Review Article

Lung cancer: a rare indication for, but frequent complication after lung transplantation

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Contributions: (I) Conception and design: D Van Raemdonck; (II) Administrative support: None; (III) Provision of study materials or patients: D Van Raemdonck; (IV) Collection and assembly of data: D Van Raemdonck, R Vos, J Yserbyt, GM Verleden; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Lung transplantation is an effective and safe therapy for carefully selected patients suffering from a variety of end-stage pulmonary diseases. Lung cancer negatively affects prognosis, particularly in patients who are no longer candidates for complete resection. Lung transplantation can be considered for carefully selected and well staged lung cancer patients with proven, lung-limited, multifocal, (minimally invasive) adenocarcinoma in situ (AIS) (previously called bronchioloalveolar cell carcinoma) causing respiratory failure. Despite a substantial risk of tumour recurrence (33–75%), lung transplantation may offer a survival benefit (50% at 5 years) with best palliation of their disease. Reports on lung transplantation for other low-grade malignancies are rare. Lung transplant candidates at higher risk for developing lung cancer [mainly previous smokers with chronic obstructive lung disease (COPD) and idiopathic pulmonary fibrosis (IPF) or older patients] should be thoroughly and repeatedly screened for lung cancer prior to listing, and preferably also during waiting list time if longer than 1 year, including the use of PET-CT scan and EBUS-assisted bronchoscopy in case of undefined, but suspicious pulmonary abnormalities. Double-lung transplantation should now replace single-lung transplantation in these high-risk patients because of a 6–9% prevalence of lung cancer developing in the remaining native lung. Patients with unexpected, early stage bronchial carcinoma in the explanted lung may have favourable survival without recurrence. Early PET-CT (at 3–6 months) following lung transplantation is advisable to detect early, subclinical disease progression. Donor lungs from (former) smokers should be well examined at retrieval. Suspicious nodules should be biopsied to avoid grafting cancer in the recipient. Close follow-up with regular visits and screening test in all recipients is needed because of the increased risk of developing a primary or secondary cancer in the allograft from either donor or recipient origin.

Keywords: Lung cancer; lung transplantation; indication; complication

Submitted Aug 30, 2016. Accepted for publication Sep 05, 2016.
doi: 10.21037/jtd.2016.11.05
View this article at: http://dx.doi.org/10.21037/jtd.2016.11.05

Introduction

Lung transplantation is an effective and safe therapy for carefully selected patients suffering from a variety of end-stage pulmonary diseases. According to the 2015 annual report of the International Society for Heart and Lung Transplantation (ISHLT), more than 50,000 adult lung transplants and nearly 4,000 adult heart-lung transplants have been entered into the ISHLT Registry until the year 2014. The median survival after primary lung transplantation for all indications is 5.7 years and the conditional median survival in recipients who survived to

1 year after the primary transplant is 7.9 years. In addition to a substantial survival benefit for the majority of patients, their quality of life may change dramatically. About a quarter of the recipients have an excellent functional status with a Karnofsky score of 100% at 3 years (1).

However, two major remaining obstacles limiting the clinical usefulness of lung transplantation as standard therapy for a larger potential of patients are donor lung shortage and chronic lung allograft dysfunction (CLAD). Donor lung shortage results in long waiting times for listed patients with a substantial risk of dying before transplantation depending on the country's number of active donors per million inhabitants. It is estimated that only 15–20% of the standard, brain-dead donors fulfill the ideal criteria for lung donation (2). Lungs from non-standard donors, such as extended-criteria donors and those succumbing after cardiocirculatory arrest are now increasingly being used with similar early and late outcome results and freedom from chronic rejection (3,4). Chronic rejection, leading to CLAD, is the most common underlying etiology of late mortality following lung transplantation present in about 50% of patients at 5 years after transplantation (1). CLAD was recently introduced as an overarching term covering different phenotypes of late allograft dysfunction, including obstructive CLAD (bronchiolitis obliterans syndrome), restrictive CLAD (restrictive allograft syndrome), and graft dysfunction due to causes not related to chronic rejection (5). As different pathophysiological mechanisms are involved in these distinct CLAD phenotypes, more personalized or targeted therapies for adequate prevention and treatment of CLAD are required to improve the long-term results after lung transplantation (6).

