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Title of the manuscript:

The impact of chronic rhinosinusitis on long-term survival in lung transplantation recipients

Running head:

Rhinosinusitis in lung transplant

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Abstract:

Conclusion:

Chronic rhinosinusitis diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012, not by computed tomography alone, is one of the prognostic factors affecting long term survival in patients with lung transplantation. Endoscopic sinus surgery might play a beneficial role in the management of lung transplantation recipients with chronic rhinosinusitis.

Objectives:

To show the effect of paranasal sinus infection on post-lung transplantation survival.

Method:

Lung transplantation recipients were included in this study. Computed tomography was performed before and after lung transplantation. The severity of chronic rhinosinusitis was evaluated by Lund-Mackay scoring system. The survival rate was calculated by the Kaplan-Meier method.

Results:

One hundred and forty-eight patients received lung transplantation for various indications. Chronic rhinosinusitis was found in 18.9% (28/148) of the lung transplantation recipients. Of 28 patients with chronic rhinosinusitis, 7 patients underwent endoscopic sinus surgery due to persistent post-nasal drip. The recipients with chronic rhinosinusitis who did not receive endoscopic sinus surgery (n = 21) showed a significantly lower survival rate as compared to the patients without chronic rhinosinusitis. There was no statistically significant difference in the

survival rate between the recipients with (n = 50) and without (n = 98) paranasal sinus abnormality on computed tomography.

Key words:

lung transplant, infection, survival rate, pneumonia, bronchiolitis obliterans

Text:

Introduction

Lung transplantation is a surgical procedure for people who have end-stage pulmonary disease to replace one or both diseased lungs with healthy lungs from a human donor. The first successful human lung transplantation was performed in the U.S.A. in 1963, however, the patient died on the 18th postoperative day [1]. Because the number of available brain-dead organs is limited, living lobar lung transplantation was introduced in 1993 [2]. Lung transplantation has been performed to treat many diseases including chronic obstructive pulmonary disease, pulmonary arterial hypertension, and cystic fibrosis [3]. During the past five decades, marked improvements in clinical results have been achieved largely due to advances in organ preservation, surgical techniques, and postoperative care. However, despite these improvements, chronic allograft rejection in the form of bronchiolitis obliterans syndrome and infection are still major factors contributing to long-term morbidity and mortality after lung transplantation.

Chronic rhinosinusitis is a common disease, and is frequently detected in the indications for lung transplantation including cystic fibrosis and diffuse panbronchiolitis [4]. Post-nasal drip from the affected paranasal sinus may induce lower respiratory infection. The sinuses can become a source of infection during post-transplantation immunosuppression. Walter et al. reported that chronic drainage with pathogen into the lung allografts was caused by the bacterial reservoir in the paranasal sinuses [5]. Several studies showed that paranasal sinus management including sinus surgery had a positive effect on post-transplantation outcomes and prevention of fatal infection in lung transplantation recipients with cystic fibrosis [6-10]. However, contrary findings have also been reported in patients with cystic fibrosis [11, 12]. The effect of paranasal sinus infection on post-lung transplantation survival in patients with cystic

fibrosis is controversial. To the best of our knowledge, no previous study reported the long-term survival rate of lung transplantation recipients with and without chronic rhinosinusitis and the role of endoscopic sinus surgery on the indications for lung transplantation other than cystic fibrosis. The purpose of this study is to evaluate the incidence of chronic rhinosinusitis and the effect of endoscopic sinus surgery in lung transplantation recipients at a single institution.

Materials and Methods

Study design

This study is a retrospective analysis from a single institution. We reviewed the medical records of patients who underwent lung transplantation between October 1998 and December 2015 at Okayama University (Okayama, Japan). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki 1975 revised in 2008, and was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (Reference number, RINRI-1835). Informed consent was obtained from all participant subjects. Demographic data on each recruited patient included a detailed history and clinical examination.

Diagnosis and severity of chronic rhinosinusitis

All patients were referred to Okayama University Hospital for lung transplantation. Prior to lung transplantation, the patients were examined with computed tomography. The diagnosis of chronic rhinosinusitis was based on the definition in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 [13]. The radiographic severity of chronic rhinosinusitis was assessed according to the Lund-MacKay computed tomography staging

system [14]. Follow-up computed tomography was performed at least once a year after discharge to evaluate chronic rhinosinusitis.

