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Lung transplantation in British Columbia: A breath of fresh air

Close collaboration between the lung transplant team and patients' health care providers has contributed substantially to the improvements in outcomes seen over the last two-and-a-half decades.

ABSTRACT: Lung transplantation has evolved over the past 25 years to become an excellent option for motivated younger patients with advanced chronic cardiopulmonary diseases who are otherwise in good health. Over the past decade in particular, there have been very substantial improvements in outcomes. Today the majority of transplants are performed on patients with cystic fibrosis, emphysema, and pulmonary fibrosis. Outcomes in British Columbia parallel the successes seen in other major programs throughout Canada and internationally. Major ongoing challenges to improving lung transplant outcomes relate to the early identification and optimal management of opportunistic infections and chronic graft rejection. A strong collaboration between the transplant clinic and the recipient's primary care and specialist physicians is needed to ensure optimal long-term outcomes.

Ongoing progress, remarkable achievements, and continuing challenges can all be seen when looking at lung transplantation in BC today. It is essential for those caring for patients with advanced respiratory disorders (respiratory and internal medicine specialists, family physicians) to have a good sense of when to refer for transplantation and when not to raise expectations unreasonably in the case of patients unlikely to benefit. Furthermore, with increasing numbers of lung transplant recipients receiving follow-up care in the community, it is important that physicians know how to care for these patients, as well as how to recognize when more specialized input from a lung transplant centre is desirable.

Successes

The field of lung transplantation has become well established over the past two-and-a-half decades, with continuous improvements in outcomes as well as expansion of the indications and application to more patients. Lung transplantation can now provide a reasonable expectation of medium- and long-term survival with excellent functional capacity and quality of life for many patients with advanced cardiopulmonary conditions. Over 25 000 lung transplants have now been performed in more than 100 centres worldwide, and approximately 1400 new transplants are performed globally on an annual basis.[1] The majority of recipients have had underlying cystic fibrosis, emphysema, or pulmonary fibrosis, although many other conditions are also amenable to lung transplantation.

Challenges

Unfortunately, the number of transplants that can be performed in BC and Canada is limited by the relatively small cadaveric organ donor pool.[2] Hence 20% to 30% of potential candidates die on the transplant list before suitable organs are identified. Several innovative strategies to increase the number of potential donor organs are currently being developed, including the use of living donors for lobar trans-

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plantation[3] and the use of donor organs after cardiac death.[4] One exciting new approach that may increase the supply of suitable lungs for transplantation involves the harvesting of selected lungs considered suboptimal for transplantation according to current criteria. These lungs are then placed on an artificial ex vivo circuit, which provides ventilation and circulation so that the organs can be monitored physiologically and subsequently transplanted if they demonstrate adequate function.[5] Preliminary in vitro data suggest that damaged donor lungs can even be "repaired" pre-transplant while on the ex vivo circuit using gene therapy.[6] This approach, although early in development, offers the prospect of substantially increasing the number of donor lungs available for transplantation.

It is essential that patients awaiting transplant remain in optimal health through attentive medical care, diet, and exercise.

In view of the current shortage of cadaveric organs, the identification of recipients with the greatest likelihood of having a successful outcome is critical. Much of the improvement in lung transplant outcomes can be attributed to advances in donor and recipient selection, operative technique, and perioperative care. The use of newer immunosuppressive agents with greater efficacy and more favorable side effect profiles has also had a major impact. The availability of new antiviral and antifungal agents has resulted in substantial reductions in morbidity and mortality, and systematic use of anti-infective surveillance and prophylactic strategies has resulted in substantial freedom from infection with pathogens that previously devastated the solid organ transplant population.

