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Lung transplantation for chronic obstructive pulmonary disease: an exercise in quality rather than quantity?

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Introductory article

Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease

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***Background**. Although certain forms of end-stage lung disease are debilitating, whether the associated mortality rate exceeds that of transplantation is unclear. We undertook analysis to clarify the survival benefit of lung transplantation for various types of end-stage lung disease. **Methods**. We analysed data for all patients listed for transplantation in the USA for emphysema, cystic fibrosis, or interstitial pulmonary fibrosis in the years 1992–94. The numbers of patients entered on the waiting list, post-transplantation, died waiting, and currently waiting were: emphysema group 1274, 843, 143, and 165; cystic fibrosis group 664, 318, 193, and 59; interstitial pulmonary fibrosis group 481, 230, 160, and 48. A time-dependent non-proportional hazard analysis was used to assess the risk of mortality after transplantation relative to that for patients on the waiting list. **Findings**. The clearest survival benefit from lung transplantation occurred in the cystic fibrosis group. The relative risks of transplantation compared with waiting were 0.87, 0.61, and 0.61 at 1 month, 6 months, and 1 year ($p=0.008$) respectively. For interstitial pulmonary fibrosis, the corresponding relative risks were 2.09, 0.71, and 0.67 ($p=0.09$). No survival benefit was apparent in the emphysema group. The risks of transplantation relative to waiting were 2.76, 1.12, and 1.10 at 1 month, 6 months, and 1 year, respectively, and the relative risk did not decrease to below 1.0 during 2 years of follow-up. **Interpretation**. These findings suggest that lung transplantation does not confer a survival benefit in patients with end-stage emphysema by 2 years of follow-up. Other benefits not accounted for in this analysis such as improved quality of life, however, may justify lung transplantation for these patients.* (*Lancet* 1998;**351**:24–7)

Lung transplantation has evolved from heart lung transplantation[1] and now comprises single,[2 3] bilateral single,[4 5] and lobar transplantation.[6] Lung transplantation is now an appropriate treatment for selected individuals who have end stage lung disease unresponsive to medical treatment, resulting in progressive clinical deterioration. A recent publication endorsed by the International Society for Heart and Lung Transplantation, the American Thoracic Society, the European Respiratory Society, and the American Society of Transplant Physicians has produced international consensus guidelines on patient selection and evaluation for these procedures.[7] The diseases amenable to the therapeutic option of lung transplantation can be divided into four main categories—namely, pulmonary vascular disease, restrictive pulmonary disease, obstructive airway disease, and suppurative disease. Pulmonary vascular diseases include primary pulmonary hypertension, pulmonary hypertension secondary to systemic disease, and Eisenmenger's syndrome. Restrictive pulmonary diseases include idiopathic pulmonary fibrosis, fibrosis secondary to connective tissue disease, sarcoidosis, and chronic allergic alveolitis. Obstructive diseases include emphysema with or without α_1-antitrypsin deficiency, Langerhan's cell granulomatosis, and lymphangioleiomyomatosis. Suppurative diseases include cystic fibrosis and bronchiectasis. It is appropriate to consider transplantation as an option when a patient's condition has deteriorated despite optimal medical treatment so that the patient's functional status is poor and less than New York Heart Association class III with an estimated life expectancy limited to 1–2 years. The timing of referral for consideration of transplantation is not based on any one factor but on a constellation of symptoms, physical

and laboratory findings. Knowledge of the natural history of each of the diseases amenable to transplantation assists in determining the appropriate time for referral and acceptance onto a waiting list. The introductory article by Hosenpud and colleagues[8] compares survival in patients waiting on active transplantation lists with those undergoing transplantation over a two year period of follow up, stratified for underlying cause of end stage lung disease, and will now be reviewed.

