Incidental Lung Cancer of Explanted Lungs from Lung Transplant Recipients: Incidence, Characteristics, and 5-Year Survival

Yong Jun Choi[1], Song Yee Kim[1], Moo Suk Park[1], Jin Gu Lee[2], Hyo Chae Paik[2], and Sang Hoon Lee[1]

Departments of [1]Internal Medicine, [2]Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Korea.

Purpose: Recent history of malignancy without 5-year disease-free interval is an absolute contraindication for lung transplantation (LTx). However, in rare cases, lung cancer may be incidentally diagnosed in the explanted lung of recipients. We evaluated the prevalence, 5-year survival, and prognosis of incidental lung cancer after LTx.

Materials and Methods: Medical records of patients who underwent LTx at Severance Hospital between January 1, 2012 and June 30, 2019 were reviewed. Patients with incidental lung cancer were included, and those with histologically proven pre-transplant lung cancer were excluded.

Results: Of the 247 patients who underwent LTx, 6 (2.4%) were diagnosed with incidental lung cancer. Interstitial lung disease (ILD) was the underlying lung disease in all patients. The median interval from the last preoperative computed tomography (CT) screening to LTx was 26 days. The most common histological type of incidental lung cancer was adenocarcinoma (n=4, 66.7%). All Stage IV cases were misdiagnosed as fibrosis on preoperative chest CT. Patients with incidental lung cancer showed lower 5-year survival than those without malignancy (median survival: 8.5 months vs. not reached, p=0.047, respectively). Patients with Stage III or IV demonstrated lower 5-year survival than those with Stage I or II and those without malignancy (median survival: 5 months, 19 months, and not reached, respectively, p=0.011).

Conclusion: Multidisciplinary preoperative screening and serial imaging studies within short intervals are required to differentiate lung malignancy from fibrotic foci. Furthermore, active pathologic examination of suspicious lung lesions is required in patients at high risk for lung cancer.

Key Words: Non-small cell lung cancer, lung transplantations, transplant recipient

INTRODUCTION

Since the first human lung transplantation (LTx) was performed in 1963, LTx has become a treatment option for various end-stage lung diseases.[1] According to a 2019 report from the Inter-

national Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation, the number of LTx has been continuously increasing and, consequently, the survival of adult recipients has been increasing; from 2010 to 2017, the median survival of these LTx recipients was 6.7 years.[2] The most common indications for LTx include chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), which account for 30.1% and 26.1% of LTx cases, respectively.[2] These diseases are associated with a common risk factor for lung cancer—cigarette smoking; therefore, COPD and IPF are known as risk factors for lung cancer. Since COPD and lung cancer share underlying genetic predispositions, such as telomere shortening, mitochondrial dysfunction, and premature aging, the risk of squamous cell carcinoma is two times higher in COPD patients than in the general population.[3] Similarly, IPF increases the risk of lung cancer from 7% to 20% through mul-

tiple common genetic, molecular, and cellular processes.[4]

Except in cases of localized non-melanoma skin cancer, although a recent history of malignancy without a 5-year disease-free interval is an absolute contraindication for LTx, the recipients with incidental lung cancer in the explanted lungs have already undergone LTx.[5] In previous studies, the prevalence of incidental lung cancer has been reported to range from 0.8% to 2.9%.[6] The association between the stage and prognosis of incidental lung cancer is not well-established, although it is generally reported that the higher stages are associated with poor survival.[6,7] Therefore, early detection of lung cancer is important in patients awaiting LTx for appropriate patient selection and improved LTx outcomes. To date, however, most relevant studies have been confined to non-Asian regions. Therefore, in this study, we aimed to evaluate the prevalence, characteristics, survival, and prognosis of incidental lung cancer after LTx in the Korean population and compare them with those reported in non-Asian populations.

MATERIALS AND METHODS

Patients and study design

We reviewed the medical records of all patients who underwent LTx at Severance Hospital between January 1, 2012, and June 30, 2019. Patients with malignancy in the explanted lung were included, and those with histologically proven lung cancer before LTx were excluded. Moreover, patients who underwent re-transplantation were also excluded (Fig. 1).

