



Lung cancer in lung transplant—management and outcomes

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Abstract: Risk factors for lung cancer and end-stage lung disease significantly overlap, therefore index of suspicion for lung cancer should be high in lung transplant candidates. Thoracic surgeons can be faced with clinical scenarios where lung cancer can be discovered in the setting of lung transplant in three distinct categories: (I) transplant candidates who are known to have active or treated lung cancer, (II) transplant recipients who have unexpected incidental cancer discovered in their lung explant, and (III) transplant recipients who develop *de novo* lung cancer in the lung allograft or native lung after single-lung transplant. While previously considered “lung-limited” disease, bronchioloalveolar carcinoma (BAC) is no longer accepted as an indication for lung transplant due to poor outcomes with high recurrence rates and reclassification as invasive cancer. Any active lung cancer is considered a contraindication to transplant; however, if there is no evidence of disease after 5 years of definitive therapy, lung transplant can be offered. Indeterminate pulmonary nodules are common in lung transplant candidates and should be evaluated in a multidisciplinary fashion. Incidental lung cancer found in explanted lungs portends poor survival. *De novo* lung cancer after transplant is more common in the native lung after single-lung transplant. Cancer that develops in the allograft can be treated with definitive local therapies and systemic therapies, but long term survival has not yet been demonstrated.

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Introduction

Lung transplantation provides significant benefit for patients with end-stage lung disease. With 59% of 5-year overall survival and significant quality of life improvements, it remains the only definitive treatment for those with advanced lung pathology (1). Continued improvements in organ allocation have decreased waitlist mortality and increased the donor pool, making lung transplantation more appealing for those with end-stage disease.

With similar risk factors including demographics, environmental exposures, and other negative influences, such as smoking, there remains a significant overlap in

patients who are at risk of developing lung cancer and end-stage lung disease requiring lung transplant. In this context, thoracic surgeons can be faced with clinical scenarios where lung cancer can be discovered in the setting of lung transplant in three distinct categories: (I) transplant candidates who are known to have active or treated lung cancer, (II) transplant recipients who have unexpected incidental cancer discovered in their lung explant, and (III) transplant recipients who develop *de novo* lung cancer in the lung allograft or native lung after single-lung transplant.

Outcomes for early-stage lung cancer in the general population are favorable, and surgical resection remains the gold standard of treatment (2). Patients with primary

lung cancer who are deemed medically unfit for standard oncologic surgical resection are relegated to alternative treatment options including limited resection, radiation therapy with or without chemotherapy, or palliative treatment alone. Solid organ transplant recipients, however, have a greater tendency to develop malignancies than the general population, with a 5-fold increase in lung cancer prevalence in lung transplant recipients (3-5). In single lung transplant recipients, there is a 13-fold increase in acquiring lung cancer in the native lung compared to the general population (4). Lung cancer arising in the allograft (compared to native lung) has been noted to have a significantly lower prevalence in both single and double lung transplants, however this is still increased from the general population (6-8). Published data have made it abundantly clear that a pulmonary malignancy in the setting of lung transplantation universally results in poor outcomes. Therefore, all efforts in contemporary practice are made to rule out pulmonary malignancy in the transplant candidacy selection process.

Formerly classified as bronchioloalveolar carcinoma (BAC), a specific subtype of adenocarcinoma, was previously considered to have the most potential benefit from transplantation. Limited in their spread to nodal or distant metastases with a slow rate of progression, these cancers were considered to be “lung-limited”. Pneumonic spread is common and typically involves multiple lobes in one or both lungs (9). Due to these characteristics, it was postulated that bilateral pneumonectomy followed by lung transplant would be potentially curative for these patients, and patients with BAC were considered for lung transplantation. Further study, conversely, has demonstrated that this is not the case. According to the latest WHO classification changes (10), BAC is now classified as advanced multifocal (diffuse or pneumonic) adenocarcinoma *in situ* (AIS) or minimally invasive adenocarcinoma (MIA). These tumors include invasive components and would, therefore, not be categorized as “non-invasive, lung limited BAC” and could not be cured by transplantation. To be clear, the term “BAC” is no longer part of lung cancer histologic vernacular. Minimally invasive adenocarcinoma or lepidic adenocarcinoma is typically reserved for and found in the clinical setting of a ground glass lesion.