Lung cancer negatively affects prognosis, especially in patients with lymph node spread or distant metastatic disease. Lung transplant candidates as well as recipients may be confronted with lung cancer (7). Occasionally, patients may present with early multifocal disease and are therefore no longer candidates for complete surgical resection. Lung transplantation in these patients may be a therapeutic option when respiratory insufficiency develops to prolong survival despite the risk for tumour recurrence. On the other hand, lung transplant recipients carry an increased risk to develop a malignancy in months to years after the procedure related to their immunosuppressive therapy. The overall prevalence of cancer is 3.7%, 16.6%, and 29.1% at 1, 5, and 10 years after lung transplantation, mainly skin or lymphoma, but also lung cancer (1). These tumours may be donor-related when grafted into the recipient or may develop *de novo* from recipient origin in the remaining native lung or in the pulmonary allograft.

The aim of this paper is to review the current literature on lung cancer in relation to lung transplantation, both as an indication for and as a complication after pulmonary allografting.

Lung cancer as an indication for lung transplantation

Primary lung cancer

Primary lung cancer caused by bronchogenic carcinoma is one of the most common forms of cancer worldwide and is the leading cause of cancer-related death in western world. Patients with a history of malignant disease within the prior 2 to 5 years are generally not eligible for pulmonary transplantation, but should be evaluated individually taking into account tumour histology, staging and adequate treatment received (8). Interestingly, the very first human lung transplantation by Hardy and associates in 1963 was in a patient with respiratory failure related to advanced bronchial carcinoma (9). Nowadays, patients with existing lung cancer developing respiratory failure are generally excluded for lung transplantation.

A potential exception to this general rule on lung cancer may be a patient with advanced multifocal (also called diffuse or pneumonic) adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) of the lung (before 2011 classified as bronchioloalveolar cell carcinoma or BAC) (10). This small distinct subgroup of bronchogenic carcinoma is characterized by the proliferation of well-differentiated tumour cells along the walls of alveoli preserving the underlying lung architecture. The disease can present as a localized lesion (ground-glass opacity) with or without a nodular component or with a diffuse multifocal pattern involving multiple lobes in one or two lungs. While the first form may be a good indication for an anatomic resection (segmentectomy or lobectomy with lymph node excision) once positron emission tomography (PET) scan suggests local invasiveness, resection in patients with the latter form often recur without systemic dissemination. These patients usually die as a result of pulmonary failure secondary to replacement of healthy, functioning lung cells by tumour. Several chemotherapy trials have shown median survival of about 1 year (11,12). Targeted drug trials have reported only minimal improvement so far (13-18). Lung

transplantation for BAC was not considered as a therapeutic option in the 2007 report on evidence-based clinical practice guidelines published by the American College of Chest Physicians (19).

The perception that advanced AIS or MIA is a potentially lethal, but lung-limited malignancy has stimulated some transplant centers to explore lung transplantation as a modality to prolong survival and to treat respiratory symptoms (20,21). In a multicenter collective series of 29 lung transplant procedures in 26 patients, de Perrot and colleagues reported in 2004 a reasonable survival (39% at 5 years) in patients with lung cancer, somewhat lower than in non-cancerous patients, but with recurrence of the tumour in 45% of the recipients between 5 and 49 months after the transplant. Five-year survival was better in 22 patients with stage I disease compared to 14 patients with stage II–III (51% versus 14%, respectively). The majority (88%) of patients with multifocal AIS survived longer with recurrence limited to the transplanted lung when compared to lung recipients with other types of (incidental) bronchogenic carcinoma with the majority rapidly developing widespread recurrence (22). In another retrospective study reported in 2012, Ahmad and colleagues queried the United Network for Organ Sharing database for patients who underwent lung transplantation from 1987 to 2010 for BAC or other forms of lung cancer. Twenty-nine patients were identified representing 0.13% of the 21,553 lung transplants during the study period (23). The degree of tumour invasion in lung explants varied in the cohort with pure BAC in only 52%, whereas 41% had some degree of invasiveness and 7% had pure adenocarcinoma. Thirty-day mortality and 5-year survival after lung transplantation for BAC was comparable with lung recipients grafted for other diagnoses (10% *vs.* 7%; P=0.44 and 57% *vs.* 50%; P=0.66, respectively). Presence of invasive tumour was associated with a trend toward decreased survival. On the other hand, lymph nodes metastases did not preclude the possibility of long-term survival in some patients. Survival after transplantation for the whole group compared favorable to that reported with chemotherapy. The authors concluded that a prospective trial is needed in patients with BAC to confirm the superior outcome after transplantation over medical therapy. Several smaller single-center series have been published with comparable survival rates, but with recurrence rates varying between 33% and 75% (24-27).