We divided the enrolled patients into two groups based on the presence of incidental lung cancer and compared the prevalence, characteristics, survival, and prognosis between them.
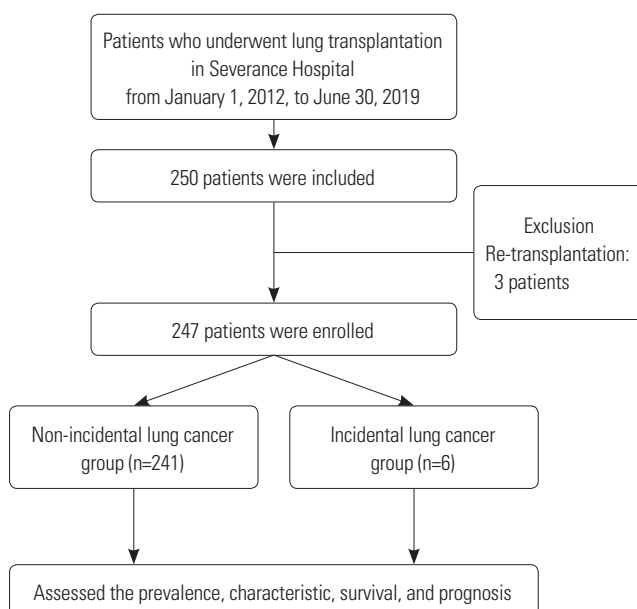
Data collection

We collected the data on baseline characteristics such as sex, age at LTx, smoking history, and the time of diagnosis and pathology of the underlying lung disease. Furthermore, information on the date and type of LTx, postoperative treatment, status of recurrence or progression, overall survival duration, death, and cause of death were collected.

All patients who were selected for LTx had undergone chest computed tomography (CT) as part of the preoperative screening. The date and findings of the two most recent CT scans before LTx were collected.

All explanted lungs underwent pathologic examination, and the pathologic stage of lung cancer was evaluated in accordance with the American Joint Committee on Cancer 8th edition TNM staging system.

Outcome measures

Recurrence was defined as radiological evidence [CT, positron emission tomography (PET), brain magnetic resonance imaging, or whole-body bone scan] or histological evidence of recurrent disease in patients with an operable stage (I, II, and IIIA). Progression was defined as the presence of radiological or histological evidence of worsening malignant disease in patients with an inoperable stage (IIIB/C and IV). The 5-year survival rates were calculated based on the duration between the transplantation and the last follow-up. Progression-free survival was defined as the duration between the date of transplantation and that of confirmation of recurrence or progression.

Statistical analysis

Statistical analysis was performed with R software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). To compare continuous variables, the Mann-Whitney U test was used for non-parametric variables, based on the normality assumptions from the Shapiro-Wilk test, and the results are presented as the median and interquartile range. The chi-square test or Fisher's exact test was used to compare categorical variables, and the results are presented as number and frequency. Kaplan-Meier curves were plotted to evaluate the cumulative 5-year survival rates. p-values<0.05 were considered statistically significant.

Ethics

This study was approved (approval no. 4-2020-2) by the Institutional Review Board of Severance Hospital. The requirement for informed consent was waived due to the retrospective nature of this study.

Fig. 1. Flowchart depicting the study design.

RESULTS

Baseline characteristics and incidence of explanted lung cancers

Among 247 patients who underwent LTx, 6 (2.4%) were diagnosed with explanted lung cancer at the time of transplantation. The baseline characteristics of these patients are summarized in Table 1. The most common causes of LTx included interstitial lung disease (ILD) (n=177; 71.7%), post-stem cell transplantation bronchiolitis obliterans (n=18; 7.3%), bronchiectasis (n= 14; 5.7%), and COPD (n=11; 4.4%). Almost all of the patients underwent bilateral LTx (n=236; 95.6%), whereas only 11 patients underwent single-LTx (right-LTx, n=10, 4.0%; left-LTx, n=1, 0.4%).

Radiologic findings

All patients with lung cancer underwent chest CT, and the interval between the last pre-transplant CT and transplantation ranged from 8 to 44 days (median 26 days). The findings from imaging investigations are described in Fig. 2 and summarized in Table 2. Five patients were diagnosed with IPF, four had the usual interstitial pneumonia (UIP) pattern, and one had a probable IPF pattern on chest CT. In cases of probable IPF, the IPF was diagnosed by using a multidisciplinary approach that comprised the subdisciplines of pulmonology, cardiothoracic surgery, radiology, and pathology.[8] On the pre-transplantation review for incidental cancer lesions on chest CT in the six patients,

Patients B, D, and F had patterns of ILD exacerbation with pneumonia, whereas patients A and E primarily had a pneumonia and an exacerbation pattern, respectively. Only Patient C had a growing nodular lesion.

