

# Ten years of lung transplantation in Switzerland: results of the Swiss Lung Transplant Registry

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## Summary

**Objective:** Lung transplantation has evolved from an experimental procedure to a viable therapeutic option in many countries. In Switzerland, the first lung transplant was performed in November 1992, more than ten years after the first successful procedure world-wide. Thenceforward, a prospective national lung transplant registry was established, principally to enable quality control.

**Patients:** The data of all patients transplanted in the two Swiss Lung Transplant centres Zurich University Hospital and Centre de Romandie (Geneva-Lausanne) were analysed.

**Results:** In 10 years 242 lung transplants have been performed. Underlying lung diseases were cystic fibrosis including bronchiectasis (32%), emphysema (32%), parenchymal disorders (19%), pulmonary hypertension (11%) and lymphangiomyomatosis (3%). There were only 3% redo procedures. The 1, 5 and 9 year survival rates were 77% (95% CI 72–82), 64% (95% CI 57–71) and

56% (95% CI 45–67), respectively. The 5 year survival rate of patients transplanted since 1998 was 72% (95% CI 64–80). Multivariate Cox regression analysis revealed that survival was significantly better in this group compared to those transplanted before 1998 (HR 0.44, 0.26–0.75). Patients aged 60 years and older (HR 5.67, 95% CI 2.50–12.89) and those with pulmonary hypertension (HR 2.01, 95% CI 1.10–3.65) had a significantly worse prognosis. The most frequent causes of death were infections (29%), bronchiolitis obliterans syndrome (25%) and multiple organ failure (14%).

**Conclusion:** The 10-year Swiss experience of lung transplantation compares favourably with the international data. The best results are obtained in cystic fibrosis, pulmonary emphysema and parenchymal disorders.

**Key words:** lung transplantation; Swiss Lung Transplant Registry

## Introduction

The first human lung transplantation was performed by James Hardy in Missouri 40 years ago [1]. The recipient, who suffered from severe emphysema and an obstructing carcinoma of the left main stem bronchus, survived 18 days after a left single lung transplant. Although Hardy's pioneer effort had failed, it demonstrated that human lung transplantation was technically feasible. Until the end of the seventies only 38 lung transplants were performed world wide with dismal results [2–4]. Only one recipient could be discharged from the hospital, but he died of pneumonia and chronic rejection 10 months after transplantation [5]. In 1983, Cooper and his colleagues performed the landmark single lung transplant procedure on a patient suffering from pulmonary fibrosis who was the first long-term survivor [6]. It was the same

group who carried out the first successful sequential bilateral lung transplantation in 1989 [7]. This procedure could also be performed in patients with suppurative lung disorders such as cystic fibrosis, and it soon replaced heart-lung transplantation in most centres. This latter technique now is mostly used for patients with un-correctable cardiac malformations and pulmonary hypertension.

Until today almost 15'000 lung transplant procedures have been reported in the Registry of the International Society for Heart and Lung Transplantation ISHLT [8, 9]. The most frequent indication was emphysema in 51% of the patients, followed by parenchymal lung disorders in 21%, cystic fibrosis in 19% and pulmonary hypertension in 6%. The current one, five and ten year survival rates are 74%, 47% and 24% respectively.

The first lung transplant in Switzerland was performed November 10, 1992 at the Zurich University Hospital [10]. In February 15, 1993 the first procedure was carried out by the Centre de Romandie. From the very beginning of the lung transplantation era in Switzerland, the two centres

established a national registry on behalf of the Swiss Transplant Working Group for Lung Transplantation STALU to ascertain the necessary quality control data. Herein we report on our activities during the past 10 years of experience.

## Patients and methods

The data of all patients transplanted in the two Swiss Lung Transplant centres Zurich University Hospital and Centre de Romandie (Geneva-Lausanne) were prospectively collected in a national registry. The following information was included: patients' age, sex, underlying disease, date of transplantation, type of transplant, ie, single or bilateral, ABO blood group and CMV serostatus of recipient and donor, and date and cause of death.

The indications and contraindications were made according to widely accepted criteria [11].