Surgical technique and management for chronic rhinosinusitis

Endoscopic sinus surgery was performed under local or general anesthesia. General anesthesia was impossible in two patients with highly significant impairment of the lung function. Frequent pre- and postoperative nasal care was performed for patients with endoscopic sinus surgery. Pharmacotherapy including macrolide therapy was administered to patients with chronic rhinosinusitis. Culture examinations from pharyngeal swabs were carried out.

Statistical analysis

Total survival was defined as the time from lung transplantation surgery to death from any cause. Data are presented as means \pm standard deviation. For statistical analysis, overall survival curves were calculated according to the Kaplan-Mayer method. A log-rank test was used to compare survival rates. Differences in proportions were tested by the chi-square test. For comparisons of quantitative data between three or more groups, the Kruskal-Wallis test was performed to establish the significance of inter-group variability. The Mann-Whitney U test was used for comparison between two groups of quantitative variables. A Cox proportional hazards model was used to examine the effect of clinical factors on the risk of mortality. Significant differences were established at a level of $P < 0.05$ (IBM SPSS Statistics; IBM, New York, U.S.A.).

Results

Demographics

The demographic features of the patients are summarized in Table 1. A total of 148 cases of lung transplantation recipients were identified. Standard post-transplantation immunosuppression was carried out with triple-drug therapy (1998-2005; cyclophosphamide, corticosteroids, and mycophenolate mofetil) (2006-2015; tacrolimus, corticosteroids, and mycophenolate mofetil) without the use of cytolytic therapy. The recipients also received anti-fungal drug, anti-viral drug, and trimethoprim/sulfamethoxazole for infection prophylaxis. Transplantation was performed using organs obtained from brain-dead donors (n = 69) and living donors (n = 79). Of these cases, 28 patients had chronic rhinosinusitis. Endoscopic sinus surgery was applied to the management of 7 chronic rhinosinusitis patients with persistent post-nasal drip.

There was no statistically significant difference in age, male/female ratio, proportion of donors (brain-dead donors / living donors), and type of transplantation (bilateral transplantation / unilateral transplantation) between the three groups (patients without chronic rhinosinusitis, chronic rhinosinusitis patients with endoscopic sinus surgery, and chronic rhinosinusitis patients without endoscopic sinus surgery). The indications for lung transplantation were statistically different between the groups ($P < 0.001$).

Lund-MacKay computed tomography score

The pre-operative mean Lund-MacKay computed tomography score was 5.0 ± 4.1 in the chronic rhinosinusitis patients without endoscopic sinus surgery (n = 21) and 11.6 ± 6.3 in the chronic rhinosinusitis patients with endoscopic sinus surgery (n = 7). There was a statistically significant difference between the two groups ($P = 0.007$).

The most recent mean Lund-MacKay computed tomography score in the chronic

rhinosinusitis patients with endoscopic sinus surgery was 4.1 ± 1.9 , significantly less than the preoperative score (11.6 ± 6.3 , $P = 0.012$).

Survival rate

The survival rate was significantly lower in the chronic rhinosinusitis patients without endoscopic sinus surgery than it was in the patients without chronic rhinosinusitis (Figure 1, $P = 0.008$). Of 7 chronic rhinosinusitis patients with endoscopic sinus surgery, 6 patients were discharged from the hospital without home oxygen therapy; one patient died from bacterial pneumonia. Although the chronic rhinosinusitis patients who received endoscopic sinus surgery had more severe chronic rhinosinusitis according to their Lund-MacKay computed tomography scores, the survival rate in patients with endoscopic sinus surgery tended to be better than that of the chronic rhinosinusitis patients without endoscopic sinus surgery (Figure 1). There was no statistically significant difference in the overall survival rate between the recipients with ($n = 50$) and without ($n = 98$) paranasal sinus abnormality on computed tomography (Figure 2). A recent study showed that the persistence of *Pseudomonas aeruginosa* in the upper airways of patients with cystic fibrosis increases the risk of graft dysfunction in lung transplantation [15]. Next, we examined the effect of *Pseudomonas aeruginosa* colonization. There was no significant difference in overall survival rates between chronic rhinosinusitis patients with and without *Pseudomonas aeruginosa* (Figure 3).

The effects of clinical factors associated with mortality are summarized in Table 2. A minimally adjusted analysis on the effect of chronic rhinosinusitis on the survival of lung transplantation recipients including age and type of transplant surgery (brain-dead donor / living donor) showed that the chronic rhinosinusitis was a significant factor affecting outcome after lung transplantation ($P = 0.016$; Hazard ratio, 2.451 (95% confidence interval, 1.178 – 5.100)). There was no statistically significant difference in long-term survival between

brain-dead donor transplantation (n = 69; 1 year survival rate, 89.7%; 3 year survival rate, 80.9%) and living donor transplantation (n = 79; 1 year survival rate, 92.4%; 3 year survival rate, 84.5%).