The greatest obstacle affecting intermediate and long-term morbidity and mortality is the development of bronchiolitis obliterans, a form of chronic graft dysfunction thought to be a manifestation of chronic rejection. This condition affects approximately 50% of patients within 5 years of lung transplantation, and its development leads to progressive deterioration of graft performance, reduction in functional capacity and quality of life, and death.[7] The causes of bronchiolitis obliterans and optimal modalities for its early detection remain poorly understood, and treatment outcomes are generally disappointing.[7]

Anticipated outcomes

The primary goal of lung transplantation is to provide a survival benefit. Several studies have demonstrated that lung transplantation confers such a benefit, particularly in patients with advanced cystic fibrosis, idiopathic pulmonary fibrosis, and idiopathic pulmonary arterial hypertension.[8,9] However, data for patients with underlying COPD or congenital heart disease provide conflicting evidence regarding survival benefit with lung transplantation.[8,9] The most recent estimates from the registry of the International Society for Heart and Lung Transplantation (ISHLT) indicate a median survival for lung transplant recipients of 5.5 years, or 7.1 years conditional to surviving the first post-transplant year.[1] Results from experienced centres and for recipients falling into lower risk categories (e.g., patients with alpha-1 antitrypsin deficiency emphysema) can be substantially better than the registry data.[10]

More than 80% of long-term lung transplant survivors report no activity limitations.[1] How to weigh expected survival benefit against gains in quality of life is a topic of considerable discussion within the transplant community. Lung transplantation for most patients is a palliative rather than a curative treatment. Certainly the patient's quality of life should be taken into account when the need for a lung transplant is assessed,[11] but owing to the shortage of donor organs as well as the potential morbidity and mortality associated with the transplant, transplantation is in most cases not recommended for quality-of-life purposes alone.

Lung transplantation in British Columbia

The Lung Transplant Program coordinated through BC Transplant is one of five programs across Canada. Based in Vancouver, the program performs 10 to 15 single- and double-lung transplants per year. More than half the lung transplant programs internationally have smaller annual volumes,

and only six programs worldwide do 50 or more transplants annually.[1] Outcomes for lung transplantation in BC are similar to those observed in other Canadian programs (**Figure 1**). Survival has improved dramatically over the past decade (**Figure 2**) thanks to many innovations in perioperative donor and recipient management, prophylaxis for opportunistic infections, and improvements in immunosuppressive medications. Pulmonary fibrosis, COPD (including COPD caused by alpha-1 antitrypsin deficiency), and cystic fibrosis are the most common reasons for lung transplantation in British Columbia (**Figure 3**) and internationally.

The BC Lung Transplant Program participates actively in the Canadian Lung Transplant Study Group, which has developed common criteria for recipient selection and many transplant processes. In order to maximize the number of recipients, the majority of lung transplants done in BC are single-lung transplants, and in many cases two single-lung transplants are performed using one organ donor. Double-lung transplants tend to be reserved for younger patients and those with chronic septic lung disease (e.g., cystic fibrosis) or severe pulmonary hypertension.

BC residents have the opportunity to undergo transplantation at one of the other Canadian lung transplant programs if they require special expertise that is not available in BC. In this circumstance, medical expenses (but not travel and living expenses) are covered by the BC Ministry of Health Services. These patients then return to be cared for in BC following the transplant.

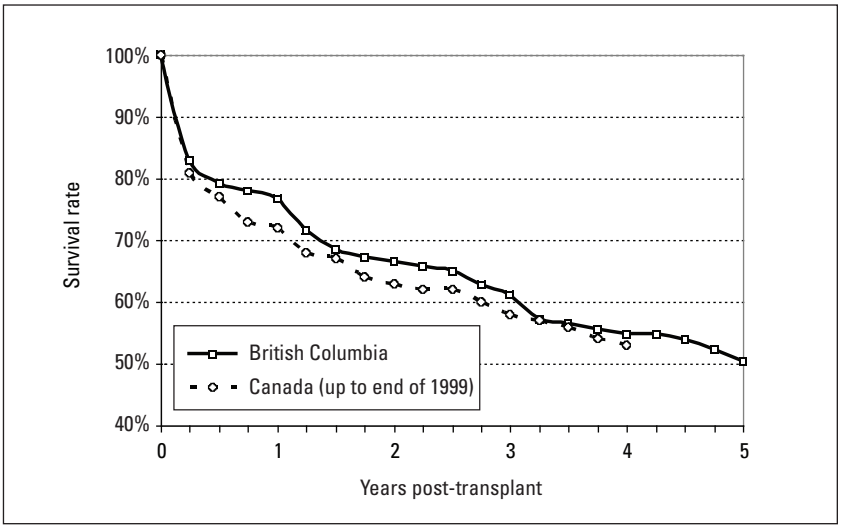

Figure 1. Patient survival following lung transplantation in BC and Canada (single, double, or heart-lung), 1989–2007.

