Original Article

The effects of total pleural covering on pneumothorax recurrence and pulmonary function in lymphangioleiomyomatosis patients without history of pleurodesis or thoracic surgeries for pneumothorax

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Background: Total pleural covering (TPC) is an innovative surgical procedure in which the entire visceral pleura is wrapped with sheets of oxidized regenerated cellulose (ORC) mesh under video-assisted thoracoscopic surgery. We have previously reported that TPC could successfully prevent pneumothorax recurrence in patients with lymphangioleiomyomatosis (LAM). However, the actual efficacy and preventive effect of TPC on pneumothorax recurrence remains unclear as many LAM patients already had pleural adhesion prior to TPC that was induced by thoracic surgery and/or pleurodesis. The purpose of this study is to evaluate the effects of TPC on pneumothorax recurrence and pulmonary function in LAM patients with no history of thoracic surgeries or pleurodesis.

Methods: We retrospectively reviewed medical charts of 52 patients (60 hemithoraces) who underwent TPC at our center, from January 2003 to September 2019, as a first surgical intervention for pneumothorax.

Results: Pneumothorax recurrence occurred in 12 patients [14 of 60 hemithoraces (23.3%)] during the observation period [27 months (14.7; 56.4) = median (lower; upper quartiles)]. The probability of recurrence-free hemithorax post TPC was 81.1% at 2.5 years and 64.1% at 5 years. TPC did not produce a significant decrease in either VC %predicted (pred) or FEV_1/FVC. The pre- *vs.* post-TPC median (lower; upper quartiles) VC %pred was 85.7% (79.7; 98.0) *vs.* 87.2% (72.3; 95.6), P=0.535 and the FEV_1/FVC was 84.6% (75.7; 89.6) *vs.* 83.0% (71.8; 87.0), P=0.667. Mechanistic/mammalian target of rapamycin (mTOR) inhibitors (mTORI) were subsequently initiated in 19 patients (36.5%) because of the progression of LAM. The postoperative FEV_1 %pred was significantly lower in patients who required mTORI than in those who did not [68.1% (57.3; 82.9) *vs.* 88.7% (84.6; 89.8), P=0.020]; the decline rate in FEV_1 %pred/year from pre to post TPC was significantly greater in LAM patients who required mTORI than in those who did not [–9.37% (–4.73; 12.9) *vs.* –1.94% (1.52; –4.50), P=0.029]. Postoperative complications were found in 25 of 52 hemithoraces (48.1 %).

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Conclusions: TPC can prevent pneumothorax recurrence without causing ventilatory impairment or severe pleural symphysis in LAM patients. TPC is an effective treatment option for LAM-associated pneumothorax based on its efficacy and safety.

Keywords: Total pleural covering (TPC); pulmonary function; lymphangioleiomyomatosis (LAM); pneumothorax; mTOR inhibitor

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Introduction

Lymphangioleiomyomatosis (LAM) is a cystic lung disease that predominantly affects middle-aged women (1-3). Pneumothorax and progressive lung function impairment are major complications in LAM. Considering the high recurrence rate of pneumothorax, a guideline on LAM diagnosis and management by the American Thoracic Society (ATS) and Japanese Respiratory Society (JRS) recommends ipsilateral pleurodesis following an initial pneumothorax rather than waiting for a recurrent pneumothorax (1,4). However, patients who had undergone lung transplantation following chemical or surgical pleurodesis experienced pleural-related postoperative complications, which indicates extensive pleural adhesion is an increased risk in lung transplantation (5). As an alternative treatment to pleurodesis, total pleural covering (TPC) was invented to prevent pneumothorax recurrence without causing pleural adhesion in LAM patients (6). TPC is a surgical technique in which the entire visceral surface of the lung is wrapped with sheets of oxidized regenerated cellulose (ORC) mesh (Ethicon SURGICEL® absorbable Hemostat gauze, Johnson & Johnson, Brunswick, NJ, USA) under video-assisted thoracoscopic surgery (VATS) (6). Kim *et al.* (7) recently reported that lung transplantation after bilateral TPC on a secondary pneumothorax in tuberous sclerosis complex (TSC)-associated LAM resulted in no postoperative complications.

In our previous study, we evaluated the effects of TPC on preventing pneumothorax recurrence and pulmonary function (6). However, the actual efficacy of TPC remains unclear since many LAM patients had thoracic surgeries and/or pleurodesis performed prior to TPC, which causes pleural adhesion and hampers the efficacy of TPC. Therefore, the purpose of this study is to evaluate the effects of TPC on pneumothorax recurrence and pulmonary function in LAM patients with no history of thoracic surgeries or pleurodesis.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2286).