Patient evaluation and selection

The recommendations of the International Society for Heart and Lung Transplantation (ISHLT) list malignancy

as the first absolute contraindication for transplantation (11). They note the necessity for at least a 2-year, but ideally 5-year, disease-free interval combined with a low predicted risk of recurrence. The concern for transplantation in the setting of active or recent cancer is due to the subsequent chronic immunosuppression required after transplant for organ preservation and the resulting susceptibility to cancer recurrence or disease progression.

There are three types of cancer presentations in the lung transplant candidacy population: patients with active cancer, patients with previously treated cancer, and patients with indeterminate pulmonary nodules. These candidates must be evaluated thoroughly by both a multidisciplinary lung tumor board and multidisciplinary pulmonary transplant team for suitability for listing and limited risk following transplant (2,11,12).

Active cancer, as discussed, is an absolute contraindication for lung transplantation. Patients with known pneumonic type adenocarcinoma are no longer considered for transplant evaluation until they reach the appropriate disease-free interval. Transplant candidates with known history of definitively treated lung cancer must be classified as disease free. The acceptable disease-free interval is not clearly defined; however, most programs, including our program, require at least five-year disease-free interval, with no evidence of disease at restaging before listing. After tumor board evaluation, these patients are assessed using computerized tomography (CT) of the chest, abdomen, and pelvis, magnetic resonance imaging (MRI) of the brain, and positron emission tomography (PET) scan to clear the candidate for further transplant evaluation.

Pulmonary nodules are common among patients with end-stage lung disease. Any candidate with suspicious or indeterminate lung nodules are presented at our multidisciplinary lung cancer tumor board and subsequently followed for at least 6 to 12 months. These nodules must be critically evaluated with CT scan every 3–6 months to demonstrate stability of both size and character. If pulmonary function allows, the patient must undergo biopsy through bronchoscopic, thoracoscopic, or transthoracic means. While false positives on PET scan are possible with baseline levels of inflammation in these patients (13), it still remains prudent to obtain PET imaging for any suspicious (enlarging or spiculated) nodules. If nodules are without avidity and there has not been any growth after appropriate surveillance, then these patients can be considered for listing. If the clinical risk or suspicion of malignancy remains high, and biopsy is either inconclusive

or unobtainable, these candidates are deemed not suitable for transplantation. After listing, candidates continue to receive regular CT chest imaging in 3–6 months intervals to ensure that there is no change or growth while awaiting transplant.

Patient outcomes

Lung transplantation for BAC

The first patient who underwent lung transplant with the indication of lung cancer was described by Dr. Hardy in 1963 (14). This patient died by day 17 due to renal failure and malnutrition complications. A second patient in 1997 underwent bilateral lung transplant for recurrent BAC by Etienne and colleagues (15). This patient had undergone thorough non-invasive testing which demonstrated localized cancer without pleural invasion or adenopathy and ultimately achieved successful results on standard immunosuppression as she remained alive and cancer free 66 months after transplant.

In the subsequent years, three patient series (16–18) describe single or double lung transplants in 2, 7, and 9 patients for the indication of lung cancer with varying results. Two-year survival, reported in all studies, ranged from 50–78%, while five-year survival, reported in only two of three studies, were 14% and 52%. Recurrence, notably, was common in these studies between 50–75%. Even with a high recurrence and mortality rate, the authors conclude that the transplants offered significant palliation in otherwise fatal and debilitating disease. One additional study (19), looking at all cases of BAC diagnosed at time of, or following transplantation identified 3 patients who had diagnosis at time of surgery and 3 diagnosed during transplant follow-up. In their homogenous group, 2-year survival was only 17%.

Using a survey of lung transplant programs in the ISHLT registry, de Perrot and colleagues (20) identified a 0.9% (n=69) incidence of bronchogenic carcinoma in explanted lungs over 8,000 transplants. Twenty-six patients underwent lung transplantation for end-stage lung disease secondary to advanced multifocal BAC. Four patients died in the immediate post-transplant period. Of the 22 remaining patients, 13 (59%) developed recurrence with a median time of 12 months following transplant. Three of these underwent re-transplantation with one perioperative mortality, one death from recurrence at 21 months, and one alive without recurrence at 7 years. Five-year and 10-year

survival in the 26 patients were 39% and 31%, respectively, while 5-year recurrence-free survival was 35%.