The operation was performed according to standardised techniques and remained basically the same throughout the whole study period [6, 7, 12, 13]. Cardiopulmonary bypass was used mainly in primary or thromboembolic pulmonary hypertension cases and only exceptionally in other patients. All transplants were ABO-matched, and none was HLA-matched. Recipients seronegative for cytomegalovirus were given seronegative organs whenever possible, but otherwise they received organs seropositive for cytomegalovirus without restrictions throughout the whole period.

The postoperative regimens at the two centres were comparable with the exception of minor details which have been described elsewhere [14–20]. The induction immunosuppressive regimen consisted of cyclosporine, azathioprine, and a 5 to 10-day course of antithymocyte globulins. In the Centre de Romandie and in Zurich basiliximab has been used for induction immunosuppression since 2000 and 2002, respectively.

Maintenance immunosuppressive drugs were cyclosporine, azathioprine and tapered dose prednisone. In Zurich, from 1999 onwards mycophenolate mofetil was routinely used instead of azathioprine [20], whereas in the Centre de Romandie it was used initially only for patients with recurrent acute rejections or drug-induced chronic renal failure [18]. In the Centre de Romandie, from 1998 on tacrolimus was used instead of cyclosporine in most patients [15].

Perioperative antibiotic prophylaxis consisted of a second or third generation cephalosporin or an anti-pseudomonas combination therapy tailored to the pre-transplant bacteriological results in cystic fibrosis patients. Postoperative antibiotic treatment was adapted according to the detected bacterial strains. *Pneumocystis carinii* prophylaxis was done with cotrimoxazole, three double

strength tablets per week. In patients with fungal colonisation azoles or inhalative amphotericine was administered [21, 22]. All patients at risk of CMV infections, ie, transplant candidates having a positive CMV serology or receiving the organ from a CMV-seropositive donor, received prolonged prophylaxis with either intravenous or oral ganciclovir for 5 to 9 months as described elsewhere for CMV [14, 19]. After a cost benefit analysis it was reduced to 3 months in the Centre de Romandie [13]. Bacterial, fungal or protozoal infections were treated according to standard criteria [23].

Patients were periodically followed up with evaluations of lung function, fiberoptic bronchoscopy, and early detection of antigens for CMV. Patients measured their own FEV<sub>1</sub> and FVC on a daily basis at home, and a decrease of 10% sustained for >2 days indicated the need for further investigation. Complete lung function evaluations were performed regularly in the pulmonary function laboratory. Regular bronchoscopy procedures were performed as part of the postoperative surveillance during the first 6 to 12 months as described elsewhere [17, 24]. Rejection and infection were evaluated through transbronchial lung biopsies, BAL cellularity, transbronchial biopsies, Gram stain, and bacterial and viral cultures. Acute rejection episodes were treated with methylprednisolone pulses. Antilymphocyte globulins were given in patients with recurrent acute rejection episodes.

Results are expressed as median and ranges, or as mean with 95% confidence intervals (95% CI) if appropriate. Standard life-table analysis and the Kaplan-Meier statistics were used to estimate overall survival distribution. 95% CIs were calculated from the Greenwood's standard errors (see Kalbfleisch and Prentice, 2002: *The Statistical Analysis of Failure Time Data*, 2<sup>nd</sup> Edition. New York; John Wiley & Sons). Potential predictors of survival were assessed with the Cox proportional hazards analysis. We included age, sex, centre, type of lung disease, transplant procedure, ie, single versus bilateral, CMV serostatus and era (until 1997 v. period since 1998) in the model, and excluded in a backward stepwise procedure the variables with a  $p > 0.1$ . In order to obviate correlated observations, retransplantations were excluded from this analysis. Data are expressed as hazard ratios (HR). A  $p$  value  $< 0.05$  was considered to be significant.