Pathology and TNM stage of explanted lung cancer

All patients with explanted lung cancer had ILD on the pathological analysis of the explanted lung: five had a UIP pattern and one had a non-specific interstitial pneumonia pattern. With regard to the pathology of lung cancer lesions, the most common cancer was adenocarcinoma (n=4; 66.6%), followed by squamous cell carcinoma (n=1; 16.7%), and carcinoid tumors (n=1; 16.7%) (Table 3). On TNM staging, three cases were identified as T4, and the largest and smallest incidental cancers were 10 cm and 0.3 cm in maximum diameter, respectively. Stage IA was identified in two cases, whereas stages IIB, IIIB, and IV were identified in one, one, and two patients, respectively. In patients with Stage IV (E, F) cancer, preoperative chest CT showed fibrotic foci with a pattern of ILD exacerbation rather than a malignant mass, and it was also accompanied by reactive lymph node enlargement in Patient F.

Prognosis and survival

The overall 5-year survival rate was 58.7%. The cumulative 5-year survival rates of the incidental lung cancer group and non-incidental lung cancer group are shown in Supplementary Fig. 1A (only online). There was a significant difference between the

Table 1. Baseline Characteristics of All Patients

Variables	Total (n=247)	Non-incidental lung cancer (n=241)	Incidental lung cancer (n=6)	p value
Age (median age)	56.0 (46.0–62.0)	56.0 (46.0–62.0)	58.5 (53.0–62.0)	0.538
Sex				1.000
Male	156 (63.2)	152 (63.1)	4 (66.7)	
Female	91 (36.8)	89 (36.9)	2 (33.3)	
Transplantation type				0.866
Bilateral lung	236 (95.6)	230 (95.5)	6 (100.0)	
Right lung	10 (4.0)	10 (4.1)	0 (0.0)	
Left lung	1 (0.4)	1 (0.4)	0 (0.0)	
Cause of transplantation				0.965
BE	14 (5.7)	14 (5.8)	0 (0.0)	
COPD	11 (4.4)	11 (4.6)	0 (0.0)	
ILD	177 (71.7)	171 (71.0)	6 (100.0)	
IPAH	5 (2.0)	5 (2.0)	0 (0.0)	
LAM	5 (2.0)	5 (2.0)	0 (0.0)	
Post-SCT BO	18 (7.3)	18 (7.5)	0 (0.0)	
TDL	4 (1.6)	4 (1.7)	0 (0.0)	
Others	13 (5.3)	13 (5.4)	0 (0.0)	
Stage				
I or II		NA	3 (50.0)	
III or IV		NA	3 (50.0)	

BE, bronchiectasis; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; LAM, lymphangioleiomyomatosis; post-SCT BO, post-stem cell transplantation bronchiolitis obliterans; TDL, tuberculosis-destroyed lung.