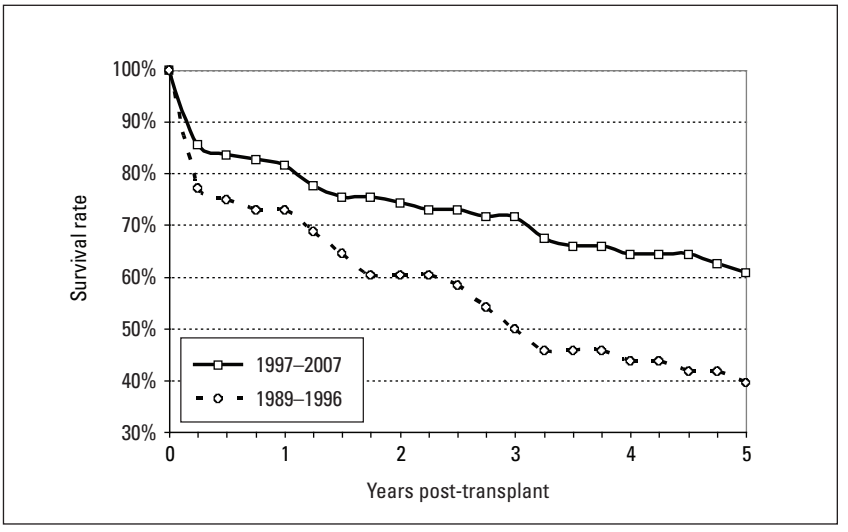

Figure 2. Patient survival following single- and double-lung transplantation in BC by year of transplant, 1989–2007.

Transplant candidates

Lung transplantation should be considered for otherwise healthy younger patients with chronic, end-stage lung disease who are failing maximal medical therapy. Potential candidates should be well informed and demonstrate adequate health behavior and a willingness to adhere to health care guidelines.[12] In BC potential transplant recipients are referred to the Lung Transplant Program coordinator (see box at end). These patients then undergo careful screening and consultations to evaluate for medical and psychological suitability. The assessment team includes individuals with expertise in nursing, respirology, thoracic surgery, anesthesiology, social work, psychology, dietetics, pharmacology, physiotherapy, and spirituality. Absolute and relative contraindications

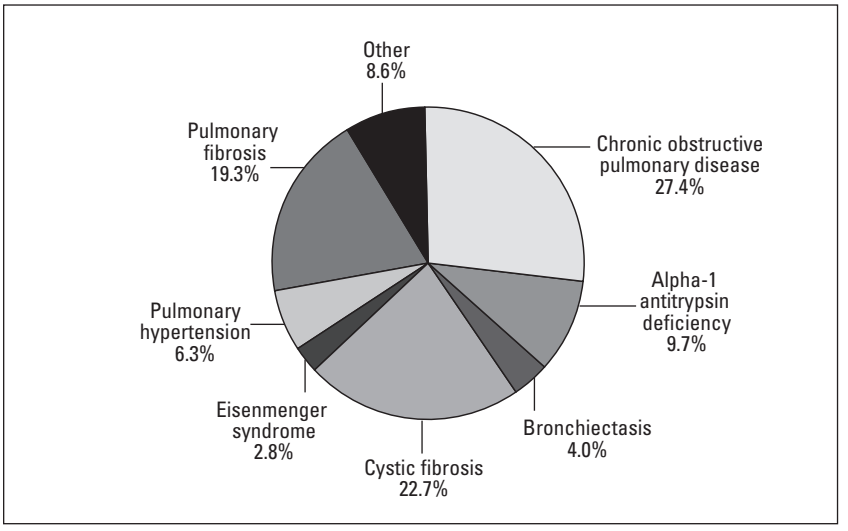

Figure 3. Patients receiving lung transplants in BC by primary diagnosis, 1989–2008.

