of the development of malignancy on survival and is addressed in the discussion.

The most common types of malignancy were SCC of the skin ($n=22$) and PTLDs ($n=17$). Other common malignancies were BCC of the skin ($n=14$) and adenocarcinoma ($n=9$) (Table 2).

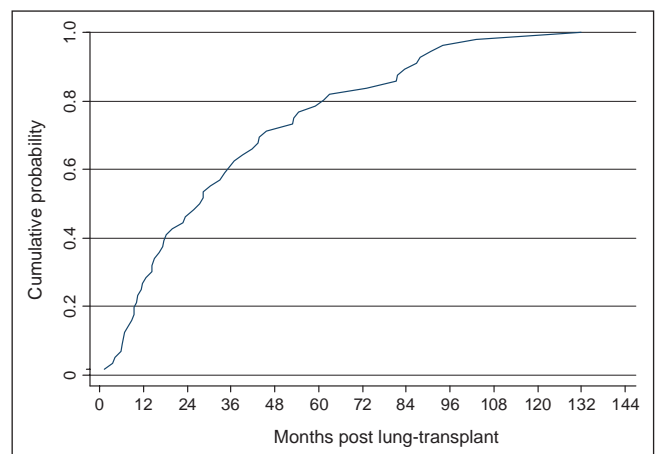


Figure 1) Cumulative probability of developing a post-transplant malignancy. Time until diagnosis of malignancy postlung and heart-lung transplantation ($n=58$). The median time until diagnosis of malignancy was slightly more than two years

TABLE 2
Patient malignancy types

Morphology of post-transplant neoplasms	n (%)
Squamous cell carcinoma of skin (1 patient had a Bowen's premalignant lesion)	22 (6.4)
Lymphoproliferative disorder	17 (5)
Basal cell carcinoma of skin	14 (4.1)
Nonbronchogenic adenocarcinoma	8 (2.3)
Bronchogenic carcinoma (3 small cell, 1 adenocarcinoma)	4 (1.1)
Malignant melanoma in skin	2 (0.6)
Kaposi sarcoma	1 (0.3)
Acute myeloid leukemia	1 (0.3)
Transitional cell carcinoma	1 (0.3)
Renal cell carcinoma	1 (0.3)
Solid organ sarcoma (unrecognized metastatic disease from previous myxosarcoma of the heart)	1 (0.3)

Of the 334 patients who received a lung transplant, 21 (6.3%) were diagnosed with a pretransplant malignancy (PTM) either before or at the time of transplantation (Table 3). Three of the PTMs were incidental findings in the explanted lung (two SCCs and one adenocarcinoma). Six of these 21 patients developed a malignancy post-transplant; two were fatal recurrences of the pretransplant malignancy, while four were curable, independent, second primary tumours. There was no significant difference in the incidence of the development of post-transplant malignancy ($P=0.10$ [Fisher's exact test]) or death as a result of post-transplant malignancy ($P=0.194$ [Fisher's exact test]), regardless of whether patients had a previous diagnosis of malignancy.

There was no significant association between any of the variables outlined in Table 1 and the development of malignancy post-transplantation ($P < 0.05$ [Fisher's exact test]). An association between a history of pretransplant malignancy ($P=0.10$ [Fisher's exact test]) or recipient seronegative EBV status at the time of transplant ($P=0.074$ [Fisher's exact test]) was evident but did not reach significance.

A younger recipient age at transplantation and recipient EBV seronegativity were strongly associated with the

TABLE 3
Outcomes of 21 patients with a diagnosis of malignancy before lung transplantation