## Results

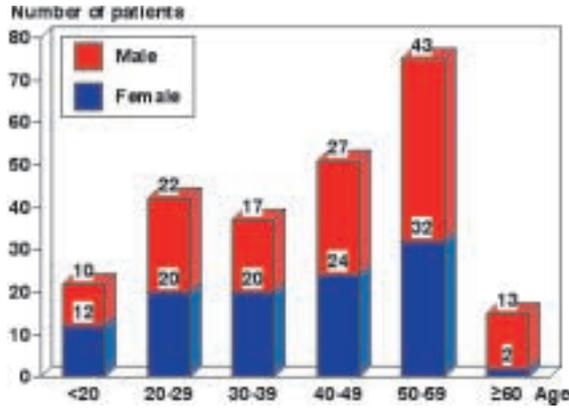
Between November 1992 and November 2002 a total of 242 lung transplants have been performed. There were 110 female and 132 male patients with a median age of 45 years (range 7 to 66 years). The age and sex distribution is shown in figure 1. Twelve of the patients (5%) were children aged below 16 years. Zurich University Hospital

performed 131 and the Centre de Romandie 111 transplant procedures. The annual transplantation rates at the two centres are shown in figure 2.

The most frequent underlying lung diseases (figure 3) were cystic fibrosis ( $n = 77$ ) including 7 cases with non-CF bronchiectasis, emphysema ( $n = 78$ ) including 23 patients with alpha-1-anti-

**Figure 1**

Age and sex distribution of the patients transplanted in Switzerland between November 1992 and November 2002 (n = 242).



trypsin deficiency and 2 with non-transplant obliterative bronchiolitis, followed by parenchymal disorders (n = 47), pulmonary hypertension (n = 26) and lymphangioleiomyomatosis (n = 6). There were only 8 retransplantations. Both lungs were transplanted in 188 and single lungs in 54 patients.

**Table 1**

Survival rates of the Swiss cohort compared to the data of the ISHLT Registry\*.

Year post-transplant	Swiss Registry (n = 242)	ISHLT Registry (n = 14'489)
1	77 (72–82)	74 (73–74)
2	71 (66–77)	65 (65–66)
3	67 (60–73)	58 (57–59)
4	65 (59–72)	52 (51–53)
5	64 (57–71)	47 (46–48)
6	63 (56–70)	41 (40–42)
7	63 (56–70)	37 (35–38)
8	60 (52–69)	32 (31–33)
9	56 (45–67)	28 (27–30)

\* Survival rates are given as mean and 95% confidence intervals. The figures from the ISHLT Registry are kindly provided by Leah Bennett Edwards, Ph.D., ISHLT Registry, Associate Director for Data Analysis, and UNOS, Assistant Director of Research, Richmond, USA

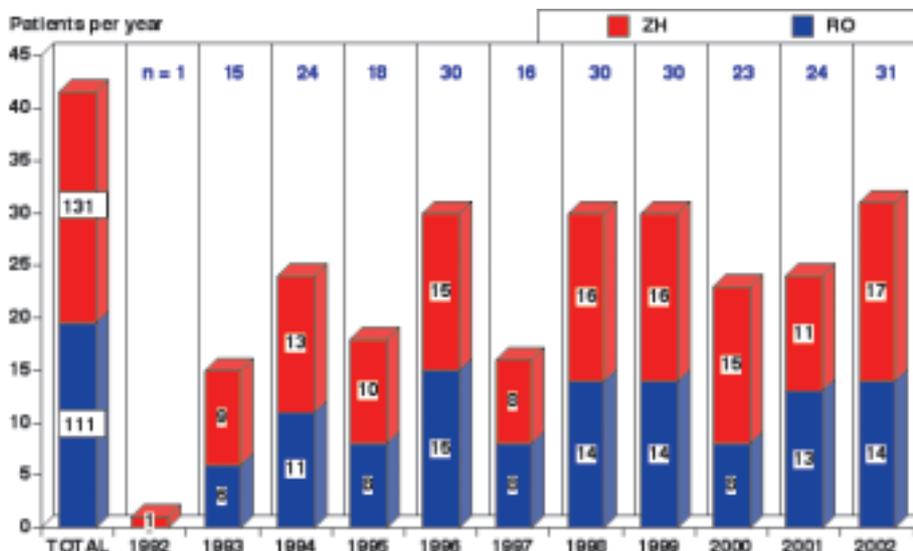
The specific diagnoses in the parenchymal disorders group were: idiopathic pulmonary fibrosis (n = 34), sarcoidosis (n = 5), Langerhans cell histiocytosis (n = 4), and one case each of acute respiratory distress syndrome, pulmonary fibrosis due to systemic sclerosis, giant cell interstitial pneumonia in a hard metal worker, and idiopathic pneumonia syndrome after bone marrow transplantation. The specific diagnoses in the pulmonary hypertension group were: idiopathic pulmonary arterial hypertension (n = 15), chronic thromboembolic pulmonary hypertension (n = 7), and one case each of pulmonary arterial hypertension related to systemic sclerosis, pulmonary arterial hypertension with significant veno-occlusive involvement, peripheral pulmonary artery stenosis, and Eisenmenger syndrome.