Source: BC Transplant

Table 1. Contraindications to lung transplantation*

Absolute contraindications to lung transplantation	Relative contraindications to lung transplantation
• Malignancy < 2 years, except cutaneous basal or squamous cell carcinoma	• Age greater than 65 years
• Untreatable dysfunction of another major organ system (e.g., heart, liver, kidney)	• Critical or unstable clinical condition
• Noncurable systemic infection, including HIV and active viral hepatitis B or C	• Severely limited functional status with poor rehabilitation potential
• Severe chest wall or spinal deformity	• Obesity (body mass index > 30 kg/m^2)
• Documented nonadherence or inability to comply with medical therapy	• Mechanical ventilation
• Untreatable psychiatric or psychological condition associated with inability to comply with medical therapy	• Colonization with highly resistant or virulent organism
• Absence of a consistent or reliable social support system	• Severe or symptomatic osteoporosis
• Substance addiction (e.g., alcohol, tobacco, narcotic) within past 6 months	• Significant medical problems that may be difficult to control (e.g., diabetes, gastroesophageal reflux)

*Adapted from Orens JB, Estenne M, Arcasoy S, et al.[12]

for lung transplantation are summarized in **Table 1**.

Once potential lung transplant candidates have undergone evaluation, each case is discussed at a structured multidisciplinary conference to determine whether lung transplantation is an appropriate option. If a decision is made by the transplant team in consultation with the patient and family to proceed, patients are "activated" on the lung transplant list and provided with a pager for rapid access.

Timing of referral

In general, referral for transplantation assessment is advisable when patients are anticipated to have a less than 50% 2- to 3-year predicted survival.[12] The chance of surviving the waiting period will obviously depend on the length of time involved and the natural history of the underlying disease. Waiting time tends to be variable and based on many factors such as height and blood type. It tends to be longer for smaller patients than taller patients and for recipients with type O blood. Patients who have idiopathic pulmonary fibrosis, cystic fibrosis, or pulmonary hypertension experience lower survival rates while awaiting lung transplantation compared with patients who have emphysema or Eisenmenger syndrome.[8,9]

Early referral is highly desirable because it permits an orderly process for assessment, management of areas of concern, and patient education before active listing. The decision to refer is generally based on a variety of clinical findings (e.g., rate of infection, oxygen need, weight loss), laboratory findings (e.g., PaO_2, $PaCO_2$), and functional findings (e.g., pulmonary function, echocardiography results, exercise capacity). It is far better to refer too early than too late.

General disease-specific guidelines for referral are summarized in **Table 2**.[12] Transplantation should be considered for any patient with end-stage lung disease on maximal medical therapy, or with NYHA class III or IV dyspnea. Patients with pulmonary fibrosis should be considered for referral at the time of diagnosis, given the tendency for relentless progression of disease. Appropriateness for lung transplantation is very difficult to predict for COPD, as there is only limited evidence that transplantation provides a survival benefit. As noted, transplant for quality-of-life reasons alone raises ethical issues related to utilization of a scarce resource.

Waiting period

Once on the lung transplant list, patients are generally able to return to wait in their home communities under the care of their referring medical

Table 2. Disease-specific guidelines for referral/transplantation*

COPD	Cystic fibrosis	Pulomonary fibrosis	Pulmonary hypertension
• BODE index > 5[13] • Pulmonary hypertension and/or cor pulmonale • History of hospitalization with hypercapneic respiratory failure • Forced expiratory volume in one second (FEV1) < 20% predicted and diffusing capacity for carbon monoxide < 20% predicted or diffuse emphysema	• FEV_1 < 30 % predicted or rapid decline in FEV_1 • Increasing frequency of exacerbations • ICU admission for respiratory exacerbation • Refractory or recurrent pneumothorax or hemoptysis • Oxygen dependent • Hypercapnea • Pulmonary hypertension	• Consider referral at time of diagnosis • Diffusing capacity for carbon monoxide <30% predicted • Decline in vital capacity >10% within 6-month follow-up • Desaturation less than 88% on 6-minute walk	• NYHA class III or IV despite maximal therapy • Failing parenteral prostanoids • 6-minute walk test < 350 m or declining • Cardiac index < 2 L/min/m^2 • Right atrial pressure > 15 mm Hg

*Adapted from Orens JB, Estenne M, Arcasoy S, et al.[12]

teams. Since patients have to be able to reach Vancouver on short notice once a suitable donor is identified, those living far from Vancouver (beyond 2 to 3 hours) may be required to relocate to a more proximate location. It is essential that patients awaiting transplant remain in optimal health through attentive medical care, diet, and exercise. Patients are reassessed every 3 to 4 months by the transplant team to ensure that they remain in adequate health to sustain the transplant procedure and perioperative period.