Methods

Study design and sample

Between January 2003 and September 2019, 74 patients (95 hemithoraces) pathologically diagnosed with LAM underwent TPC at the Pneumothorax Research Center, Nissan Tamagawa Hospital, Japan. The medical charts of all these patients were reviewed to determine the subset that had not undergone prior interventions that could impede the efficacy of TPC in terms of pneumothorax recurrence and pulmonary function. *Figure 1* illustrates the study eligibility criteria as well as the analytical approach that was used to evaluate the true efficacy of TPC on pneumothorax recurrence and pulmonary function in LAM patients. Patients and hemithoraces that had chemical or surgical pleurodesis and/or any surgical interventions prior to TPC were excluded. Pneumothorax recurrence was counted only when patients had been diagnosed via chest X-ray or computed tomography.

TPC

TPC is a surgical technique in which the entire visceral pleura of the lung is wrapped with sheets of ORC mesh under VATS, thereby reinforcing the affected visceral pleura and preventing pneumothorax recurrence. TPC was invented to prevent pneumothorax recurrence without causing frank pleural adhesion in LAM patients and its technical procedure has already been described in detail in our previous study (6). Over 10 sheets of 3”×4” ORC mesh are required to perfectly wrap the whole visceral pleura in

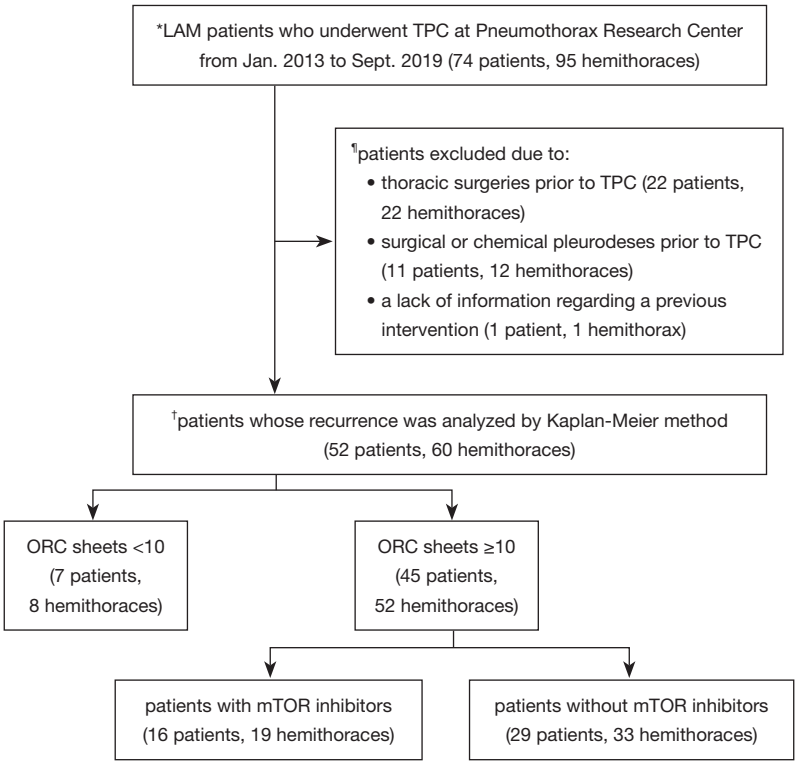

Figure 1 Study eligibility criteria and flow of data analysis. * ¶ † Note that the number of LAM patients whose recurrence was estimated by the Kaplan-Meier method (n=52)† is not (the number of LAM patients at the initial evaluation)* minus (the number of LAM patients excluded due the reasons listed)¶. This occurred because LAM patients who had TPC in both hemithoraces were either included or excluded, depending on the absence or existence of prior interventions. LAM, lymphangioleiomyomatosis; TPC, total pleural covering; ORC, oxidized regenerated cellulose; mTOR, mechanistic/mammalian target of rapamycin.

a hemithorax. The number of sheets of ORC mesh applied for TPC appeared to influence the subsequent probability of pneumothorax recurrence; TPC with <10 sheets of ORC mesh resulted in a higher probability of pneumothorax recurrence than TPC performed with ≥10 sheets (6). An insufficient number of ORC mesh sheets had been used for TPC in some cases due to insufficient lung lobulation and/or pleural adhesion. Postoperative complication was identified using the Clavien-Dindo classification system (8).

Pulmonary function tests (PFT)

Vital capacity (VC), forced expiratory volume in 1 second (FEV_1), and forced vital capacity (FVC) were measured by spirometry (CHESTAC-8900; Chest M.I. Inc., Tokyo, Japan). Diffusing capacity for carbon monoxide (DLco) was assessed using a single breath method. The reference values obtained from the Japanese Respiratory Society (9) were utilized to calculate the % predicted (pred) values.

Statistical analysis

The Mann-Whitney U-test was used to compare continuous variables (i.e., age and pulmonary function). They were expressed as median (lower; upper quartiles) where appropriate. The probability of pneumothorax recurrence-free hemithorax post TPC was estimated by the Kaplan-Meier method. Log-rank tests were conducted to determine the probability of recurrence-free hemithorax post TPC, both overall and between groups based on the number of ORC sheets used in TPC (≥10 ORC *vs.* <10 ORC). A P value <0.05 was considered statistically significant. All statistical analyses were performed using the software 'EZR,' which is a graphical user interface for R (The R foundation for Statistical Computing) (10).

