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Explanted malignancies after lung transplantation: the University of Michigan experience

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Abstract

The management of patients with an explanted malignancy after lung transplantation is not well understood. We reviewed our institutional experience and outcomes at a single academic medical centre between December 1997 and April 2021 for patients with malignancies of all histologic types identified on explant pathology. Primary lung cancers were reclassified using the 8th Edition TNM staging and the 2021 World Health Organization histologic classification of lung cancers. Of the 733 patients undergoing lung transplantation, 15 (2.05%) were found to have malignancy on the explanted lungs, including 6 (0.82%) primary lung cancers. Four patients were found to have early-stage lung cancers, while 2 patients had advanced-stage IV disease. Survival ranged from 0 to 109 months for the entire cohort with median 23.2 [49.9] months in those with primary lung cancers. There were 2 recurrences following explanted stage I (15 months) and stage IV (53 months) diseases. Other explant pathologies included carcinoid tumourlets in 6 patients, lymphoma in 2 and metastatic leiomyosarcoma in 1. In conclusion, explanted lung malignancies are an infrequent but significant finding on explant pathology. Further data are needed to better characterize and stratify this patient cohort.

Keywords: Lung transplant • Lung cancer • Patient survival

INTRODUCTION

Lung transplantation is an effective therapeutic modality for patients with end-stage pulmonary failure, commonly encountered as a result of chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis. Both conditions, however, are associated with an increased risk of primary pulmonary malignancies, classically considered to be a contraindication to transplantation. Detection of suspicious nodules can be challenging in the presence of widespread fibrotic changes and parenchymal destruction, such that unexpected malignancies are occasionally diagnosed histologically on explanted lungs. In this study, we reviewed our individual institutional experience and outcomes associated with all explanted malignancies after lung transplantation, including pathological reclassification of primary lung cancers.

PATIENTS AND METHODS

We conducted a retrospective chart review including all patients undergoing lung transplantation at a single academic medical centre during the study period of December 1997 to April 2021. Patients found to have an explanted malignancy of any histologic classification were identified by sequentially examining all pathology reports. All cases of primary lung cancers identified were reviewed by a pulmonary pathologist with re-classification and re-staging using the 2021 World Health Organization (WHO) histologic classification of lung cancers and the 8th Edition TNM staging.

Survival and recurrence were defined as the time from lung transplantation to the last follow-up or to the date of radiographically identified or biopsy-proven recurrent malignancy, respectively. Standard follow-up surveillance was performed per the National Comprehensive Cancer Network (NCCN) algorithm. Data presented as median [interquartile range] unless stated otherwise.

This retrospective study was deemed exempt by the University of Michigan institutional review board (HUM00083784).

RESULTS

Of the 733 patients undergoing lung transplantation, 15 (2.05%) were found to have a malignancy on explant pathology, including 6 (0.82%) primary lung cancers (Table 1). Adenocarcinoma was the most common histologic subtype ($n = 4$) of the primary lung cancers, followed by squamous cell carcinoma ($n = 2$). Stage

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Table 1: Patient characteristics and explant pathologies

Age, sex	Smoking (pack years)	Indication	LAS	Transplant	Explant histology	Stage	CT (months)	Recurrence (months)	Survival (months)
61, M	Former (20)	PAH	–	Single	Squamous cell T1b N0 Mx	IA2	30	15	18
58, F	Former (40)	COPD	–	Single	Carcinoid tumourlets		12	–	0
33, F	Former (20)	COPD	–	Bilateral	Adenocarcinoma T1a N0 Mx	IA1	48	–	2
56, F	Former (70)	COPD	–	Single	Adenocarcinoma T3 N1 Mx	IIIA	30	–	2
45, F	Never smoker	BO	33.42	Bilateral	Carcinoid tumourlets		1	–	14
40, F	Former (22)	COPD	38.87	Bilateral	Adenocarcinoma Tis N0 Mx	–	3[a]	–	27
60, F	Former (100)	COPD	31.28	Single	Carcinoid tumourlets		3[b]	–	98
45, F	Former (8)	ILD	34.00	Single	Metastatic leiomyosarcoma		14	–	64
52, F	Former (30)	BO	43.53	Bilateral	Carcinoid tumourlets		7	–	109[c]
46, M	Former (1)	ILD	42.85	Bilateral	Adenocarcinoma T4 N0 M1a	IIIA	2[a,b]	53	92[c]
66, M	Never smoker	ILD	37.27	Bilateral	Squamous cell T1a N0 M0	IA1	19	–	66[c]
53, F	Never smoker	CF	40.08	Bilateral	Carcinoid tumourlets		5	–	31[c]
61, F	Never smoker	ILD	42.26	Bilateral	MALT lymphoma		2	–	6
49, F	Never smoker	CF	39.87	Bilateral	Carcinoid tumourlets		2	–	15[c]
48, M	Never smoker	ILD	42.66	Bilateral	MALT lymphoma		0	–	5[c]

[a]Tissue biopsy.
[b]Preoperative PET scan.
[c]Living.
F: female; M: male; LAS: lung allocation score; BO: bronchiolitis obliterans; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; MALT: mucosa-associated lymphoid tissue; PAH: pulmonary arterial hypertension.

