Primary Lung Cancer in Lung Transplant Recipients

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Risk factors for lung cancer in lung transplant recipients are a history of smoking and immunosuppression, to which adds increasing use of lungs from donors with a smoking history. The three typical presentations are incidental diagnosis on the explanted lung, concerning less than 2%; lung cancer developing on the lung graft, accounting for less than 1%; and incidence of lung cancer on the native lung, estimated at 9%. Treatment along available guidelines may be hampered by decreased lung function owing to chronic rejection or adverse effects of immunosuppression. Prognosis is comparable to a general population in resected stage I cancer and is less favorable in advanced stages.

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After 3 decades of clinical experience, lung transplantation (LTx) has evolved from a high-risk procedure with an uncertain outcome toward a validated radical treatment for end-stage respiratory disease. In 2009 more than 3,200 transplantations were performed worldwide [1]. Immediate and long-term survival has gradually improved since 1988 [1]. Malignancies are a common problem after LTx: at least one malignancy is diagnosed in 13% of 5-year survivors and in 28% of 10-year survivors [1]. Solid tumors are the third cause of death among recipients surviving more than 1 year [2].

As consequence of the gradually increasing posttransplant survival, the prevalence of malignancies is expected to increase. Five-year survival was estimated at 53% during the most recent period reported by the International Society of Heart and Lung Transplantation Registry [1], and may exceed 60% in some selected centers of excellence [3, 4]. As a result, LTx recipients now present with the strongest standardized incidence ratio for lung cancer after solid organ transplantation [5]. Compared with the general population, patients who receive heart or lung allograft have a relative risk for bronchogenic carcinoma of 9.9 [6].

Risk Factors for Lung Cancer Related to LTx

Recognized risk factors are environmental exposure of the recipient and the relatively stronger immunosuppression used in LTx recipients, to which is added chronic lung disease [7]. Increasing use of extended donor lungs, including those of smokers, leads to a potential additional risk.

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Recipient Risk Factors

In a general population, the risk for lung cancer increases with age: crossing the age of 60 years doubles the risk for lung cancer [8]. We should stress that 20% of LTxs performed since 2001 have been in recipients older than 59 years [1]. Further, mean age at the time of LTx has progressively increased to 50.8 years in 2009. Contemporary survival rates offer a decade of survival to 29% of recipients, who will cross the risk-threshold of 60 years [1].

Terminal respiratory illness qualifying for LTx and lung cancer share common occupational and environmental risk factors, of which smoking is the most frequent; in addition, exposure to asbestos or silica should also be mentioned. An independent risk is credited to interstitial lung diseases, such as idiopathic pulmonary fibrosis and systemic sclerosis, because of overlapping molecular pathogenic pathways [9]. Passive smoke exposure is a recognized risk factor [10, 11]. Genetic abnormalities of the epithelial growth factor receptor can lead to terminal respiratory unit type adenocarcinoma, even in nonsmokers, and is typically more frequent in Asian women [12].

Immunosuppression used for solid organ transplants generates a human immunodeficiency virus–infection like effect, doubling the risk for virus-induced malignancy [13]. In addition, immunosuppression may decrease the immune antitumoral response [14, 15]. Immunosuppressive drugs also act directly on carcinogenic pathways. Calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, may enhance tumor progression by inhibition of DNA repair [16], antiapoptotic effect in damaged cells [17, 18], and inhibition of cell adhesion favoring cell migration and metastatic spread [19, 20]. Azathioprine may induce squamous cell carcinoma of the skin [21, 22] and favors microsatellite DNA instability in myelodysplastic syndromes [23].