Ethical statement

This study was approved by the ethics committee of Nissan

Table 1 Characteristics of study participants

Variable	Full sample (N=52 pts/60 hts)	ORC ≥10 group (n=45 pts/52 hts)	ORC <10 group (n=7 pts/8 hts)
Baseline characteristics			
Age at 1st PTX, yr	31.5 (28.0; 36.0)†	32.0 (28.0; 36.0)†	30.5 (28.8; 34.0)†
Age at TPC, yr	33.5 (30.8; 37.0)†	34.0 (30.8; 37.3)†	32.0 (30.8; 34.0)†
Type of LAM			
Sporadic/TSC, # pts	46/6	40/5	6/1
Side of TPC (R/L)	31/29	25/27	6/2
Clinical features after TPC			
Comorbidities, # pts			
Chylothrax‡	4	4	0
Chyloperitoneum‡	2	1	1
Lymphangioma	4	3	1
Present and past smoker, # pts	7	6	1
Recurrence of PTX	12 pts/14 hts	8 pts/9 hts	4 pt/5 hts
Sporadic/TSC, # pts	12/0	8/0	4/0
Period from TPC to PTX recurrence, mths	21 (7; 46.3)†	21 (9.5; 50)†	14 (4.5; 44.5)†
mTORI initiated§	19 pts/23 hts	16 pts/19 hts	3 pts/4 hts
Period from TPC to mTORI initiation, mths	45 (17; 103)	29 (13; 67)	126 (60.8; 144)†

†, presented as median (lower; upper quartiles); ‡, only patients whose effusion was confirmed as chylous were included; §, there was a patient who had received sirolimus prior to her first pneumothorax on the operative side. TPC, total pleural covering; LAM, lymphangioleiomyomatosis; ORC, oxidized regenerated cellulose.

Tamagawa Hospital, Tokyo, Japan (No. 2019-015) and patient consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Patient characteristics

Seventy-four LAM patients (95 hemithoraces) underwent TPC at our center from January 2003 to September 2019. All of them were women, aged 21 to 59 at time of TPC. Twenty-two patients (35 hemithoraces) were excluded from the analyses due to various interventions prior to TPC: bullectomy (20 hemithoraces); TPC at another hospital (2 hemithoraces); surgical pleurodesis (4 hemithoraces); chemical pleurodesis (8 hemithoraces); and an intervention with no detailed information available in the medical chart (1 hemothorax). The remaining 52 eligible patients (60 hemithoraces) were retrospectively evaluated in this study (*Figure 1*). Characteristics of the study sample are shown in *Table 1*. Forty-six patients had been diagnosed with sporadic LAM whereas 6 patients had TSC-associated LAM. The median (lower; upper quartiles) age at TPC was 33.5 (30.8; 37.0) years. Since our previous study demonstrated that the probability of pneumothorax recurrence post TPC was lower among hemithoraces when 10 or more sheets of 3"×4" ORC were applied for TPC (6), the 52 patients (60 hemithoraces) were categorized into 2 groups based on the number of ORC sheets used for TPC: patients with <10 ORC sheets (n=7, 8 hemithoraces) and patients with ≥10 ORC sheets (n=45, 52 hemithoraces) (*Figure 1*). Eventually, 29 patients (35 hemithoraces) were overlapped with those in our previous study (6), while 23 patients (25 hemithoraces) were unique to this study.

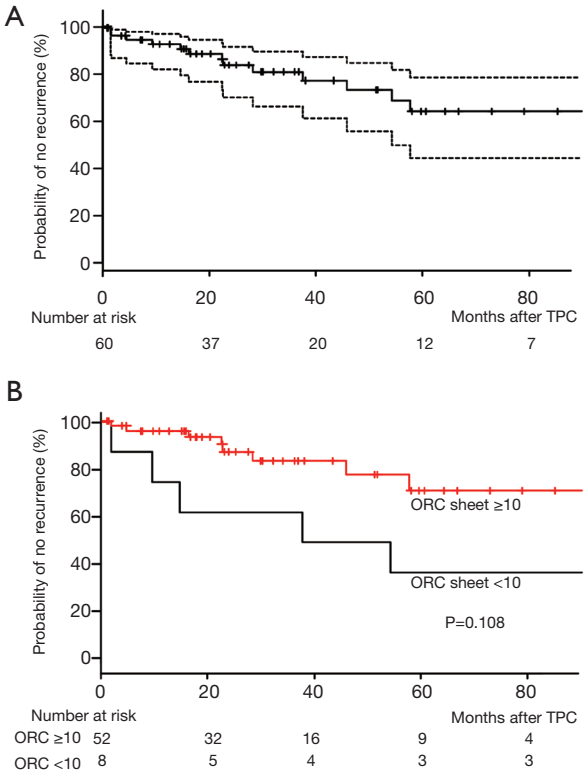

Figure 2 Kaplan-Meier estimate of the probability of recurrence-free hemithorax post TPC. (A) The overall probability of no pneumothorax recurrence among all 60 hemithoraces. Dotted lines show the range of the 95% confidence interval. (B) The probability of no pneumothorax recurrence, comparing hemithoraces in the ORC ≥10 sheets *vs.* ORC <10 sheets groups. The number of subjects being followed at each time interval was provided as number at risk. TPC, total pleural covering; ORC, oxidized regenerated cellulose.