Patient	Malignancy morphology		Time between diagnosis of malignancy and transplant, years	Post-transplant outcome, years	Patient age at transplant, years (sex)	Indication for transplant
	Post-transplant	Pretransplant				
1	Squamous cell carcinoma of ear (2.1 years post-transplant)	Basal cell carcinoma of skin	4.6	Survival, 5.4	61.9 (Male)	Emphysema
	Adenocarcinoma of sigmoid colon (4.1 years post-transplant)	Squamous cell carcinoma of lung	0 (found in explanted lung)			
2	Post-transplant lymphoproliferative disorder (0.96 years post-transplant)	Squamous intraepithelial neoplasia of cervix	6.4	Survival, 3.6	31.2 (Female)	Cystic fibrosis
		Adenocarcinoma of lung	7			
3	Squamous cell carcinoma of ear (1.9 years post-transplant)	Adenocarcinoma of prostate	5.95	Survival, 2.1	66.6 (Male)	Emphysema
4	Squamous cell carcinoma of skin at 4.9 years post-transplant	Squamous cell carcinoma of skin	1.57	Death (6.2 years post-transplant due to bronchiolitis obliterans)	55.1 (Male)	Emphysema
5	Metastatic disease in liver and spine	Myxosarcoma of heart	1.74	Death (due to metastatic disease at 0.8 years post-transplant)	19.6 (Female)	Cardiac sarcoma
6	Adenocarcinoma in breast	Adenocarcinoma of breast	7.2	Death (malignancy 0.79 years post-transplant)	59.9 (Female)	Emphysema
7	None	Squamous cell carcinoma in explanted lung	0 (found in explanted lung)	Survival, 3.8	50.1 (Female)	Pulmonary fibrosis
8	None	Adenocarcinoma of lung	0 (found in explanted lung)	Survival, 1.42	63.2 (Male)	Emphysema
9	None	Squamous cell carcinoma of face and neck	9.8	Survival, 7.1	60 (Male)	Emphysema
10	None	Basal cell carcinoma of skin	4.5	Survival, 1.1	61.3 (Female)	Emphysema
11	None	Squamous cell carcinoma of cervix	18.6	Survival, 3.8	52 (Female)	Interstitial lung disease, pulmonary hypertension and scleroderma
12	None	Squamous cell carcinoma of uterus	21.3	Survival, 5	61 (Female)	Emphysema
13	None	Malignant melanoma of the choroid in the eye	7.8	Survival, 4.5	63 (Male)	Emphysema
14	None	Acute myeloid leukemia	8.6	Survival, 3.1	39.2 (Female)	Fibrosis of lungs due to graft versus host disease from bone marrow transplant
15	None	Renal cell carcinoma of kidney	8.6	4.3 years post-transplant	67.6 (Male)	Emphysema
16	None	Papillary transitional cell carcinoma of bladder	5.6	Survival, 0.9	60.1 (Male)	Emphysema
17	None	Malignant melanoma of skin	0.75	Survival, 1.9	43 (Female)	Alpha 1 anti-trypsin
18	None	Infiltrating duct adenocarcinoma of breast	7.2	Survival, 2	52.1 (Female)	Emphysema
19	None	Adenocarcinoma of lung	4.3	Survival, 0.5	67.4 (Female)	Emphysema
20	None	Squamous cell carcinoma of cervix	27.4	Death (1 year post-transplant due to infection)	60.4 (Female)	Emphysema
21	None	Basal cell carcinoma of skin	11.3	Death (3 months post-transplant due to infection)	57 (Female)	Pulmonary fibrosis

TABLE 4
Logistic regression model for the development of post-transplant lymphoproliferative disorders (n=15)

	OR	Standard error	z	P> z	95% CI
Age at transplantation	0.991	0.025	-0.35	0.723	0.944–1.041
Recipient Epstein-Barr virus seropositivity	0.172	0.109	-2.79	0.005	0.049–0.593
Donor smoking history	0.583	0.420	-0.75	0.454	0.142–2.39

development of PTLDs ($P < 0.001$). Each decade of increasing age was associated with a reduced risk of the development of a PTLD (OR=0.64 per decade; 95% CI 0.46 to 0.89). However, the prevalence of EBV seronegativity decreased with increments of increasing age ($P < 0.0001$ [Fisher's exact test]). When adjusted for age at transplantation and smoking history of the recipient, EBV seronegativity significantly increased the risk for the development of PTLDs (Table 4).

Mortality and survival analysis

Death due to malignancy was the third most common cause of death in the post-transplant population (Table 5). Fourteen patients who developed malignancy died as a result of it. The fatal forms of cancer in the present population were PTLD (n=5), small cell lung carcinoma (n=3), esophageal cancer (n=2), liver and bone metastases from a myxosarcoma of the heart (n=1), metastatic breast cancer (n=1), SCC of the head and neck (n=1), and advanced SCC of the tongue (n=1). The myxosarcoma was considered to be an exceptional case and is discussed below.