two groups in the cumulative survival (5-year survival rate: 16.7% vs. 59.8%; median survival: 8.5 vs. not reached, respectively, *p*= 0.047). When the incidental lung cancer group was divided into two groups based on the cancer stages, the group with Stage III or IV cancer demonstrated significantly lower 5-year survival than those with Stage I or II cancer and those without incidental lung cancer (5-year survival rate: 59.8%, 33.3%, and 16.7%; median survival: 5, 19, and not reached, respectively, *p*=0.011)
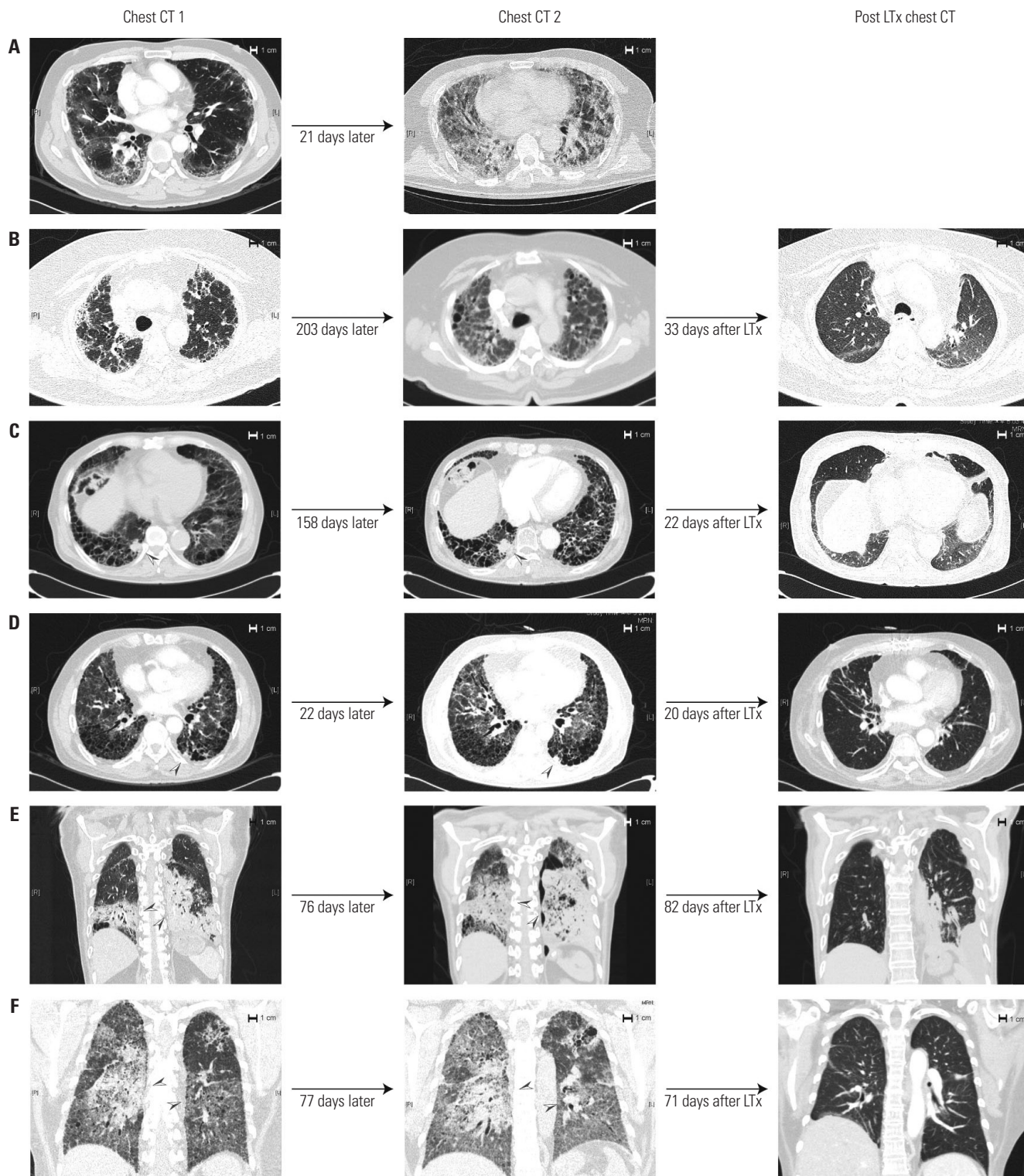

Fig. 2. Chest CT images of the patients with incidental lung cancer. CT 1 and CT 2 were defined as the two most recent CTs performed prior to surgery. The arrow marks malignant lesions. (A) and (B) demonstrated no definite malignancy, (C) and (D) demonstrated suspicious focal malignancy, (E) and (F) demonstrated diffuse malignancy in fibrotic lesion. CT, computed tomography; LTx, lung transplantation.

Table 2. Radiologic Findings of Incidental Lung Cancer in Lung Transplant Recipients

Patients	Chest CT 1*	Chest CT 2*	Interval to LTx (days)
	Finding	Finding	
A	Probable IPF	Probable IPF with pneumonitis	42
B	UIP	Progressive UIP with acute exacerbation and combined pneumonia	17
C	UIP with right lower lobe subpleural nodule	UIP with growing right lower lobe subpleural nodule	44
D	UIP	Exacerbation of UIP, with focal pneumonia	10
E	UIP	Exacerbation of UIP	8
F	NSIP	Progressive NSIP with bronchopneumonia, enlarged lymph nodes in the bilateral hilar and paratracheal area	35

CT, computed tomography; LTx, lung transplantation; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia.
*CT 1 and CT 2 were defined as the two most recent CTs performed prior to surgery.