In another study using the United Network for Organ Sharing (UNOS) database, Ahmad and colleagues (12) found 29 patients of 21,553 lung transplants (0.13%) during their study period of 1987 to 2010 with the diagnosis of BAC at transplant. By comparison to the general lung transplant population, these patients were more likely to have better forced expiratory volume in 1 second percent predicted (60% *vs.* 35%, $P<0.0001$) and were more likely to receive double-lung transplants (79% *vs.* 54%, $P=0.006$). On review of histology, 14 (52%) had pure BAC, 11 (41%) had presence of invasion or other features of adenocarcinoma, and 2 (7%) were found to be predominantly adenocarcinoma. Twenty patients had evaluable lymph nodes; 5 (18.5%) demonstrated hilar involvement and 4 (14.8%) had mediastinal involvement. These pathologic findings corroborate the incorrect classification of BAC as lung-limited disease.

Thirty-day mortality (10% *vs.* 7%) and 5-year survival (57% *vs.* 50%) were similar between the BAC group and the overall transplant population, $P=0.44$ and $P=0.66$, respectively. For those who had invasion on pathology there was a trend towards worse overall survival (HR 2.24, $P=0.2$). Lymph node involvement did not portend worse survival (HR 1.12, $P=0.9$).

Additional studies reviewing patients who underwent lung transplantation with known cancer diagnosis are listed in *Table 1* (12,15–17,20–23). The high recurrence rates across these studies underscore the fact that transplantation in this population is not curative. The change from a “lung-limited” diagnosis of BAC to AIS and MIA as invasive entities helps to elucidate the reason for these poor outcomes (10).

Incidental cancers in explant

Incidental cancers at time of transplant have been found at a rate around 0.5–2.0% (*Table 2*) (13,19,20,24–30).

The additional 43 patients identified from de Perrot and colleagues’ study (20) had incidentally found cancer in the explanted lungs. They were transplanted with majority indications of emphysema (n=26) and idiopathic pulmonary fibrosis (n=11). Based on TNM staging, they noted 19 with T1N0, 3 with T2N0, 12 with T2N1, and 2 with T1N2 or T2N2. Multifocal BAC was noted in 6 patients with single lung involvement and bilateral in 1 patient. Five patients with stage I disease died with recurrent disease within 12 months after transplantation. Nine patients with stage II

Table 1 Lung transplant for lung cancer*

Author, year	Patients (n)	Tumor diagnosis	Transplant type	Recurrence rate	Overall survival
Etienne <i>et al.</i> (15), 1997	1	BAC	100% Double	0%	100% 5-yr
Garver <i>et al.</i> (16), 1999	7	BAC	29% Single	57%	71% 2-yr
			71% Double		14% 5-yr
Paloyan <i>et al.</i> (17), 2000	2	BAC	100% Double	50%	50% 2-yr
Geltner <i>et al.</i> (21), 2002	1	BAC	100% Double	0%	100% 2-yr
Zorn <i>et al.</i> (18), 2003	9	BAC	22% Single	75%	78% 2-yr
			78% Double		52% 5-yr
de Perrot <i>et al.</i> (20), 2004	26	BAC	35% Single	59%	60% 2-yr
			65% Double		45% 5-yr
Ahmad <i>et al.</i> (12), 2012	29	ACA	21% Single	59%	62% 2-yr
			79% Double		57% 5-yr

*, Reprinted from Thoracic Surgery Clinics, 24/4, Kachala SS, Murthy SC, Lung transplantation for multifocal lung adenocarcinoma (multifocal lung carcinoma), 485-91, 2014, with permission from Elsevier. BAC, bronchioloalveolar carcinoma; ACA, adenocarcinoma.

Table 2 Incidentally found lung cancer

Author, year	Patients (n)	Tumor diagnosis	Transplant type	Recurrence rate	Overall survival
Stagner <i>et al.</i> (24), 2001	1	ACA only	100% Double	100%	0% 2-yr
Arcasoy <i>et al.</i> (19), 2001	2	NSCLC	50% Single; 50% Double	–	20% 2-yr
de Perrot <i>et al.</i> (20), 2004	43	BAC, NSCLC	–	42%	28% 2-yr; 7% 5-yr
Strollo <i>et al.</i> (13), 2013	22	NSCLC	23% Single; 77% Double	18%	–
Du <i>et al.</i> (25), 2015	8	NSCLC, SCLC	53% Single; 47% Double	–	–
Grewal <i>et al.</i> (26), 2015	6	ACA only	–	67%	17% 2-yr;
Panchabhai <i>et al.</i> (27), 2018	24	NSCLC	54% Single; 46% Double	33%	45% 2-yr;
Chatron <i>et al.</i> (28), 2019	8	NSCLC	100% Double	13%	–
Ahmad <i>et al.</i> (29), 2019	29	NSCLC, SCLC	52% Single; 48% Double	32%	30% 2-yr; 14% 5-yr

ACA, adenocarcinoma; NSCLC, non-small cell lung cancer; BAC, bronchioloalveolar carcinoma; SCLC, small cell lung cancer.

or III died from recurrence with a median of 8 months, and, of the seven BAC patients, three recurred.