Pneumothorax recurrence post TPC

We found pneumothorax recurrence in 12/46 (26.1%) of the sporadic LAM patients but no recurrence in the 6 TSC-associated LAM patients. The overall recurrence rate based on number of hemithoraces was 14/60 hemithoraces (23.3%) over the median 27-month [14.7; 56.4 (lower; upper quartiles)] observation period (*Table 1*). The overall probability of recurrence-free hemithorax (n=52 patients, 60 hemithoraces), was 81.1% at 2.5 years and 64.1% at 5 years post TPC (*Figure 2A*). The probability of recurrence-free hemithorax post TPC in the ORC ≥10 group (n=45 patients, 52 hemithoraces) was 83.8% at 2.5 years and 71.7% at 5 years, while the probabilities in the ORC <10 group (n=7 patients, 8 hemithoraces) were

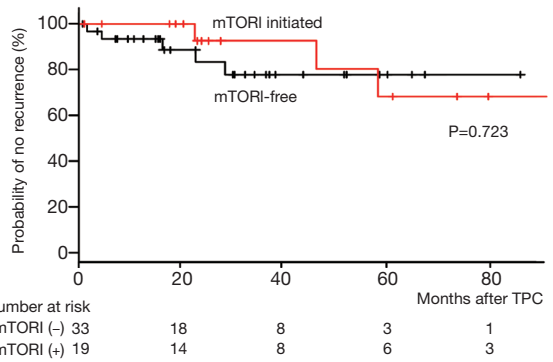

Figure 3 Kaplan-Meier estimate of the probability of recurrence-free hemithorax post TPC in relation to mTORI initiation. Number at risk: the number of subjects being followed at each time interval was provided as number at risk. TPC, total pleural covering; mTORI, mTOR inhibitors.

62.5% and 37.5% respectively at the same time points (*Figure 2B*). No statistically significant difference in the probability of recurrence-free hemithorax post TPC was found between these two groups (P=0.108). Compared to our previous report (6) however, the overall probability of recurrence-free hemithorax post TPC was slightly lower at 5 years in the present study, but still resides within the 95% confidence interval of our previous result (6).

We next calculated the probability of recurrence-free hemithorax post TPC in relation to the potential influence of mTOR inhibitors (mTORI). When we analyzed only the ≥10 ORC sheets group (*Figure 1*), 16 patients (19 hemithoraces) began mTORI treatment post TPC: sirolimus for 15 patients (18 hemithoraces) and everolimus for 1 TSC-associated LAM patient (1 hemithorax). The median time period from the date of TPC to first mTORI prescription date in the ≥10 ORC sheets group was 29 (13; 67) months (*Table 1*). Within the ≥10 ORC sheets group, there was no significant difference in the probability of recurrence-free hemithorax post TPC between patients who initiated mTORI (n=16, 19 hemithoraces) and those who did not (n=29, 33 hemithoraces), P=0.723 (*Figure 3*).

The impact of TPC on the pulmonary function

We investigated the impact of TPC on the pulmonary function of patients who had undergone this procedure. In order to determine the true impact of TPC on pulmonary function, we collected PFT data only from patients who had TPC with ≥10

Table 2 Results of PFTs post TPC in LAM patients with or without prior contralateral interventions

Variable	Group A (9 pts/9hts)	Group B (24 pts/24 hts)	Total (33 pts/33 hts)	P value
Age at 1st PTX, yr	31.0 (29.0; 32.0)	32.5 (28.8; 36.3)	32.0 (29.0; 35.0)	0.209
Age at TPC, yr	34.0 (30.0; 36.0)	34.0 (31.3; 43.3)	34.0 (30.0; 37.0)	0.465
VC (L)	2.50 (2.33; 2.57)	2.66 (2.29; 3.09)	2.57 (2.31; 2.88)	0.342
VC %pred (%)	71.9 (65.8; 81.8)	80.8 (70.1; 93.3)	76.8 (65.8; 85.6)	0.332
FVC (L)	2.38 (2.20; 2.57)	2.64 (2.16; 3.05)	2.50 (2.16; 2.83)	0.266
FVC %pred (%)	72.5 (64.1; 79.5)	82.8 (71.9; 93.0)	79.5 (64.8; 89.8)	0.111
FEV_1 (L)	2.06 (1.52; 2.23)	2.07 (1.78; 2.43)	2.06 (1.75; 2.34)	0.585
FEV_1 %pred (%)	69.8 (50.7; 78.3)	79.8 (61.2; 89.3)	76.2 (60.7; 88.2)	0.309
FEV_1/FVC (%)	78.9 (69.1; 83.0)	83.3 (72.5; 87.6)	82.8 (71.5; 87.5)	0.462
DLco (mL/min/mmHg)†	12.6 (10.8; 15.3)	13.9 (10.8; 16.1)	13.7 (10.8; 16.1)	0.775
DLco %pred (%)†	54.2 (45.6; 65.2)	61.1 (48.1; 69.6)	58.7 (47.1; 69.6)	0.696