Introductory article

Hosenpud and colleagues undertook analysis of data on the joint United Network for Organ Sharing/International Society of Heart and Lung Transplantation Thoracic Registry. The aim was to clarify the actual survival benefit of lung transplantation in patients with cystic fibrosis, idiopathic pulmonary fibrosis, and emphysema. Using a time dependent non-proportional hazard analysis[9] the risk of mortality after transplantation relative to that in patients on the waiting list was assessed. This analysis assumed there was a constant death rate on the waiting list as has been demonstrated in patients on renal dialysis awaiting cadaveric renal transplantation.[10] However, since no peer reviewed data on waiting list mortality is available for patients awaiting lung transplantation, this model may not be appropriate. The data suggested a survival benefit following lung transplantation for patients with cystic fibrosis and idiopathic pulmonary fibrosis. By contrast, in patients with emphysema the mortality rate on the waiting list was low so survival following transplantation did not exceed waiting list survival during the two year follow up. Some caution is needed over the interpretation of these findings. Firstly, because the data were derived from many centres prior to publication of international guidelines, the participating centres were unlikely to have a uniform listing policy for all patients. Moreover, some centres employ a policy of listing patients at an earlier stage in the development of severe lung dysfunction given the long waiting time for lung transplant candidates.[11 12] This practice clearly biases the analysis towards waiting list survival. The data presented selectively report the experience in the USA where waiting time is an important determinant of organ allocation which encourages larger transplant centres to list patients early. In fairness, however, the Dutch lung transplant group[13] have also published data demonstrating no difference in survival in patients with emphysema who were transplanted compared with those remaining on the waiting list, although this study was underpowered to derive a clear conclusion. A second concern arises if the reader assumes that analysis of group mean data means that no patient with emphysema will benefit in terms of survival following lung transplantation. It is clear that patients with emphysema who are hypoxaemic, hypercapnic, underweight, with pulmonary hypertension and a history of previous intubation for an episode of severe type II respiratory failure complicating an exacerbation have a very different prognosis when compared with a disabled but stable patient. It is worth reviewing indicators for prognosis in chronic obstructive pulmonary disease (COPD) and current approaches regarding transplantation for this condition in order to put the introductory article in perspective.

Predictors of survival

Over the last 40 years many investigators have attempted to determine which factors influence the survival of patients with emphysema. Risk factors initially believed to be important by some authors have subsequently been shown to be relatively unimportant by others. Indeed, many papers have been published showing considerable differences in five and 10 year survival for such patients. With these provisos in mind, this section will review the data from many studies in an attempt to clarify which factors are most important in determining how long patients with COPD and emphysema live. One of the problems in comparing such studies relates to the characteristics of patients included and whether the predominant pathological abnormality for the airflow obstruction was chronic obstructive bronchitis or emphysema. Initial landmark studies by Burrows and colleagues[14] showed that ventilatory capacity, resting heart rate, hypercarbia, and evidence of cor pulmonale were most predictive of survival. It was also noted that patients with a body weight close to ideal had a better survival than did those who were underweight.

Subsequently, a number of authors have identified numerous positive and negative practices relating to survival. The presence and high value of the following factors confer survival advantage: forced expiratory volume in one second (FEV_1), arterial oxygen pressure (Pa_{O_2}), degree of reversibility of FEV_1, exercise capacity, transfer factor, vital capacity, and atopy. On the other hand, the presence and high value of the following factors confer survival disadvantage: age, decline in FEV_1 on serial testing, resting heart rate, arterial carbon dioxide pressure (Pa_{CO_2}), cor pulmonale, malnutrition, and α_1-antitrypsin deficiency.

LUNG FUNCTION

The initial level of FEV_1 has been identified as the single most important predictor of survival, with the rate of decline in FEV_1 on serial testing enhancing the prediction of outcome. In the normal ageing population the FEV_1 decreases by 20–30 ml each year, whereas in emphysema and COPD decreases of 40–80 ml/year have been reported.[15] Smokers who continue to smoke have a more rapid decline. If the results of studies in patients whose mean FEV_1 at presentation was around 30% of predicted are pooled,[16 17] mean survival rates at three, five, and 10 years are 69%, 52%, and 27%, respectively. Important, however, is the wide variability in survival seen in individual patients presenting with similar results of lung function. The study by Anthonisen *et al*[16] showed that other physiological factors which had a minor adverse effect on survival included a lower transfer factor, higher functional residual capacity, and higher total lung capacity.