The one, three, five and nine-year survival rates were 77%, 67%, 64% and 56%, respectively, which compares favourably with the results of the registry of the International Society of Heart and Lung Transplantation ISHLT (figure 4). The 5-year survival rate of patients transplanted in Switzerland since 1998 was 72% (95% CI 64–80) compared with 57% (95% CI 48–66) in those receiving a transplant before that time point. Although a direct statistical comparison was not done, it becomes evident from the comparison of the 95% confidence intervals of the survival data from the Swiss and the ISHLT registry, respectively, that the Swiss figures significantly surpass those of the ISHLT from the third postoperative year on (table 1).

Eighty patients died after a median of 152 days (1 to 3310 days) after transplantation. The most frequent causes of death (table 2) were infections in 23 patients (29%) caused by bacteria (n = 13), viruses (n = 4), fungi (n = 5) and 1 M. tuberculosis (n = 1), followed by bronchiolitis obliterans syndrome in 20 instances (25%) and multiple organ failure in 9 patients (14%). Less frequent causes of death were neoplasia (3 post-transplant lympho-

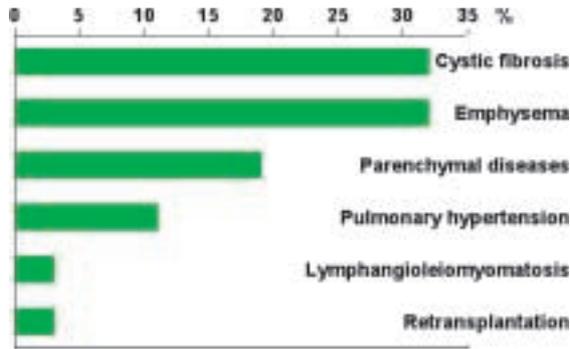
**Figure 2**

Annual transplantation rates in the two centres (ZH = Zurich University Hospital; RO = Centre de Romandie).



**Figure 3**

Distribution of the main diagnostic groups.



proliferative disorders, 3 carcinomas), gastrointestinal complications (3 perforated diverticulitis, 2 mesenteric infarctions), central nervous system disorders (2 idiopathic hyper-ammonaemia, 2 hypoxic-ischaemic encephalopathy, 1 cerebral oedema due to superior vena cava thrombosis), cardiac failure, and accidents. Only 5 patients (2% of all transplant recipients) died as a direct or indirect consequence of technical problems: pulmonary artery rupture (1) and thrombosis (1), haemorrhage after stenting of airway stenosis (1),

after central venous catheter misplacement (1), and after transbronchial lung biopsy (1).

The most frequent causes of death (table 2) within the first postoperative month were multiple organ failure (35%), infections (27%), central nervous system disorders (15%) and cardiac failure (12%). The most frequent causes of death between postoperative month two and twelve were infections (40%) and bronchiolitis obliterans syndrome (18%). The most frequent causes of death after the first postoperative year were bronchiolitis obliterans syndrome (54%), neoplasia (21%), and infections (17%).