The survival distribution between those who did and those who did not develop a post-transplant malignancy determined by the Kaplan-Meier method differed ($P = 0.018$ Wilcoxon [Breslow]). Before 108 months (approximately nine years), individuals diagnosed with a post-transplant malignancy had an increased survival; however, after the ninth year post-transplant, they had a decreased survival rate (Figure 2). The median survival time in individuals without a post-transplant malignancy was 66.8 months (95% CI 44.5 to 87.9 months) compared with 81.9 months (95% CI 66.9 to 111.2 months) for those diagnosed with post-transplant malignancy. Patients who developed malignancy and died as a result of it had a significantly shorter survival time than those who died as a result of other causes (Figure 3).

Survival distribution determined by the Kaplan-Meier method did not differ between patients who did and those who did not develop a PTLD ($P = 0.91$ [log-rank statistic]). The median survival time of individuals without a PTLD was 68.6 months (95% CI 51.2 to 87.9 months) compared with 58.9 months (95% CI 18.2 to undetermined, due to small sample size) for those diagnosed with a PTLD.

DISCUSSION

Overall, malignancy following cardiothoracic transplantation is increased compared with the general population, as reported recently by Roithmaier et al (9). The overall incidence of malignancy in our centre was 17% and predominantly consisted of SCC, BCC and PTLDs, which is well within the reported range of 16% to 18.7% (5,6). Malignancy accounted for 12% of all deaths post-lung and heart-lung transplantation in our series, which is higher than that reported by the International Society for Heart and Lung Transplantation (6.5%) (10). This could be due to a more complete follow-up in the present smaller series.

TABLE 5
Cause of death for patients receiving lung and heart transplants (n=116)

Cause of death	Overall, n (%)	Survival, n		
		<1 year	1 to 5 years	>5 years
Infection	26 (22)	10	8	8
Bronchiolitis obliterans	24 (20)	3	12	9
Malignancy	14 (12)	4	6	4
Bronchial dehiscence	12 (10)	11	1	0
Acute rejection	8 (7)	0	3	0
Immediate graft failure	7 (6)	7	0	0
Gastrointestinal complication	4 (3)	4	1	0
Other	21 (21)	10	9	2

Other causes of death include cardiovascular disease, coagulopathies, intracranial air emboli, hemorrhage, renal failure, complications to scleroderma and unknown

We attempted to describe the risk factors for the development of all forms of malignancy in the post-transplant period. However, no variable that we analyzed demonstrated significance for the development of all forms of malignancy. A model specific for the development of PTLDs was significant when recipient age, recipient EBV seronegativity and smoking history at the time of transplantation were included. Donor-recipient EBV mismatch was not used in the model, and recipient EBV seronegativity was more strongly associated with the development of PTLD than a donor-recipient EBV mismatch ($P = 0.055$ versus $P = 0.119$, respectively [Fisher's exact test]).

The strongest association with malignancy in the post-transplant period was a PTM. Six of the 21 cases in the PTM group developed a post-transplant malignancy, and two of these six cases were recurrences. The first was a breast cancer diagnosed 7.1 years before transplant, which was fatal at 288 days post-transplant. PTM has been identified as a large risk in other solid organ transplantations (11). The second case of recurrence was a potential curative heart-lung transplant for a 19-year-old woman with myxosarcoma of the heart. There was no apparent metastatic disease at the time of transplant; however, approximately 10 months after transplant, metastases in her liver and spine were evident.

Bronchogenic carcinoma developed in 1.17% (four of 342) of the cohort, occurring in 2.35% (two of 85) of single lung transplant (SLTx) recipients and 0.82% (two of 257) of bilateral lung and heart-lung recipients. Of the SLTx recipients, both tumours developed in the native lung and only one recipient was a smoker. The development of bronchogenic carcinoma has been noted in all forms of solid organ transplantation and has been linked primarily to patients with a smoking history as well as to oncogenes transferred at the time of transplantation (12). For pulmonary transplantation specifically, SLTx has been shown to have a greater risk for the development of

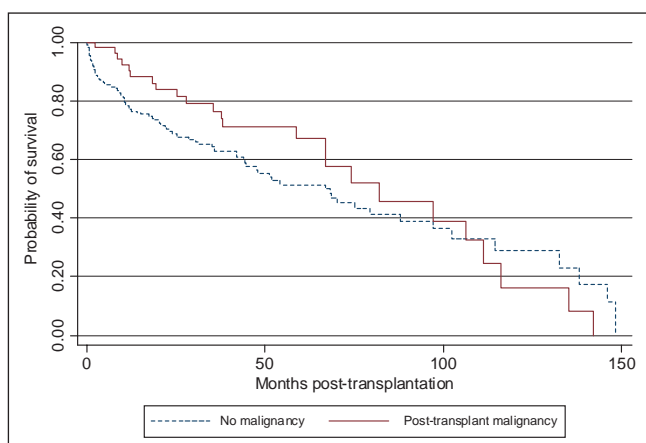


Figure 2) Kaplan-Meier survival estimate. Lung transplant recipients who developed a malignancy had a longer median survival time than those who did not develop a malignancy ($P=0.018$ Wilcoxon [Breslow])