Table 3. Pathologic Findings of Incidental Lung Cancer in Lung Transplant Recipients

Patients	Whole lung	Lung cancer lesion			
	Pathology	Pathology	Maximum diameter (cm)	Location	Stage (TNM)
A	UIP	Adenocarcinoma, acinar type	Multiple	RUL, RML, RLL	IIIB (pT4N3M0)
B	UIP	Typical carcinoid tumor	0.3	LUL	IA (T1aN0M0)
C	UIP	Invasive adenocarcinoma, acinar predominant	2.5	RLL	IIB (pT2aN1M0)
D	UIP	Squamous cell carcinomas	0.5	LLL	IA (pT1aN0M0)
E	UIP	Invasive mucinous adenocarcinoma	Right: 10 / left: 10	RUL, RML, RLL, LUL, LLL	IVA (pT4N3M1a)
F	CFIP	Adenocarcinoma, invasive acinar predominant	Right: 10 / left: 10	RUL, RML, RLL, LUL, LLL	IVB (pT4N1aM1c)

UIP, usual interstitial pneumonia; CFIP, chronic fibrosing interstitial pneumonia; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 4. Post-Transplant Treatment and Prognoses of Cancer Patients

Patient	Metastasis at diagnosis	Cancer therapy	Duration of cancer therapy (months)	Cause of death	Immunosuppressive agent	Progression site
A	None	None		Pneumonia	MMF, tacrolimus	None
B	None	None		Pneumonia	MMF, tacrolimus	None
C	None	None		Drug induced TTP	MMF, tacrolimus	None
D	None	None		Alive	MMF, tacrolimus	None
E	Pleura	None		Cancer progression	MMF, tacrolimus	Bone
F	Bone, brain	Afatinib	6	Cancer progression	MMF, tacrolimus	Brain

TTP, thrombotic thrombocytopenic purpura; MMF, mycophenolate mofetil.

(Supplementary Fig. 1B, only online).

No recurrence was observed in this study. Progression was observed in two cases and occurred in all Stage IV patients (Table 4). The most common causes of death were pneumonia (n= 2; 33.3%) and cancer progression (n=2; 33.3%).

DISCUSSION

In this study, the prevalence of incidental lung cancer in the explanted lung was 2.4%, which was similar to that reported in previous studies.[6] However, all patients with explanted lung cancer had underlying IPF in the present study, which was a different finding compared to previous studies. Panchabhai, et al.[9] reported that, among a total of 24 patients with incidental lung cancer, 16 (66.7%) had ILD and 8 (33.3%) had COPD. Similar-

ly, Strollo, et al.[10] reported that 11 (50%) and 10 (45.5%) patients in their study sample of 22 patients with incidental lung cancer had COPD and ILD, respectively. The absence of COPD patients in the present study is attributed to the LTx trend in Korea. Unlike in other countries, a considerably greater number of LTx are performed for IPF than for COPD in Korea. According to the Korean Network for Organ Sharing (KONOS), in 2019, among a total of 92 LTx, IPF accounted for 41 (44.6%) cases; in 2018, emphysema accounted for only 1 (1.9%) LTx case. Another possibility is that lung nodules are more easily distinguishable on preoperative screening in COPD patients than in ILD patients, which may have resulted in fewer incidental lung cancers being found intraoperatively during LTx in COPD patients.[11]

IPF is a well-known risk factor of lung cancer. Several studies have reported the prevalence of lung cancer in IPF patients in the range of 3.0−45.7%, with an approximately five times high-

er risk than the general population.[12-14] In an autopsy study, the prevalence of lung cancer in IPF patients was 48.2%, suggesting that many cases of lung cancer in IPF patients remain undiagnosed.[15] One of the causes for this is that the underlying IPF occasionally makes it difficult to differentiate between lung malignancy and fibrotic foci,[9] and this misdiagnosis is more frequent in patients with end-stage lung disease or a flare-up of IPF that requires LTx.

Despite various preoperative screening imaging modalities, including thoracic high-resolution CT, incidental cancers in the explanted lung are observed in 1–3% of all LTx cases.[16] In most of the incidental lung cancer patients in this study, it was difficult to distinguish between cancer and exacerbated lesions, even in Stage IV cancer patients. These difficulties have been reported in a previous study wherein radiologists, who were blinded to the pathologic diagnosis of recipients, reviewed preoperative screening images of patients with incidental lung cancer.[10] However, they could not confidently identify malignancy in 12 (54.5%) of a total of 22 patients. Recently, LTx has been suggested as an effective treatment for patients with early lung cancer. Glanville and Wilson[17] recommended screening imaging studies to be conducted every 3 months to ascertain changes in the cancer stage in patients who are awaiting transplantation for non-small cell lung cancer. Similarly, we can also make similar recommendation that, for the early detection of lung cancer, chest imaging should be performed in patients who are at high risk for lung cancer at least once every 3 months while awaiting LTx. However, this recommendation needs to be validated through further research. PET alone may not be helpful for detecting malignancies due to many false-positive results secondary to inflammatory changes, although a combination of PET with chest CT may facilitate the evaluation of malignancies, especially in cases with distant metastasis. Furthermore, the identification of tumor markers may be helpful in the preoperative diagnosis of incidental lung cancers in patients at high risk for lung cancer.