The multivariate Cox regression analysis revealed that there was no difference in survival between the two centres. Neither sex, type of transplant (single v. bilateral) nor the donor/recipient serostatus for cytomegalovirus influenced the survival rate. However, patients aged 60 years and older (HR 5.67, 95% CI 2.50-12.89) and those with pulmonary hypertension (HR 2.01, 95% CI 1.10-3.65) had a significantly worse prognosis. On the other hand, patients transplanted since 1998 had a significantly improved survival (HR 0.44, 0.26-0.75).

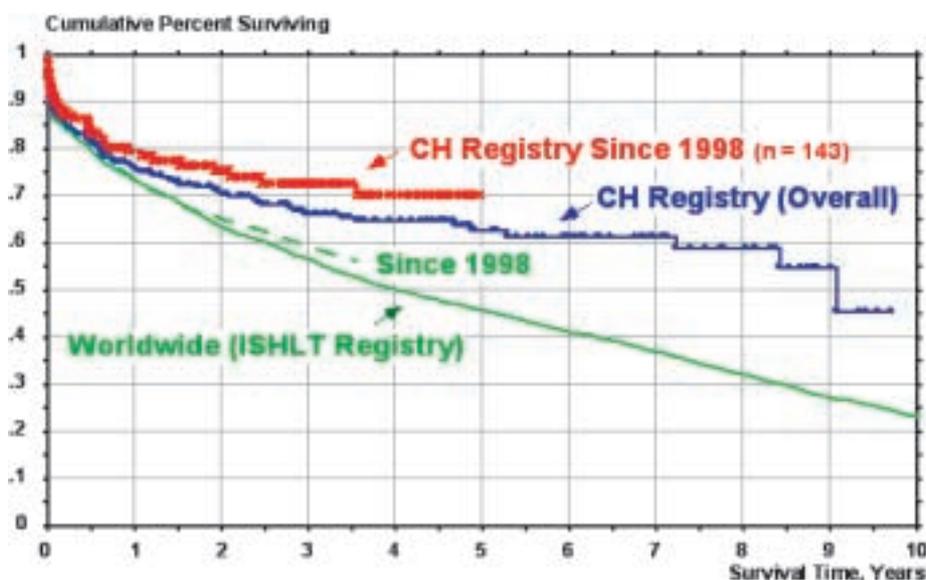
**Table 2**

Causes of death in 80 lung transplant recipients.

Cause of death	first month (n = 26)	month 2 to 12 (n = 30)	year 2 and later (n = 24)	overall
Infection	7	12	4	23
Bronchiolitis obliterans syndrome		7	13	20
Multiple organ failure	9	2		11
Neoplasia		1	5	6
Gastrointestinal complications	1	3	1	5
Central nervous system disorders	4	1		5
Graft-related technical problems	2	3		5
Cardiac failure	3			3
Accidents		1	1	2

**Figure 4**

Kaplan-Meier estimates of overall survival after lung transplantation in Switzerland compared to the data of the Registry of the International Society for Heart and Lung Transplantation (ISHLT). The patients transplanted in Switzerland since 1998 had a significantly improved prognosis (hazard ratio 0.44; p = 0.002).



## Discussion

The results of our 10-years' experience demonstrate that in Switzerland lung transplantation has been established as a viable therapeutic option in the management of end-stage diseases of the lungs and the pulmonary circulation. Our survival rates are clearly superior to those reported in the international registry, and they have even improved during the recent years. The reasons for this success are many-fold, but among the first is the fact that in both centres a constant, dedicated and highly motivated team with close relationships to the international transplant community has been responsible for the two programmes. The constancy of an experienced team is of utmost importance for the careful selection of patients, the competent surgical techniques, the sophisticated perioperative management, meticulous surveillance and complex long-term management.

Careful selection of patients is the backbone of successful lung transplantation [25, 26]. Only one third of the patients suffer from relatively common diseases such as pulmonary emphysema [27]. Another third consists of patients with cystic fibrosis, which is quite uncommon in relation to the general population, but for which the indication criteria are well established [11]. The remainder of cases consists of very rare lung disorders such as pulmonary fibrosis [28], sarcoidosis, Langerhans' cell granulomatosis, lymphangioleiomyomatosis [29], obliterative bronchiolitis and disorders of the pulmonary circulation [30]. Especially in the latter group of patients, the complex and highly specialised management of the disease itself goes along with the evaluation for a lung transplantation and depends on an experienced team of specialists for orphan's lung disease. The importance of careful selection of potential lung transplant candidates is underscored by our data, which demonstrate a significantly worse survival in patients aged 60 or higher and in those with pulmonary hypertension.