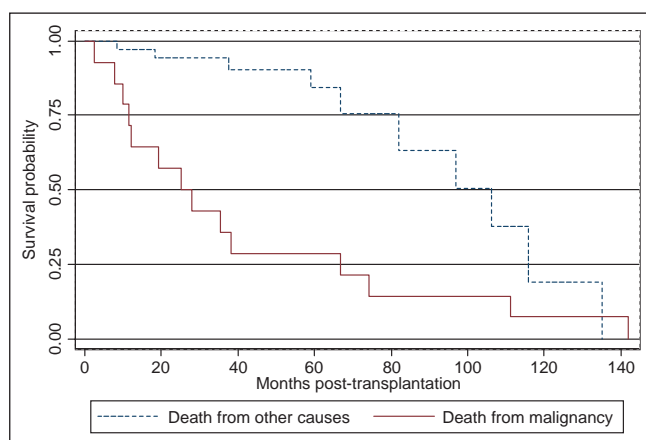


Figure 3) Kaplan-Meier survival estimates. In patients who developed malignancy post-transplant ($n=58$), those who died as a result of their malignancy ($n=14$) had a significantly shorter survival than those who died of other causes ($n=45$) ($P<0.001$ Wilcoxon [Breslow])

bronchogenic carcinoma (13); however, several studies have reported findings of bronchogenic carcinoma in bilateral lung transplant recipients (14,15).

Smoking is a proven risk factor for lung and nonlung cancers. In the renal transplant population, smoking has been shown to have an RR of 1.91 for the development of malignancy; quitting smoking more than five years before transplantation was not beneficial (16). In the present cohort, a smoking history (as well as a diagnosis of chronic obstructive pulmonary disease) was not associated with the development of malignancy or the incidence of bronchogenic carcinoma post-transplant. One of two SLTx recipients who developed a bronchogenic carcinoma was a previous smoker who underwent transplant for emphysema, while the other was a nonsmoker with severe idiopathic pulmonary fibrosis (IPF).

In our series, the three patients who developed a fatal course of small cell bronchogenic carcinoma were originally diagnosed with IPF. Although the diagnostic indication for transplantation was not statistically significant for the development of any malignancy ($P=0.885$), IPF showed an increased prevalence of malignancy in our series. Fifty-six patients had IPF (16% of the

population), 25% of whom developed malignancy. This may be attributable to their previous use of immunosuppression as treatment for their IPF.

We measured the exposure of each patient to each immunosuppressive therapy by the number of months each patient was on that respective drug and assumed that each patient was within the target dosage. There were no statistically significant differences between any immunosuppressant and the incidence of malignancy. This has been reported in other clinical literature (10,17) despite certain *in vitro* studies predicting otherwise (18,19).

As previously reported in other solid organ transplant studies (20-22), the results of the present study showed no association between malignancy and decreased survival. Our study did not show statistical significance between a history of malignancy and the development of post-transplant malignancy. However, two important factors regarding the effect of malignancy on survival were distinguished. First, in Figure 1, we showed that the time to development of malignancy is significant, with a median time of greater than two years. Second, we showed that not all malignancies were fatal and that individuals who died as a result of their malignancy had a significantly shorter survival time than those who developed malignancy but died of other causes. Furthermore, we demonstrated in two specific cases that certain PTMs can have rapid and aggressive onset post-transplantation. This offers an interesting perspective to the principle that previous malignancy within two years is a contraindication to lung transplantation (23-25).

CONCLUSION

The development of malignancy is common and is a significant concern in the postlung and heart-lung transplant patient. Development of malignancy was not associated with decreased survival. This may be secondary to the length of time required to develop malignancy and the fact that not all malignancies that developed were fatal. The median time to develop malignancy was greater than two years. As well, the patients who died as a result of their malignancy had a significantly shorter survival than those who died due to nonmalignant causes ($P<0.001$). Of the variables analyzed, EBV seronegativity at the time of transplant was identified as being a significant risk factor for a PTLD.

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