In addition to preoperative imaging, preoperative pathological examination of the suspected lesions is also important. However, biopsies of suspected lesions can be dangerous, as invasive procedures may result in pneumothorax, empyema, pneumonia, and respiratory insufficiency, which are critically injurious to patients with end-stage IPF.[18] In comparison, endobronchial ultrasound-guided bronchoscopic biopsy of suspicious lung lesions or lymph nodes has been considered to be a less invasive diagnostic modality in patients with end-stage IPF.[19]

In a recent literature review of 13 articles on explanted lung cancer, the most common type of histologic cancer was adenocarcinoma (n=51, 48.6%), followed by squamous cell carcinoma (n=24, 22.9%).[9] Similarly, in the present study, adenocarcinoma and squamous carcinoma were identified in four patients (66.6%) and one patient (16.7%), respectively.

According to a 2019 KONOS report, the cumulative 5-year survival rate of all LTx recipients in Korea was 48.3%. In the present study, the cumulative 5-year survival rates in all patients, non-incidental lung cancer patients, and incidental cancer patients were 58.7%, 59.8%, and 16.7%, respectively. Furthermore, the stage of incidental lung cancer correlated with the overall survival. Most previous studies have reported that a lower stage is associated with a higher survival rate. According to a previous study by de Perrot, et al.,[7] the 5-year survival rate was significantly higher in patients with Stage I cancer (51%) than in those with Stages II and III cancer (14%). Similarly, we observed a negative association between the stage of lung cancer and 5-year survival rate in the present study.

Furthermore, the prognosis of incidental lung cancer in LTx recipients is related to the appropriate treatment.[20] However, the therapeutic strategy in incidental lung cancer has not been well-established. Only some case series have described adjuvant chemotherapy in incidental lung cancer at the T2N1 stage; however, the effect of treatment was still unclear.[20] Moreover, targeted therapies can be used in the presence of specific mutations.

Despite inadequate clinical data, the post-LTx use of immunosuppressive agents may cause the progression or recurrence of incidental lung cancer.[9] Especially, calcineurin inhibitors have been reported to be associated with tumor progression through various mechanisms, such as the disruption of apoptosis and DNA repair.[21,22] However, mTOR inhibitors have been observed to decrease cancer progression in recipients of kidney transplantation.[23,24] Therefore, an individualized post-LTx immunosuppression strategy is necessary, and further studies are required to develop the criteria to guide individualized therapy.

The present study had some limitations. Mainly, since the size of the study sample was small, the results cannot be generalized. A multicenter study with a larger sample is required to validate the results of this study. In addition, the retrospective design of this study may have resulted in some unexpected bias in the investigative process.

In conclusion, similar to the results of previous non-Asian studies, the prevalence of incidental lung cancer in LTx recipients in this study was 2.4%. The 5-year survival rate of LTx recipients with incidental lung cancer was significantly lower than that of people without cancer. To reduce the incidence of incidental lung cancer, a multidisciplinary review of the preoperative screening studies, as well as serial imaging studies, are required. Furthermore, active histopathological examination of suspicious lung lesions is required to identify malignancy.

AUTHOR CONTRIBUTIONS

Yong Jun Choi and Sang Hoon Lee. Writing—review & editing: Yong Jun Choi and Sang Hoon Lee. Approval of final manuscript: all authors.

ORCID iDs

Yong Jun Choi https://orcid.org/0000-0002-6114-2059
Song Yee Kim https://orcid.org/0000-0001-8627-486X
Moo Suk Park https://orcid.org/0000-0003-0820-7615
Jin Gu Lee https://orcid.org/0000-0003-2767-6505
Hyo Chae Paik https://orcid.org/0000-0001-9309-8235
Sang Hoon Lee https://orcid.org/0000-0002-7706-5318

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