However, newer immunosuppressive drugs, such as mycophenolate mofetil (MMF) and inhibitors of mammalian target of rapamycin (mTOR), demonstrate

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Abbreviations and Acronyms

BAC = bronchioloalveolar carcinoma
BLTx = bilateral lung transplantation
BOS = bronchiolitis obliterans syndrome
CNIs = calcineurin inhibitors
COPD = chronic obstructive pulmonary disease
DFI = disease-free interval
LTx = lung transplantation
MMF = mycophenolate mofetil
NM = not mentioned
P-Y = pack-years
SLTx = single lung transplantation
SqCC = squamous cell carcinoma

the ability to reduce tumor progression [24–26]. There is no evidence that steroids enhance tumor progression.

Single LTx (SLTx) creates a situation of combined risks, when the remaining native lung formerly exposed to inhaled risk factors is subjected to the stress of immunosuppression.

Donor Risk Factors

The increased use of marginal donor lungs includes lungs from smokers and those of advanced age. Data from the United Network for Organ Sharing registry show that use of lungs from donors aged older than 55 years has doubled from 2000 (5.8%) to 2009 (10.0%) [27]. From 2005 to 2011, 766 donors used for 5,900 bilateral LTx (BLTx; 13%) were heavy smokers (>20 pack years) [28]. Although the risk of incidental carcinoma at the time of donor lung harvest is easy to evaluate, there are few and controversial data on the long-term risk of lung cancer after transplantation of marginal lungs.

Material and Methods

We reviewed Medline 1990 to September 2013 using the Ovid interface, limiting the search to articles published in English and using the following search words: "bronchogenic carcinoma.mp" *and/or* "lung cancer.mp" *and* "lung transplantation.mp" *and/or* "lung allograft." We found 989 references from which we retrieved manually the relevant articles. We focused on three settings: (1) lung carcinoma in the explanted recipient lung, (2) lung carcinoma occurring in the native lung after SLTx, and (3) lung carcinoma occurring in a transplanted lung. Eventually, we found 30 articles dealing with lung cancer associated with LTx.

Results

Clinically Occult Bronchogenic Carcinoma in the Explanted Recipient Lung

We identified 11 referring references [29–39] (Tables 1, 2). We excluded transplantation for bronchioloalveolar carcinoma. Occult cancer was defined as small tumor foci (1) ignored by pretransplant imaging and discovered intraoperatively or (2) indeterminate nodules without any characteristics of malignancy.

Incidental bronchogenic carcinoma of the explanted lung raises several questions regarding follow-up of patients listed for LTx:

1. Should patients listed for LTx be periodically screened for new parenchymal abnormalities?

Table 1. Reported Cases and Cases Series of Primary Lung Cancer Incidentally Found in the Explanted Lung of Recipients During the Lung Transplant Procedure

Reference	Cases/No. of LTx (%)	Recipient Age at LTx (y)	Smoking History	LTx Indication
Svendsen [29]	2	57 58	Yes Yes	COPD COPD
Stagner [30]	1/45 (2)	55	Yes	Fibrosis
Arcasoy [31]	2/251 (0.8)	52 64	Yes 100 P-Y Yes 84 P-Y	COPD COPD
De Perrot [32]	5/852 (0.6)	NM	NM	Emphysema (n = 2) Fibrosis (n = 3)
De Perrot [33]	43/8000 (0.5)	Median age 56	Yes (n = 35)	Emphysema (n = 26) Fibrosis (n = 11)
Abrahams [34]	4/214 (2)	Mean age 57	Yes (n = 2)	Emphysema (n = 3) Fibrosis (n = 1)
Ritchie [35]	1	41	NM	Fibrosis
Delgado [36]	1/129 (0.8)	Excluded from the study, no other information available		
Minai [37]	4/520 (0.8)	Excluded from the study, no other information available		
Raviv [38]	2/211 (0.9)	68 NM	Yes No	Primary pulmonary hypertension Fibrosis
Strollo [39]	17/759 (2.2)	61	Yes (n = 17)	Fibrosis (n = 8) Emphysema (n = 7) Fibrosis & emphysema (n = 2)

COPD = chronic obstructive pulmonary disease; LTx = lung transplant; NM = not mentioned in the article; P-Y = pack-years.