Data are presented as median (lower; upper quartiles) values. Group A includes patients who had contralateral interventions prior to TPC whereas Group B had none. As all patients did not have PFTs conducted both pre and post TPC, only post-TPC PFT data were analyzed [33pts (33 hts)]. †, DLco results were available for a total of 27 patients (27 hemithoraces): 8 patients (8 hemithoraces) in Group A and 19 patients (19 hemithoraces) in Group B. The period from TPC to post-TPC spirometry was 20 (6; 30.5) for Group A and 13.5 (4.25; 23.8) months for Group B. PFT, pulmonary function test; TPC, total pleural covering; LAM, lymphangioleiomyomatosis; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; DLco, diffusing capacity for carbon monoxide.

ORC sheets (45 patients, 52 hemithoraces). Additionally, we used only PFT results within 3 years after TPC to minimize the influence of underlying disease progression.

Post-TPC pulmonary function with or without prior contralateral interventions

Table 2 presents PFT results based on the presence or absence of contralateral interventions prior to TPC. Among the 45 patients (52 hemithoraces) in the ≥10 ORC sheets group, post-TPC PFT data were available for 33 patients (33 hemithoraces). The 33 patients and hemithoraces were classified into 2 groups based on their history of prior contralateral interventions: Group A included hemithoraces with contralateral interventions prior to TPC and Group B included hemithoraces without prior contralateral interventions. In Group A, 9 patients (9 hemithoraces) who underwent TPC as a first surgical intervention on the ipsilateral hemithorax, had had various prior interventions on the contralateral side: TPC as a first intervention (n=5); TPC performed after a history of other interventions (n=2); and thoracic surgeries other than TPC (n=2). We compared the results of post-TPC PFTs between Group A and Group B to measure the influence of prior contralateral interventions on pulmonary function.

Group A patients showed lower pulmonary function in all variables than Group B patients, although none of the differences reached statistical significance. The median postoperative VC %pred and FEV_1/FVC in Group B were 80.8% and 83.3% respectively, indicating that TPC did not cause either restrictive or obstructive ventilatory impairment.

Comparison between pre- and post-TPC pulmonary function and the rate of change per year

Among the 24 patients (24 hemithoraces) in Group B, 14 patients (14 hemithoraces) had both pre- and post-TPC PFT data available for analysis. We compared pre- to postoperative pulmonary function for these 14 patients (*Table 3*).

Although both DLco and DLco %pred were mildly to moderately impaired at baseline due to LAM, TPC did not make a statistically significant decrease in various measures of pulmonary function within the postoperative 3 years.

Comparison by mTORI initiation during the postoperative period

The 14 patients (14 hemithoraces) who had both pre- and post-TPC PFT data available for analysis were further classified into 2 groups based on mTORI initiation during the

Table 3 Pre- *vs.* post-TPC comparison of PFT results

Variable	Total (14 pts/14 hts)	P value
Age at 1st PTX, yr	30.5 (27.3; 35.8)	
Age at TPC, yr	33.0 (29.0; 43.8)	
VC (L)		0.566
Pre	2.81 (2.63; 3.63)	
Post	2.88 (2.28; 3.36)	
VC %pred (%)		0.535
Pre	85.7 (79.7; 98.0)	
Post	87.2 (72.3; 95.6)	
FVC (L)		0.603
Pre	2.78 (2.45; 3.63)	
Post	2.79 (2.28; 3.24)	
FVC %pred (%)		0.701
Pre	86.9 (78.4; 106)	
Post	87.1 (74.3; 97.6)	
FEV_1 (L)		0.301
Pre	2.40 (2.01; 2.60)	
Post	2.17 (1.83; 2.47)	
FEV_1 %pred (%)		0.265
Pre	86.8 (77.5; 96.0)	
Post	86.5 (64.9; 88.9)	
FEV_1/FVC (%)		0.667
Pre	84.6 (75.7; 89.6)	
Post	83.0 (71.8; 87.0)	
DLco (mL/min/mmHg)†		0.699
Pre	14.9 (13.0; 18.0)	
Post	14.3 (12.2; 16.4)	
DLco %pred (%)†		0.748
Pre	66.6 (54.7; 78.7)	
Post	64.1 (53.2; 70.8)	

Data are presented as median (lower; upper quartiles) values. †, pre- and post-DLco results were available for 11 patients. The period from spirometry to TPC was 4.0 (0; 10) months whereas the period from TPC to spirometry post TPC was 10 (3.5; 18.5) months. TPC, total pleural covering; PFT, pulmonary function test; LAM, lymphangioleiomyomatosis; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; DLco, diffusing capacity for carbon monoxide.