Discussion

Lung transplantation is one of the possible therapeutic options for patients with advanced lung failure. Multiple factors affect the outcome of lung transplantation. Postoperative immunosuppressive treatment is required for patients with lung transplantation. Infection is the major cause of death after lung transplantation, and infectious complications are the key issue in the management of patients with lung transplantation. Both fungal and bacterial infection in the upper airway as well as viral infection can cause serious complications. Invasive fungal rhinosinusitis and bacteremia caused by bacterial rhinosinusitis have been reported as the cause of death in patients with lung transplantation [16-18]. The persistence of a specific pathogen (*Pseudomonas aeruginosa*) in paranasal sinus is considered a significant risk factor for graft dysfunction and nasal polyposis [15, 19]. In this study, we showed that chronic rhinosinusitis was found in 18.9% (28/148) and that there was no statistically significant difference in the survival rate between recipients with chronic rhinosinusitis with and without *Pseudomonas aeruginosa* in the airway.

Several studies have reported the relationship between rhinosinusitis and lung transplantation in patients with cystic fibrosis. Ciofu et al. showed that extensive sinus surgery before lung transplantation might prevent infection of the new lung [20]. Vital et al. reported that sinus surgery and daily nasal douching had a positive effect on post-transplantation survival and the development of bronchiolitis obliterans syndrome [6, 7]. Holzmann et al. showed that successful sinus management led to a statistically significant lower incidence of tracheobronchitis and pneumonia after lung transplantation [9]. Gutiérrez et al. stated that

endoscopic surgery should be performed in those patients in whom medical treatment failed to clear the sinuses [8]. In contrast, Leung et al. stated that pre- transplantation sinus surgery for patients with cystic fibrosis did not appear to prevent lung graft recolonization and was not associated with overall survival [12]. These studies involved only lung transplantation recipients with cystic fibrosis; the effect of endoscopic sinus surgery on other indications for lung transplantation has not been reported. There remains considerable controversy about how to treat chronic rhinosinusitis in patients with lung transplantation. Our findings suggest that sufficient therapy including surgical care is beneficial in the clinical management of lung transplantation recipients with intractable chronic rhinosinusitis.

In conclusion, this is the first study to investigate the long-term survival rate of lung transplantation recipients with and without chronic rhinosinusitis. Chronic rhinosinusitis was frequently found in lung transplantation recipients. Pre- and post-transplantation care for chronic rhinosinusitis in lung transplantation recipients may be one of the important therapies to prevent serious complications. Chronic rhinosinusitis is sometimes diagnosed by radiological examination only. Our findings suggest that asymptomatic soft-tissue shadow in the paranasal sinus on computed tomography is not a prognostic factor. However, the presence of chronic rhinosinusitis as diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 has a significant effect on long-term survival in the transplantation recipients. Endoscopic sinus surgery might be an effective therapeutic option in the management of lung transplantation candidates with chronic rhinosinusitis. Because we only performed endoscopic sinus surgery for 7 patients, further studies are needed to establish the role of endoscopic sinus surgery for patients undergoing lung transplantation. The principal limitation of this study is small sample size. The high proportion of living donor lobar transplantation is uncommon in other areas of the world, and is also one of the limitations of this study. Future studies are required to develop the management strategy for chronic

rhinosinusitis in lung transplantation recipients.

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Figure captions:

Figure 1: Overall survival curves of lung transplantation recipients without chronic rhinosinusitis, lung transplantation recipients with chronic rhinosinusitis without endoscopic sinus surgery, and lung transplantation recipients with chronic rhinosinusitis with endoscopic sinus surgery assessed by Kaplan-Meier survival estimates. (CRS, chronic rhinosinusitis; ESS, endoscopic sinus surgery)

Figure 2: Overall survival curves of lung transplantation recipients with and without soft-tissue shadow in paranasal sinus on computed tomography assessed by Kaplan-Meier survival estimates. (CT: computed tomography)

Figure 3: Overall survival curves of lung transplantation recipients with chronic rhinosinusitis with and without *Pseudomonas aeruginosa* in the airway assessed by Kaplan-Meier survival estimates.