Our recently reported institutional data (29) found 31 explants with unexpected malignancies out of 1,710 lung transplants. Twenty-nine of these were primary lung cancer, one with metastatic colon cancer, and one with mucosa-associated lymphoid tissue lymphoma. Transplant diagnoses included chronic obstructive pulmonary disease (n=15) and interstitial pulmonary fibrosis (n=16) with a mean LAS of 38.4. Adenocarcinoma was the most common histologic subtype (59%) and the majority were stage I (n=15). The

remaining 14 patients included 10 stage II, 2 stage IIIA, and 2 stage IV. One patient was categorized retrospectively as stage IV given primary non-small cell lung cancer (NSCLC) in contralateral mediastinal nodes and a spinal lesion that rapidly enlarged following transplant. The other patient with stage IV disease was transplanted during an acute exacerbation of IPF on venovenous extracorporeal oxygenation and was found to have mucinous adenocarcinoma in all lobes after explantation.

Recurrence or progression of disease was noted in 8 patients with a median time to recurrence of 14 months.

Most progression of disease was noted to be extrathoracic spread (n=6) and all 8 of these patients succumbed to their cancer. Median time from recurrence to death was only 4.5 months. Those with stage I and II disease had 55% 5-year recurrence-free survival. Overall survival for stage I disease was 87%, 26%, and 17% at 1, 3, and 5 years, respectively, while stage II disease overall survival was 78% and 11% at 1 and 3 years. When all patients were considered as a group, 1-, 3-, and 5-year survival was 78%, 18%, and 14%, respectively.

Strollo and colleagues (13) assessed incidentally found cancers at time of transplant at their own institution and found out of 759 lung transplant recipients, 22 cases (2.9%) had incidental cancer, 17 of which were lung cancer. They retrospectively reviewed CT scans and reports completed prior to transplant, which occurred at a mean of 4 months prior. They were able to correctly identify 10 of the 22 lesions retrospectively, and found the reports to have a miss rate for CT-positive findings of 20%. Their study underlines the difficult nature of identifying occult malignancies with concurrent diffuse lung disease and multiple CT abnormalities in this patient population.

Ultimately cancers found in lung explants, while typically earlier stage, still carry a poor prognosis. At our institution, when cancer is diagnosed in the explanted lung, subsequent work-up includes MRI of the brain and PET scan at 4–6 weeks following transplant to evaluate for metastatic disease. Follow-up CT scans are performed every 6 months. Medical oncology evaluation is routinely obtained in these patients, but treatment options are severely limited by chemotoxicity (specifically nephrotoxicity) and physical debilitation. Modified chemotherapy regimens are used in this patient population due to relatively poor outcomes with full-dose systemic chemotherapy (25).

New lung cancer after transplantation

The development of cancer after solid organ transplant is significantly increased from that of the general population. A combination of chronic immunosuppression and underlying risk factors makes the development of lung cancer after lung transplant a possible complication. Lung cancer found after transplant can develop in the native lung of single-lung recipients or in the lung allograft in single or double lung recipients. Tumors in the allograft may arise from an undetected primary or secondary malignancy from the donor at time of transplant or a new primary or secondary malignancy from the recipient after transplant

(Table 3) (4,5,19,24–26,28,31–36).

Cancers arising in the lung allograft as an undiagnosed donor cancer is rare, likely attributable to rigorous donor selection criteria (8,37,38). Limited donor pools have led to increasing use of expanded donors with older age. The increased risk that this poses must be continually assessed.

In a single center study of 847 lung transplant patients from 2005 to 2013 (25), 17 (12%) were diagnosed with lung cancer. Eight of the cases were diagnosed in the explanted lung, 5 were diagnosed in the native remaining lung, 3 were found in the transplanted allograft, and 1 was unknown. Stage I/II were most common (n=11), one patient had stage III, and five were diagnosed at stage IV. NSCLC was more common (n=15) than small cell lung cancer (SCLC). Diagnosis of malignancy for those detected in the native (not explanted) lung or allograft was at a median of 26.7 months after transplant.