0 disease was found in 1 patient, stage I in 3 and stage IV in 2. Additional explanted malignancies included carcinoid tumourlets in 6 patients (0.82%), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in 2 (0.27%) and metastatic leiomyosarcoma in 1 (0.14%).

Observed survival ranged from 0 to 109 months for the entire cohort with median 23.2 [49.9] months for those with primary lung cancers, including disease recurrences in 2 of the 6 patients (stage I, 15 months; stage IV, 53 months). None of the patients in this cohort received adjuvant therapy initially.

All patients had a chest CT performed prior to lung transplantation, with a median interval time from last scan to transplant of 5.0 [14.5] months. Of note, this interval decreased from 30.0 [9.0] months during the pre-lung allocation score era to 3.0 [4.0] months after the initiation of the lung allocation score. Six patients had evidence of lung nodules on preoperative CT imaging. Two patients had follow-up PET scans before transplantation, which revealed (i) non-FDG-avid peripheral pulmonary nodules and (ii) a large, FDG-avid airspace opacity with small, mildly FDG-avid airspace opacities bilaterally found to be biopsy-proven moderately differentiated adenocarcinoma. The mediastinal staging was negative.

DISCUSSION

Over the study period, 2.04% of patients ($n = 15$) were found to have a malignancy of any kind, including primary lung cancers, carcinoid tumourlets, lymphoma and other metastatic diseases. Our incidence rate of 0.82% for explanted lung cancers is consistent with estimates of roughly ∼1–2% in recent case series (Table 2) [1–6].

While earlier multicentre studies have demonstrated the feasibility of long-term survival in patients with more indolent subtypes of lung cancer, it is uncertain whether current histologic classifications and TNM staging for lung adenocarcinomas as applied here will further divide patients into different prognostic groups. A recent study [1] stratified survival outcomes by stage at explant and reported overall survival (OS) of 87%, 26% and 17% for patients with stage I disease at 1, 3 and 5 years, respectively, while patients with stage III and IV diseases died within 1 year. Others [2–4] have similarly reported a reduced OS when a malignancy was identified on explant pathology, where moderate to poorly differentiated malignancies had a worse prognosis. In contrast, a study from Vienna [5] demonstrated a remarkable 5-year OS of 90.5% for patients with explanted lung cancer ($n = 11$) compared to 58.9% for all other patients.

We observed a wide range of survival including disease recurrence in 2 patients. Notably, 1 patient in our cohort who underwent bilateral transplantation with biopsy-proven adenocarcinoma was surviving at follow-up at 7 years despite cancer recurrence, while another survived >5 years after lung transplantation with metastatic leiomyosarcoma discovered on explant pathology. Patients with carcinoid tumourlets also appeared to do well. However, given the relatively few numbers of patients in each of these studies, more general conclusions are difficult to draw. To better characterize patient outcomes, guide post-transplant patient management and understand outcomes based on pathologic subtype, we have initiated and are currently recruiting for a multi-institutional study for these patients, a data collection template is appended in Supplementary Material, Table S1.

Limitations

Nevertheless, our data must be interpreted in light of several limitations. The small number of cases precludes advanced statistical

Table 2: Meta-analysis of single-centre reports

Study	Size	Incidence, *n* (%)	Histopathology	Survival	Recurrence, *n* (%)
Strollo *et al.* [6]	759	22 (2.90)	13 (I/II), 2 (III), 2 (IV), 3 (metastases) 2 (lymphoproliferative)	–	–
Grewal *et al.* [2]	462	6 (1.30)	2 (I), 4 (III)	36[a], 6 months (I) 16.5 (7–25) months (III)	–
Nakajima *et al.* [3]	853	13 (1.52)	4 (I), 5 (II) 1 (III), 3 (IV)	Median 339 days 3-Year OS 11%	9 (69.2)
Klikovits *et al.* [5]	1262	11 (0.87)	10 (I), 1 (II)	5-Year OS 90.5%	0
Panchabhai *et al.* [4]	1303	24 (1.84)	13 (I), 8 (II) 3 (III), 1 (IV)	–	8 (33.3)
Ahmad *et al.* [1]	1710	31 (1.81)	15 (I), 10 (II) 2 (III), 2 (IV) 1 (metastasis), 1 (MALT)	1-, 3- and 5-year OS 78, 18, 14%	8 (25.8)

[a]Living.
MALT: mucosa-associated lymphoid tissue.

modelling or does it allow for a robust comparator group. Given the duration of the study period considered here, there was also inadequate staging in some patients early on including few patients undergoing preoperative PET scans. Similarly, although the pathology was reviewed and updated for this study, the analysis was limited by the length of time and availability, and while a detailed analysis of pathological subsets (such as outcomes for lepidic adenocarcinomas) would no doubt be extremely useful for clinical decisions, the small number of patients precluded such an analysis. However, clinical selection of these patients is critical and our results merely represent what centres considering transplant in this population might expect among an uncommon but important subset of patients.

CONCLUSION

In summary, review of our institutional experience suggests that explanted malignancies identified after lung transplant are relatively infrequent, but significant findings. Larger, multicentre studies are needed with a focus on obtaining better pathological classification of explanted lung cancers and prospective data on both overall survival and lung cancer-specific survival.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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