HYPOXAEMIA, PULMONARY HYPERTENSION, AND COR PULMONALE

Hypoxaemia and the onset of cor pulmonale have been shown to be important predictors of survival by many investigators. The NIH nocturnal oxygen therapy trial (NOTT) and Medical Research Council (MRC) trial showed that long term oxygen therapy clearly improved survival.[18–20] In the NOTT study, patients with COPD and functional characteristics including mean FEV_1 of 29% predicted, Pa_{O_2} of 6.8 kPa, and Pa_{CO_2} of 5.7 kPa had a two year survival of 59% without supplemental oxygen, 59.2% with nocturnal oxygen, and 88% with continuous oxygen (average 19 hours of oxygen therapy). In the MRC trial patients with COPD with functional characteristics including a mean FEV_1 of

0.65 litres, mean Pa_{O_2} of 6.8 kPa, and Pa_{CO_2} of 7.2 kPa had a mean survival of 25% if they received no supplemental oxygen and 41% in those receiving oxygen. Survival advantage is only seen in those patients who cease smoking and this in itself has been shown to influence survival in patients with emphysema including those who have already developed airflow obstruction.[17] Continued smoking carries a particularly bad prognosis in patients with COPD who have homozygous α_1-antitrypsin deficiency.[21]

NUTRITIONAL STATUS

The prognosis in patients with emphysema has been reported to be related to nutritional status.[22] The relationship is independent of FEV_1 and the lower the weight below ideal the poorer the survival. The relationship is strongest in patients whose FEV_1 is above 47% predicted.

SUMMARY

Although many factors have been shown to relate to survival in patients with emphysema and COPD, age and baseline post-bronchodilator FEV_1 remain the best, albeit imperfect, predictors of prognosis. The wide variability in survival in patients with severe airflow obstruction, however, should cause clinicians to be cautious when attempting to estimate and discuss prognosis with individual patients.

Guidelines for referral of patients with COPD for transplant assessment

It is important that every effort should be made to exclude asthma and to treat maximally any reversible component of the airways disease prior to referral to transplant work up. Pulmonary rehabilitation and long term oxygen therapy, when appropriate, should also be included in medical management prior to referral to a transplant centre. Other treatment options such as volume reduction surgery for patients with emphysema should be considered in appropriate candidates.[23–25] Patients with COPD are considered to be potentially in the transplant window if they meet the following criteria: FEV_1 <25% predicted after bronchodilators and/or Pa_{CO_2} >7.3 kPa and/or raised pulmonary artery pressures with progressive cor pulmonale. Preference should be given to those patients with raised Pa_{CO_2} with progressive deterioration who require long term oxygen therapy as they have the poorest prognosis.[26]

Results of transplantation for COPD

Lung transplantation remains an appropriate consideration for individuals who have end stage emphysema and who show a progressive deterioration in quality of life and exercise tolerance. The successful introduction of volume reduction surgery and careful selection of patients has added an alternative surgical treatment option to lung transplantation patients with severe diffuse emphysema. The criteria for lung reduction surgery continues to evolve although it is clear that all patients should have ceased smoking and have a marked disability despite completing a comprehensive pulmonary rehabilitation programme. All patients should have considerable airflow obstruction with an FEV_1 of less than 35% predicted and marked thoracic hyperinflation. The lungs should show sufficient heterogeneity in the distribution of emphysema to provide the surgeon with target areas of non-functioning volume occupying lung which is amenable to surgical resection. Lung volume reduction surgery and lung transplantation should not be considered as mutually exclusive procedures. There is now clear evidence that patients can undergo successful lung transplantation following volume reduction surgery.