3-year follow-up period post TPC (*Table 4*). Group C included 6 patients (6 hemithoraces) who had mTORI initiated *vs.* Group D with 8 patients (8 hemithoraces) who did not. We compared the PFT results pre and post TPC between these 2 groups. In Group C patients, the postoperative PFT results closest to mTORI initiation were analyzed.

Group C patients tended to have lower preoperative DLco %pred values than Group D patients (P=0.082). This suggests that patients in Group C were in a more advanced stage of LAM than Group D patients prior to TPC. In addition, postoperative FEV_1/FVC tended to be lower in Group C than in Group D, P=0.059. Notably, postoperative FEV_1 %pred (P=0.020) as well as the rate of change per year in FEV_1 %pred (P=0.029) were significantly lower in Group C than in Group D (*Table 4*).

Pulmonary function after bilateral TPC

Seven patients underwent bilateral TPCs at different times as the first surgical treatment for pneumothorax on each hemithorax. PFTs were performed after the 2nd TPC in 5 of 7 patients and the median period from the 2nd TPC to spirometry was 9 (2; 18) months. As shown in *Table 5*, moderate degrees of restrictive ventilatory impairment and decreased diffusing capacity were present.

Postoperative complications

Postoperative complications occurred in 25 of 52 hemithoraces (48.1%); Grade II, 14 hemithoraces (26.9%), Grade IIIa, 10 hemithoraces (19.2%), and Grade IIIb, a hemithorax (0.2%). The most frequent complications were prolonged postoperative air leak (n=13) defined as persistent air leak beyond 7 days, under Grade II, accounted for 52.0% of all complications. Grade IIIb complication occurred in the patient with dense pleural adhesion at the time of TPC, requiring reoperation at postoperative day 2 to control bleeding.

Discussion

This retrospective study focused on the effects of TPC in relation to the prevention of pneumothorax recurrence and postoperative lung function in LAM patients with no history of thoracic surgeries and/or pleurodesis. Unexpectedly, regardless of the number of ORC sheets applied for TPC,

Table 4 Comparison of PFTs between LAM patients with or without mTORI treatment

Variable	Group C (6 pts/6 hts)	Change per year (%pred or %)	Group D (8 pts/8 hts)	Change per year (%pred or %)	P value
Age at 1st PTX, yr	32.0 (27.5; 35.8)		30.5 (27.8; 34.3)		
Age at TPC, yr	32.5 (29.0; 41.3)		33.0 (31.3; 44.3)		
VC (L)					
Pre	2.74 (2.63; 3.28)		2.93 (2.53; 3.70)		0.950
Post	2.70 (2.31; 3.17)		2.97 (2.34; 3.47)		0.605
VC %pred (%)					
Pre	89.0 (84.0; 96.1)	–5.66 (–2.40; –8.65)	83.7 (78.3; 101)	–2.11 (0.40; –5.57)	0.852
Post	86.8 (67.0; 93.5)		87.4 (73.5; 97.1)		0.605
FVC (L)					
Pre	2.70 (2.58; 3.43)		2.89 (2.41; 3.60)		1.000
Post	2.62 (2.31; 3.03)		2.93 (2.34; 3.39)		0.491
FVC %pred (%)					
Pre	88.8 (77.0; 103)	–7.66 (–2.32; –9.43)	83.6 (79.0; 104)	0.69 (5.00; –3.10)	1.000
Post	86.6 (69.4; 91.9)		89.3 (76.4; 106)		0.414
FEV_1 (L)					
Pre	2.15 (2.04; 2.33)		2.50 (2.33; 2.71)		0.282
Post	1.89 (1.62; 2.10)		2.32 (2.12; 2.57)		0.106
FEV_1 %pred (%)					
Pre	80.0 (69.6; 93.5)	–9.37‡ (–4.73; –12.9)	90.6 (82.9; 94.9)	–1.94 (1.52; –4.50)	0.491
Post	68.1 (57.3; 82.9)		88.7 (84.6; 89.8)		0.020
FEV_1/FVC (%)					
Pre	78.9 (60.6; 86.7)	–2.52 (–1.21; –4.06)	87.6 (80.7; 89.9)	0.29 (0.49; –1.21)	0.282
Post	76.2 (53.4; 82.2)		85.4 (80.6; 90.3)		0.059
DLco (mL/min/mmHg)†					
Pre	12.0 (7.86; 14.9)		16.3 (14.6; 18.3)		0.177
Post	11.6 (8.44; 14.7)		15.9 (13.8; 16.9)		0.230
DLco %pred (%)†					
Pre	50.7 (35.9; 66.6)	–5.15 (–2.96; –5.84)	73.0 (65.3; 78.8)	–4.96 (–2.15; –5.71)	0.082
Post	36.3 (34.4; 55.8)		68.8 (57.5; 73.2)		0.164