Based on the reported results mentioned above, lung transplantation can be considered as a valuable option for carefully selected patients with respiratory failure secondary to advanced multifocal, pulmonary lepidic predominant AIS or MIA. The disease should be proven on biopsy. In addition, the patient should be properly staged with chest and abdominal computed tomography (CT) scans, PET scan, brain magnetic resonance imaging, bone scan, and endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) and/or mediastinoscopic biopsy of mediastinal nodes to rule out evidence for nodal and extra-thoracic metastases prior to listing. Some investigations can be repeated every 3 months while on the waiting list. Some teams advocate invasive mediastinal staging with mediastinoscopy at the time of lung offer with a back-up recipient standby in case metastatic nodal disease is found on frozen section. All cases should have been discussed at a multidisciplinary tumour board meeting prior to listing. Whether such patients should ever be transplanted in the light of a limited donor pool and whether these patients should receive priority in lung allocation over other listed patients, remain ethical questions for further debate.

On the other hand, lung transplantation appears not to be a good treatment option for patients presenting with more common subtypes of bronchial carcinoma who have limited pulmonary reserve or whose tumour is surgically not amenable for complete resection. Nevertheless patients with unforeseen stage I bronchial carcinoma discovered in the explanted lung during actual transplantation may survive without recurrence for many years comparable to recipients transplanted for other diagnoses. Patients with more advanced disease, however, will do poorly after lung transplantation as they have a high chance to develop recurrences and to die within 1 year with widespread metastases (22,28-34).

It is well known that lung transplant candidates with chronic obstructive lung disease (COPD) and idiopathic pulmonary fibrosis (IPF) are at high risk of developing lung cancer as a result of previous exposure to cigarette smoking (35-37). In a recent study by the Toronto Lung Transplant group, unexpected lung cancer was diagnosed in explanted lungs in 13/853 (1.52%) of all transplants performed between 2003 and 2012. The incidence was somewhat higher in IPF (2.8%) versus COPD patients (1.57%) (38). A similar percentage of incidental lung cancer (2%) was found in an older study from the Cleveland Clinic Foundation (30). In a nice review of the available literature up to 2013, Olland and co-authors found that the prevalence of incidental lung cancer in the explanted lung ranged from 0.8–2.2% with adenocarcinoma being the most frequent histology (39). COPD/emphysema was the most

common indication for lung transplantation with recipient age averaging about 56 years.

Rigorous pre-transplant screening to rule out unknown malignancies is mandatory in all candidates prior to listing (8). However, pre-transplant lung cancer diagnosis is not always obvious in these patients often presenting with lung infiltrates or indeterminate pulmonary nodules on chest CT scan. Many of the abnormalities may well be inflammatory or infectious changes. Lung cancers arising in the background of a lung with interstitial changes are difficult to recognize as tumour (40). Biopsy of these lesions with invasive techniques may be hazardous in patients with limited pulmonary reserve and includes a risk of persistent airleak, residual pneumothorax, empyema, pneumonia, and respiratory insufficiency. Thoracic imaging should be repeated in listed patients at 3–6 months interval to follow the evolution in these lung abnormalities. PET scan may not be so helpful in detecting malignancies with many false positive results in inflammatory changes (41). Nowadays, radial or linear EBUS of suspicious lung lesions or lymph nodes respectively, is one of the less invasive diagnostic modalities that can be considered in patients with a high risk pulmonary disease (42).