Choice of operation

There are several reasons why unilateral lung transplantation is an attractive option in patients with emphysema. The procedure is technically straightforward and most recipients do not have pleural adhesions. Furthermore, the functional results of single lung transplantation are acceptable, most patients achieving an FEV_1 of 50% predicted. These improvements are not as dramatic as those achieved following bilateral lung transplantation.[27] There are, however, no major differences in maximum exercise performance and in general a significant degree of limitation persists with maximum oxygen consumption ranging between 45% and 52% predicted for both procedures. Patients who remain free of obliterative bronchiolitis do, however, enjoy a normal lifestyle and a good quality of life.[28] The obvious advantage of single lung transplantation over bilateral lung transplantation is that this procedure enables more transplantations to be conducted if both donor lungs are acceptable. Critics of the single lung transplantation option are concerned about hyperinflation of the native lung and potential compression of the contralateral graft. Although volume reduction on the opposite side can be considered, the use of single lung transplantation may be best limited to those patients without bulbous

LEARNING POINTS

* **Lung transplantation does not confer a survival advantage for patients with advanced emphysema who were listed in the USA.**
* **Lung transplantation does confer a survival advantage for patients with cystic fibrosis or idiopathic pulmonary fibrosis.**
* **Lung transplantation confers an improved quality of life in recipients irrespective of underlying diagnosis.**
* **Debate remains as to whether single or bilateral lung transplantation is the best option for patients with emphysema.**

disease and those older patients of smaller stature who may be less able to tolerate the more major bilateral procedure. Furthermore, there is evidence that long term survival is slightly better in bilateral recipients than in their unilateral counterparts.[27 29] The preference is therefore to offer bilateral lung transplantation to younger patients and those of larger stature.

The long term outcome of patients with COPD undergoing single or bilateral lung transplantation is limited by the development of obliterative bronchiolitis, defined by progressive airflow obstruction and deterioration in graft function. Obliterative bronchiolitis is characterised histologically by inflammation and fibrosis of small airways. The current five year survival of 50–60% following lung transplantation is significantly lower than other solid organ transplants and is predominantly a result of the development of obliterative bronchiolitis. Sepsis accounts for up to 30% of late deaths and may occur in the presence of, and be predisposed to, obliterative bronchiolitis.

Conclusions

The introductory article by Hosenpud *et al* and its message for both potential transplant candidates with COPD and their carers is thought provoking. It must be emphasised that the analysis assessed only duration of survival, not quality of life. Several studies have shown substantial improvement in indices of health quality in patients undergoing lung transplantation including those with a preoperative diagnosis of emphysema.[28 30 31] The decision whether to offer lung transplantation to a patient with emphysema is therefore complex and must take into account not only the duration of expected survival but also quality of life issues. It is clear, however, that severely disabled patients who do not have features suggesting life threatening disease should be made aware that their survival may not be prolonged by transplantation. In practice, the vast majority of patients in this situation wish to be accepted onto the waiting list so the onus of responsibility regarding suitability for listing is carried by the transplant assessment committee. It is interesting that the principal gain from transplantation for patients with emphysema is quality of life, with demonstration that the best outcome in this area for this group of patients can be achieved with the worst economy of donor organs—namely, bilateral lung transplantation. It is reassuring to know that patients with idiopathic pulmonary fibrosis and cystic fibrosis derive improvements in both quantity and quality of life following appropriate transplantation.

Whilst the results of the introductory article suggest that lung transplantation for patients with emphysema is difficult to justify on the grounds of survival considerations alone, it is clear that there are individual patients with emphysema who will derive survival advantages from transplantation. Moreover, the findings are exclusively based on data from the USA where waiting time is an important determinant of organ allocation. This policy supports the listing of patients at an early stage and may not accurately reflect practice regarding listing outside the USA. The publication o international guidelines for the selection of lung transplant candidates is timely and will hopefully aid transplant physicians and surgeons in listing candidates for lung transplantation at an appropriate time.

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