Data are presented as median (lower; upper quartiles) values. Group C received mTORI treatment post-TPC [n=10 (10 hts)] and Group D did not [n=14 (14hts)]. Both pre- and post-TPC PFT data were available for 6 pts (6 hts) in Group C and 8 pts (8 hts) in Group D. †, DLco results were available for 3 patients in Group C and 6 patients in Group D; ‡, change in FEV1 %pred (%) per year was significantly greater in Group C than in Group D (P=0.029). The period of months from spirometry to TPC was 4.5 (1.25; 10) and 1 (0; 5) for Groups C and D, respectively, and from TPC to spirometry was 13 (5.25; 27.5) and 17 (8.75; 20.8) for Groups C and D, respectively. PFT, pulmonary function test; mTORI, mTOR inhibitors; LAM, lymphangioleiomyomatosis; TPC, total pleural covering; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; DLco, diffusing capacity for carbon monoxide.

Table 5 PFT results post bilateral TPC

Pulmonary function	After bilateral TPC (n=5)
VC (L)	2.34 (2.33; 2.57)
VC %pred (%)	69.3 (64.7; 75.5)
FVC (L)	2.23 (2.20; 2.38)
FVC %pred (%)	64.7 (64.1; 72.5)
FEV_1 (L)	2.06 (1.52; 2.21)
FEV_1 %pred (%)	69.8 (50.7; 78.1)
FEV_1/FVC (%)	76.3 (69.1; 82.2)
DLco (mL/min/mmHg)[†]	12.9 (9.9; 15.6)
DLco %pred (%)[†]	54.2 (41.9; 65.2)

Data are presented as median (lower; upper quartiles) values. Post-bilateral TPC PFT data were available for analysis in 5 LAM patients (5 hemithoraces). [†], DLco results were available for 4 patients. PFT, pulmonary function test; TPC, total pleural covering; LAM, lymphangioleiomyomatosis; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; DLco, diffusing capacity for carbon monoxide.

the probability of recurrence-free hemithorax was slightly lower than the results of our previous analysis, which included TPC outcomes in LAM patients with focal or scattered pleural symphysis (6). One of the possible reasons for this result might be that thoracic surgeons changed during the research period. Six thoracic surgeons conducted TPC under the supervision of the inventor (MK) of TPC. All of them were experienced thoracic surgeons, but 5 had few experiences with thoracic surgery of LAM lungs and 4 had almost no experience performing TPC before joining our hospital. Actually, there are a couple of important checkpoints at which surgeons' skills would influence the total number of ORC sheets used for TPC and the finish of TPC, i.e., whether the entire surface of the lung is fully enclosed by ORC sheets. First, surgeons need to decide the degrees of crinkle of each ORC sheet as well as of the overlap between the adjoining two ORC sheets when applied for the mildly deflated lung surface; the surgeons have to image the lung surface remains entirely wrapped by ORC sheets even after the lung fully expand. Second, they need to decide which orientation of ORC sheet is appropriate to affix to the lung surface place by place. Third, how much fibrin glue should be dropped after the entire lung surface is wrapped. It is true that to assess all these checkpoints is especially challenging to surgeons in training. Another reason may be the retrospective design of our studies that might have produced variability across the 2 studies.

The probability of recurrence-free hemithorax post TPC regardless of the number of ORC sheets used was almost identical in both studies at 2.5 years (80.8% in our previous study *vs.* 81.1% in this study), and at 5 years the probability still resided within the 95% confidence interval of the probability found in our previous study (6). The slightly lower recurrence-free probability in the period >2.5 years might reflect the characteristics of this study population, particularly the severity of underlying LAM.

Gonano *et al.* (11) recently reported the probability of recurrence-free hemithorax after surgical or chemical pleurodesis was 68% at 5 years, which is slightly higher than that of TPC (64.1%). But still, we are certain of the advantage and superiority of TPC because TPC is free from severe pleural symphysis even if it developed, in contrast with surgical or chemical pleurodesis. Severe pleural adhesions cause difficulty in dissociating the lung from thoracic wall in the subsequent thoracic surgery and even have a risk of massive hemorrhage at lung transplantation. Furthermore, pleurodesis usually results in patchy pleural adhesions rather than uniform pleural adhesion throughout the entire hemothorax. Once pneumothorax recurs in this condition, patchy and severe pleural adhesions make a subsequent treatment very difficult, and then frequently results in the chronic pneumothorax which may profoundly impair lung function. The risk of chronic pneumothorax is apparently more problematic after pleurodesis than TPC, especially in the cystic lung disease with progressive nature and propensity of recurring pneumothorax, just like LAM.