Secondary lung cancer

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumour with variable biological and clinical behavior most frequently presenting in the liver. The Leuven Lung Transplant Group recently reported on a small case series with three patients after combined or serial liver and lung transplantation for EHE metastatic to the lung resulting in pulmonary failure. Although the disease was not always cured, long-term outcomes after lung transplantation were favorable up to 8 years, even in patients who initially presented with extrapulmonary metastases (43).

Lung transplantation for secondary lung cancer from other primary tumours (chondrosarcoma, uterine leiomyoma, thyroid) are anecdotal (22,44).

Lung cancer as a complication after lung transplantation

Solid organ transplant recipients have an increased risk to develop a malignancy in years thereafter. This is attributed to the long-term use of immunosuppressants that also inhibit the functioning of tumour suppressor genes and T-cells (45). The risk to develop lung cancer in transplant recipients is 20–25 times higher compared to the general population with an overall incidence of about 4% after lung transplantation (46). According to the ISHLT Registry, lung recipients who survive for 5 years are reported to present with any solid organ tumour other than skin or lymphoma (bladder, lung, breast, prostate, liver, colon, neck) in about 5%. Malignancies other than lymphoma are responsible for about 14% of all deaths more than 5–10 years after lung transplantation (1).

Lung cancer will mainly occur in solid organ recipients with a smoking history (47,48), but also non-smokers are at higher risk compared to the general population (49). Beside long-term immunosuppressive therapy and previous cigarette smoking, advanced age at transplantation likely attributes to this higher lung cancer incidence as an additional risk factor.

Lung cancer after lung transplantation can present in various forms: (I) as already discussed, lung cancer can be an incidental finding in the explanted lungs; (II) patients after single-lung transplantation may develop a bronchial carcinoma in the remaining native lung; (III) lung recipients may harbor a previously undetected primary or secondary lung cancer in the allograft that originates from the donor; (IV) finally, patients may develop a new primary or secondary lung cancer from recipient origin in the donor lungs.

Primary lung cancer in the remaining native lung after single-lung transplantation

Opportunistic infections, hyperinflation, pneumothorax, and primary lung cancer are the most common complications encountered in the native lung during follow-up of single-lung transplant recipients (50). In one of the largest series published to date, these complications occurred in about 14% of all patients after single-lung transplantation with a significant reduction in post-transplant survival. Native lung pneumonectomy is often needed to control the problem and to safe patient's life (51). This high incidence of native lung problems questions the role of single-lung transplantation in patients with COPD/emphysema and IPF and has resulted in a worldwide shift from single-lung to double-lung transplantation in recent years with better survival results (1).

One of the first larger series on bronchogenic carcinoma after lung transplantation including patients from seven U.S. centers was published by Collins and co-authors in 2002. In that series, 24 out of 975 (2.5%) single-lung transplant recipients developed a bronchogenic carcinoma in the

native lung including 18/859 (2%) patients with COPD and 6/147 (4%) IPF (52). We have recently reviewed our own experience at the University Hospitals in Leuven, Belgium. Nine of 92 (9.8%) single-lung transplants for emphysema or lung fibrosis developed a bronchial carcinoma in their native lung at a mean follow-up of 41±27 months. In contrast, only 4 of 224 (1.8%) bilateral-lung transplant patients (also for emphysema or fibrosis) developed a bronchial carcinoma (P=0.0026). At diagnosis, four patients had local disease (cT1N0M0 and cT2N0M0), whereas all others had locoregionally advanced or metastatic disease. Five patients were surgically treated. All other patients (except 2 who died very soon after diagnosis) were treated with chemotherapy with or without radiotherapy. The median survival after diagnosis was only 10±7 months, with a significant survival difference between patients with limited versus extensive disease (P=0.037). The latter had a median survival of only 6 months compared with 21 months for patients with limited stages of bronchial carcinoma (53). Based on the nice review by Olland *et al.* and our further literature search, 19 papers (31,32,52-68) have described primary lung cancer in the native lung after single-lung transplantation. The delay between the transplant and the diagnosis based on chest imaging or symptoms during follow up, was 4 to 119 months (39). The incidence ranged from 0.4% to 8.9% of all cases after single-lung transplantation with an increase in more recent reports. The majority of patients present with higher-stage disease no longer amenable for curative resection. Prognosis with chemotherapy and/or radiotherapy alone was poor with an aggressive and frequently fatal course. Only 1/4 patients survived despite treatment, the majority of these patients had early stage lung cancer and underwent curative resection. In a study by Dickson and colleagues, beside increasing age >60 years at transplantation [hazard risk (HR):1.03] and smoking history (HR: 1.03), single-lung transplantation (HR: 4.31) was the most prominent risk factor to develop primary lung cancer in the remaining native lung (54). These findings suggest that increased attention should focus on careful surveillance of changes in the native lung in all single-lung transplant recipients for early diagnosis and that double lung transplantation should be favoured in patients with COPD and IPF to avoid this complication.