Of the 17 patients, 12 had potential curable disease. For the five patients diagnosed with stage I disease in the explanted lung, no adjuvant treatment was pursued, and two later developed recurrences in the transplanted lung. Two of three patients diagnosed with stage II disease in their explanted lung underwent adjuvant chemotherapy. For one patient with stage II disease in their native lung, lobectomy was performed. This patient developed metastatic disease after 5 months and died 7 months after initiation of chemotherapy. In two patients with cancer in the allograft (1 stage I SCLC, 1 stage II NSCLC) radiation followed by chemotherapy was employed. Median survival for those with cancer in their explanted lung was 24 months compared to 4.8 months in those that developed cancer after transplantation.

In the Transplant Cancer Match (TCM) study combining the US Scientific Registry of Transplant Recipients (SRTR) with 17 state and regional cancer registries (4), 8,993 first-time lung transplant recipients were evaluated. During follow-up, 183 cases of lung cancer were found at a median of 3.9 years. The vast majority of cases (n=169, 92%) were in single-lung recipients and the majority of those were in the native lung (n=153, 91%). Two-year overall survival after transplant diagnosis was around 20%.

New cancer diagnosis after transplant portends worse prognosis. A significant portion of post-lung transplant lung cancer is late-stage on presentation even in this closely followed population. For early-stage disease, surgery or stereotactic body radiation therapy (SBRT) may provide some benefit, but overall survival is significantly shortened compared to the non-transplant population.

Table 3 Lung cancer after lung transplant

Author, Year	Patients (n)	Tumor diagnosis	Transplant type	Tumor location	Stage >IIIA*	Overall survival
Stagner <i>et al.</i> (24), 2001	1	SCC only	100% Double	100% Allograft	0%	1% 2-yr
Arcasoy <i>et al.</i> (19), 2001	4	NSCLC	100% Single	100% Native	50%	20% 2-yr
Collins <i>et al.</i> (31), 2002	24	NSCLC, SCLC	100% Single	100% Native	44%	-
Dickson <i>et al.</i> (32), 2006	9	NSCLC	100% Single	100% Native	33%	25% 5-yr
Minai <i>et al.</i> (33), 2008	12	NSCLC, SCLC	92% Single; 8% Double	8% Allograft; 92% Native	-	-
Raviv <i>et al.</i> (34), 2011	7	NSCLC	100% Single	14% Allograft; 86% Native	71%	-
Yserbyt <i>et al.</i> (35), 2012	13	NSCLC, SCLC	69% Single; 31% Double	31% Allograft; 69% Native	62%	40% 5-yr
Espinosa <i>et al.</i> (36), 2012	9	NSCLC, SCLC	89% Single; 11% Double	100% Native	22%	-
Grewal <i>et al.</i> (26), 2015	9	NSCLC	78% Single; 22% Double	67% Allograft; 33% Native	56%	17% 2-yr
Du <i>et al.</i> (25), 2015	9	NSCLC, SCLC	53% Single; 47% Double	55% Allograft; 45% Native	67%	-
Pérez-Callejo <i>et al.</i> (5), 2018	18	NSCLC, SCLC	70% Single; 30% Double	33% Allograft; 67% Native	70%	57% 5-yr
Chatron <i>et al.</i> (28), 2019	11	NSCLC	82% Single; 18% Double	27% Allograft; 73% Native	55%	18% 2-yr
Triplette <i>et al.</i> (4), 2019	183	NSCLC, SCLC	45% Single; 55% Double	16% Allograft; 84% Native	46%	20% 2-yr

*, at diagnosis. SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Conclusions

Lung transplantation in the setting of known active lung cancer has a high rate of recurrence with poor post-transplant outcomes and thus is an absolute contraindication for lung transplant listing. With proper patient selection, multidisciplinary lung cancer tumor board and lung transplant selection committee evaluation, and significant attention to follow up, appropriate candidates with previously treated lung cancer and low recurrence risk can be safely listed and transplanted. Incidentally found tumors at time of transplantation have variable outcomes based on stage and histology, and, even with a rate around 2%, underline the importance of thorough explant histologic evaluation.

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