Compared to both the full sample and the ORC ≥10 sheets group, the pneumothorax recurrence-free probability in LAM patients who had TPC with ORC <10 sheets was markedly higher than the result in our previous report (6). This may be because we excluded the influence of thoracic interventions prior to TPC, which usually cause severe pleural adhesions and hamper the procedure and efficacy of TPC. In this study, no statistically significant difference was found in the recurrence-free probability post TPC between the ORC ≥10 sheets and ORC <10 sheets groups. This is likely due to the small number of LAM patients in the ORC <10 sheets group [7 patients (8 hemothoraces) *vs.* 45 patients (52 hemothoraces) in the ORC ≥10 sheets group]. We examined the reasons for the fewer number of ORC sheets applied on the 7 patients (8 hemithoraces) and discovered that pleural adhesions due to a repeated pneumothorax were observed only in 2 hemithoraces whereas the remaining

6 hemithoraces were free from pleural adhesions. We found that these 6 hemithoraces underwent TPC between the years 2003 and 2007, a time period during which our TPC technique had not yet been established. Accordingly, this result may indicate that postoperative pneumothorax recurrences are not influenced simply by the number of ORC sheets utilized for TPC, if TPC is performed on hemithoraces with no severe pleural adhesions.

TPC is inherently prone to cause a restrictive ventilatory impairment since it will make the visceral pleura 3–9 times thicker (12). In order to understand the true impact of TPC on lung function, we analyzed postoperative lung function only in LAM patients whose ipsilateral hemithoraces had no history of thoracic surgeries and/or pleurodesis. Additionally, we carefully evaluated the influence of contralateral interventions on pulmonary function in the LAM patients who had already received some interventions on a contralateral hemithorax. We then found that unilateral TPC showed a marginal impact on VC %pred and FVC %pred whereas bilateral TPC caused a moderate degree of restrictive ventilatory impairment. Since there is a trade-off between the lower frequency of pneumothorax recurrence by reinforcement of visceral pleura and the loss of pulmonary function, the lung function impairment after bilateral TPC could still be acceptable.

TPC is an intervention to the pleura, and thus would not prevent the development of parenchymal cysts. Therefore, mTORI has been prescribed to LAM patients in case they need to stabilize pulmonary function after TPC. The ATS/JRS clinical practice guideline recommends prescribing sirolimus if LAM patients have abnormal lung function defined as FEV1 <70%pred or progressively declining FEV1 (13). Because of impaired or declining lung function during the subsequent period post TPC, 18 out of the 52 LAM patients were given sirolimus and 1 TSC-associated LAM patient was given everolimus. Indeed, LAM patients who initiated sirolimus or everolimus (Group C) post TPC tended to have lower preoperative DLco %pred compared to LAM patients who had been free of mTORI (Group D). Additionally, both FEV1 %pred and the rate of change per year in FEV1 %pred became significantly lower in Group C than in Group D. Therefore, LAM patients who required mTORI after TPC are likely to suffer from more progressive LAM.

Although the effect of sirolimus on the recurrence of pneumothorax remains unknown, no significant difference found in the postoperative recurrence-free probability may imply that mTORI prevents pneumothorax recurrence in patients with progressive LAM. Zhou *et al.* (14) reported a similar observation that 5 LAM patients who had experienced repeat episodes of pneumothorax showed no recurrence after initiation of sirolimus therapy. However, further study is needed to determine if sirolimus prevents pneumothorax recurrence because we have treated 3 LAM patients who developed pneumothorax while taking sirolimus (being on sirolimus for 3, 5, and 7 years, respectively) (unpublished data).

TPC could therefore be an effective alternative to control LAM-associated pneumothorax recurrence. The British Thoracic Society guideline for the management of spontaneous pneumothorax recommends simple aspiration and/or small-bore chest tube drainage, depending on the size of pneumothorax, which are both less invasive and less likely to cause severe pleural adhesions (15). TPC could be a useful treatment option for LAM patients who have undergone simple aspiration and/or small-bore chest tube drainage which failed to cure pneumothorax in terms of lower recurrence rate, low morbidity, and not producing severe pleural symphysis. The current ATS/JRS guideline on LAM diagnosis and management suggests that LAM patients be offered ipsilateral pleurodesis after their initial pneumothorax, placing greater value on reduction in morbidity and the costs associated with a recurrent pneumothorax than on the adverse effects of pleurodesis (4). However, the gradual popularization of TPC and its successful applications for intractable pneumothorax resulting from conditions other than LAM (16-20) as well as the use of mTORI, are expected to change future recommendations for the management of LAM-associated pneumothorax to focus on the efficacy of lowering recurrence, safety, and no pleural symphysis.

Our study had several limitations. First, this was a retrospective study performed in a single hospital. The study sample size is relatively small, but we still believe our findings are noteworthy given the rarity of LAM. Second, not all the patients underwent PFTs both pre and post TPC, and therefore a limited amount of PFT data were available for analysis. Third, the remote effects of thickened visceral pleura on pulmonary function and patients' activity remain unknown. To this end, a longer observation period is necessary, but this would be compromised by the progression of underlying LAM.

Conclusions

We conclude that TPC effectively reduce pneumothorax recurrence without causing ventilatory impairment or pleural adhesion in LAM patients. Our results suggest that

TPC is an effective treatment option for LAM-associated pneumothorax in terms of the prevention of pneumothorax recurrence and the impact on pulmonary function.

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