Surgical expertise is the *sine qua non* condition for successful lung transplantation. It is quite remarkable that only five of our patients (2%) died because of technical problems, and in only three of them the cause of death was directly or indirectly related to surgery. Whereas other lung transplant programmes still suffer from a significant proportion of patients with bronchial anastomotic complications, only one patient in our series died because of haemorrhage after stenting of a bronchial anastomotic stenosis.

The perioperative management of the lung transplant recipient is highly demanding. About 10% of our patients died during this period, multiple organ failure being the most frequent cause followed by cardiac failure. In most of these patients the exact reason for the organ failure could not be determined. Early allograft dysfunction due to re-perfusion injury, acute rejection or occult

infections may have played a role. There is clearly need for improvement in this period. However, even in the retrospective analysis of these cases, it is difficult to determine, how this could have been accomplished.

The intermediate and long-term management of these patients is determined by the most frequent complications, ie, infections and bronchiolitis obliterans syndrome. Meticulous postoperative surveillance, prophylactic measures and pre-emptive antimicrobial treatment of infections are crucial [22, 23, 31]. It is striking, that after bronchiolitis obliterans syndrome bacterial infections were the most frequent specific cause of death. Therefore, in the future, emphasis on early diagnosis and aggressive treatment even only on suspicion of this complication, is a primary goal.

The fact that only a few patients were lost to viral or fungal infections reflects our policies of long-term ganciclovir prophylaxis [14, 19] and pre-emptive antifungal strategies [21, 22]. The benefit of cytomegalovirus prophylaxis is also underscored by the fact that neither cytomegalovirus-seropositive lung transplant recipients nor seronegative recipients of seropositive organs had an impaired prognosis.

Bronchiolitis obliterans syndrome (BOS) still presents the most important single cause of death after lung transplantation [32]. It is believed to be caused by various immunological and non-immunological injuries to the pulmonary allograft with a common final pathway often presenting as progressive airflow obstruction with histological features of obliterative bronchiolitis. The most frequently discussed risk factors are infections, such as with cytomegalovirus, chronic aspiration and recurrent acute rejection [33]. The number and the severity of acute rejection episodes are the most clearly defined risk factors. Many acute rejection episodes occur during the first months after lung transplantation and are often asymptomatic. Therefore, regular surveillance transbronchial lung biopsies [24], which are carried out in both centres, are crucial for picking-up and treating these acute rejection episodes early and thereby possibly reducing the incidence of BOS. Moreover, it may also be important to recognise late acute rejection episodes early, in particular the moment the lung function decreases or does not recover after an inter-current pulmonary infection. These infections, irrespective of type, are well known as triggers of innate and then specific cellular immunity [34].

So far, as published elsewhere [20], the potential benefit of our policy of a strict and comprehensive surveillance after lung transplantation may be underscored by the low risk of BOS of about 22–25% after three to five years compared to the figures reported in literature that are constantly higher than 50%.

Although it is well known from the international registry data [8], that centres performing only 10 or 5 lung transplants per year have a higher mortality at 14% and 21%, respectively, we feel that our excellent results in comparison to the benchmark data and despite a maximum annual case load of about 30 transplants in Switzerland, which leads to a annual transplantation rate of about 15 per centre, justify the maintenance of two lung transplant centres in our country.

In conclusion, lung transplantation has become a viable therapeutic option for severely disabled patients with the best results being obtained in cystic fibrosis, pulmonary emphysema and fibrosis. The 10-year Swiss experience compares

very favourably with the international benchmark data. Strategies to prevent bronchiolitis obliterans, probably representing sequelae of early or late acute rejection episodes, infections, and non-immune injuries to the lung allograft, are crucial.

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