Primary lung cancer in the allograft

Bronchial carcinoma developing in the transplanted lung is much more rare compared to the native lung. Referring to the study by Olland *et al.* and our own literature search, 12 references (31,47,53,61,63,66-72) were found reporting on primary lung cancer developing in the transplanted lung, most often after double-lung transplantation. The prevalence of bronchogenic carcinoma in the transplanted lung ranged from 0.3% to 0.4% (39). This is lower than what was found in our own series from the Leuven Lung Transplant Group with a prevalence of 4/224 (1.8%) patients, all after double-lung transplantation for emphysema or fibrosis (53).

The finding of a lung cancer in the allograft brings up the question whether tumour cells originate from the donor or recipient. Three biomolecular techniques on tumour cells are available to investigate this question: (I) genotyping; (II) FISH-detection of chromosome Y when donor and recipient genders differ; (III) human leucocyte antigen phenotyping. When the tumour originates from the donor, this questions whether the cancer was already present, but undetectable at the time of lung harvesting. Careful evaluation of donor lungs with imaging (chest X-ray or sometimes chest-CT) and macroscopic inspection and palpation is therefore needed at the time of organ retrieval, especially in donors with a heavy (>20 pack years) smoking history. Abnormal and suspicious nodules or infiltrates should be biopsied and analyzed with frozen section. The risk of transplanting cancer cells form donor to recipient may rise in the future with the increasing use of extended-criteria donor lungs including older donors >55 years (73,74) and donors with more extensive smoking history (75,76). The current evidence in the literature suggests that lungs from carefully selected older donors and smokers can be safely used for transplantation. Patients should, however, be fully informed of the risks involved with lungs from smokers and the worse outcome compared with those receiving non-smoker lungs (77,78).

It is well known that bronchial chimerism exist after lung transplantation. Recipient lymphocytes, macrophages, and epithelial cells can be found in the graft after the first month (79). This finding can explain anecdotal case reports of primary lung cancer in the allograft from recipient origin (72). It also explains the substantial risk of recurrence of BAC in lung recipients transplanted for this indication as discussed previously (27).

Transplant recipients with newly diagnosed lung cancer should be treated according to the currently existing guidelines. Nevertheless, not all treatment options may be possible and limited by patient's health condition and post-transplant morbidity (80). Fit patients with early stage lung cancer and good pulmonary reserve should undergo

proper staging and complete tumour resection whenever possible. A successful case of thoracoscopic lobectomy after previous thoracotomy for bilateral lung transplantation was recently reported by our group (81). Patients with predicted limited pulmonary reserve after resection as a result of established CLAD or patients with inoperable tumours, are no longer surgical candidates and should be treated with chemotherapy and/or radiotherapy. Patients with serious side effects of long-term immunosuppression such as diabetes, renal failure, hypertension, or cardiovascular comorbidity may have increased risk both for resection and chemotherapy. No good data exist whether standard triple immunosuppressive therapy should preferentially be tapered or switched to other immunosuppressants with antineoplastic properties such as m-TOR inhibitors.

Secondary lung cancer in the allograft

Transplanting a solid organ carries an unavoidable, but low risk of transmitting an infectious or neoplastic disease from donor to recipient (82). The risk of donor transmitted malignancies should be weight against the urgency to receive a transplant graft.