The median waiting time for receiving a lung transplant in British Columbia is 11 months for a single-lung transplant and 5 months for a double-lung transplant.[14] Once donor lungs suitable for transplantation are identified, the lungs are matched to a recipient based on donor and recipient blood type, body size, HLA profile, and recipient time on the wait list. Patients on the list who are deteriorating rapidly may be given priority.

Perioperative period

The lung transplant surgery is performed at Vancouver General Hospital by the thoracic surgery and thoracic anesthesia teams. Post-transplant, patients are managed in the intensive care unit and are often extubated within the first day or two after surgery. When stable, they are transferred to a step-down unit on the thoracic surgery ward and usually stay in hospital 2 to 3 weeks in total. Upon discharge, they are followed closely by the transplant team in the Solid Organ Transplant Clinic located in the Gordon and Leslie Diamond Health Care Centre at Vancouver General. Patients from outside the Vancouver area must relocate to the Lower Mainland for about 3 months following their transplant, and can return home once medically stable.

Common complications

Lung transplantation is not without complications, and in some ways may be viewed as the replacement of one chronic condition with another. Rejection, infection, and malignancy are all seen following transplantation.

Acute rejection is most common in the first year and is generally treatable with changes in the immunosuppressive regimen, which usually consists of a calcineurin inhibitor (tacrolimus or cyclosporine), a cell cycle inhibitor (mycophenolate mofetil or azathioprine), and a low dose of prednisone. After the first year post-transplant, the primary cause of death is chronic rejection, or bronchiolitis obliterans. This manifests as progressive small airways disease and is largely untreatable.

Infection is a risk throughout the post-transplant period. Bacterial infections are most common, but viral infections (particularly cytomegalovirus), fungal infections, and mycobacterial infections may also be problematic.

Malignancy related to ongoing immunosuppression is common following solid organ transplantation.[1] Lymphoproliferative disease risk is increased post-transplant, particularly early on when patients are more immunosuppressed. Skin malignancies are common and may be fatal, and the risk of colon and breast cancer is increased. Annual dermatological examination as well as careful attention to age-specific screening recommendations for colon and breast cancer should be a priority.

Hypertension, kidney disease, diabetes mellitus, and dyslipdemia are all more prevalent in solid organ transplant recipients compared with the general population[1] because of predisposing lifestyle factors and as side effects of the immunosuppressive medications. Rigorous attention must be paid to identifying and controlling the modifiable risk factors for these conditions.

Medical follow-up

Once lung transplant recipients have recovered from the transplant procedure and are medically stable, they can return to their home communities. There they will continue to be followed periodically by the transplant clinic in collaboration with the referring medical practitioners and community allied health teams as required.

Attention and commitment to a healthy diet and exercise are essential. The transplant team takes responsibility for long-term management of transplant-related issues. However, routine care and health screening is best provided by the family physician, and close collaboration between the transplant clinic, the family physician, and specialists in the home community is both valued and essential. This collaboration is in the best interests of transplant recipients, optimizing their outcomes and minimizing inconvenience related to travel for follow-up. Open communication between the transplant clinic and the most responsible physicians is critical. On an annual basis, recipients undergo an extensive set of tests coordinated by the transplant clinic to evaluate graft function and general health. The transplant team remains involved in care as long as the patient is living in BC.

Conclusions

Lung transplantation has taken its place as a standard component in the management of advanced pulmonary diseases. It can offer excellent outcomes in terms of survival, functional capacity, and health-related quality of life. Ideal candidates are younger individuals who are in good health apart from the lung disease and who have an adequate support network. Transplant recipients must be committed to long-term medical follow-up, lifelong immunosuppression, and a healthy lifestyle. A close collaboration between the lung transplant team and the patient's physicians is extremely important to ensure best possible outcomes.

Competing interests

None declared.

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Lung Transplant Program

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