Secondary malignancies in the lung from other primary tumours have been reported occasionally (83,84). Metastatic nodules occurring in the lung after transplantation are usually donor-derived and originate from a tumour that was previously unknown in the donor or considered, at the time of organ retrieval, to have a low risk of metastasizing to other donor organs. Most frequent tumours in the donor are those in the central nervous system (CNS) responsible for brain death or an abdominal tumour such as renal cell carcinoma not discovered until after kidney removal (84,85). Upon discovery, the thoracic team should then be informed as soon as possible so that a decision can be made whether or not to abandon the lung transplant procedure already started in the recipient. Once the lung has been transplanted prior to diagnosis of an incidental tumour in the donor, the recipient should be closely followed or listed for urgent allograft explanation and retransplantation in case of high likeliness of developing pulmonary metastases in the near future (83). A study from the Israel Penn International Transplant Tumor Registry revealed that some donors dying from an intracerebral bleeding from an undiagnosed CNS tumour in fact had a brain metastasis from another primary tumour such as melanoma, renal cell carcinoma, sarcoma, etc. (86). Misdiagnosis in the donor may lead to significant and often fatal consequences in the recipient resulting in diffuse metastatic disease (83,86).

As discussed previously, lung recipients have an increased risk of developing other solid organ tumours (colon, breast, bladder, prostate, cervix, neck) related to long-term immunosuppressive therapy; these primary tumours from recipient origin may also spread hematogenously with pulmonary nodules subsequently appearing in the pulmonary allograft, likely to be metastases.

From all the above, we should remember that lung transplant recipients have a life-long increased risk of developing lung cancer after the procedure as a result of older age, immunosuppressive therapy, and donor and/or recipient smoking history. Careful and close follow up of all transplant recipients is therefore of utmost importance with regular radiological and nuclear imaging and invasive diagnostic techniques (bronchoscopic, whether or not EBUS-guided, or surgical biopsy of pulmonary abnormalities) when indicated.

Conclusions

Lung transplantation can be considered for carefully selected and well-staged patients with proven, lung-limited, multifocal, predominantly lepidic growth type, (minimally invasive) AIS causing respiratory failure. Despite a substantial risk of tumour recurrence (33–75%), lung transplantation may offer a survival benefit (50% at 5 years) with best palliation of their disease. Whether these patients should be listed or get priority on the waiting list depends on the organ availability and median waiting time at the local transplant center.

Lung transplant candidates at higher risk for developing lung cancer (mainly former smokers with COPD or IPF) should be thoroughly and repeatedly screened prior to and during listing including the use of PET-CT scan and EBUS-guided bronchoscopy in case of undefined and suspicious pulmonary abnormalities. Double-lung transplantation should now replace single-lung transplantation in these high-risk patients because of a 6–9% prevalence of lung cancer developing in the remaining native lung. Patients with unexpected, early stage bronchial carcinoma in the explanted lung may have favorable survival without recurrence.

Donor lungs from (former) smokers should be well examined at retrieval. Suspicious nodules should be biopsied to avoid grafting cancer in the recipient.

Close follow-up with regular visits and screening test in all recipients is needed because of the increased risk of developing a primary or secondary cancer in the allograft from donor or recipient origin.

Acknowledgements

Funding: D Van Raemdonck was a former senior clinical investigator of the Research Foundation Flanders (FWO), Belgium (G.3C04.99). R Vos is supported by a Starting Grant (STG/15/023) of the University Hospitals Leuven (UZL), Belgium, and is a senior research fellow supported by the FWO (12G8715N). J Yserbyt is supported by a grant from the FWO, Belgium (1702816N). H Decaluwe is supported by a Predoctoral Grant of the Clinical Research Fund of UZL. GM Verleden is supported by the FWO (G.0679.12 and G.0679.12).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Van Raemdonck D, Vos R, Yserbyt J, Decaluwe H, De Leyn P, Verleden GM. Lung cancer: a rare indication for, but frequent complication after lung transplantation. J Thorac Dis 2016;8(Suppl 11):S915-S924. doi: 10.21037/jtd.2016.11.05

