Original Article

Lung autotransplantation for advanced central lung cancer after neoadjuvant immuno-chemotherapy: a case series study

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Background: For locally advanced central lung cancer, lung autotransplantation allows for complete tumor resection while maximizing the preservation of lung parenchyma. Neoadjuvant chemotherapy combined with immunotherapy has shown benefits for patients with advanced lung cancer, providing longer progression-free survival compared to chemotherapy alone. This study aims to evaluate the feasibility and safety of neoadjuvant immuno-chemotherapy followed by lung autotransplantation in the treatment of locally advanced central non-small cell lung cancer (NSCLC).

Methods: We retrospectively analyzed ten patients with central NSCLC who underwent lung autotransplantation after neoadjuvant immuno-chemotherapy from June 2019 to December 2023. Of the grafts, there was 1 right upper lobe, 3 right lower lobe, 1 left lower lobe, 5 basal segments (3 right and 2 left). Nine cases were performed *ex situ* except one *in situ* without graft perfusion. All patients were followed up regularly.

Results: Ten cases received neoadjuvant immuno-chemotherapy [programmed cell death protein 1 (PD-1) inhibitor combined with platinum plus paclitaxel], the average number of cycles was 2.3±0.5 cycles, and the average interval between neoadjuvant therapy and surgery was 35.0±13.3 days. Following treatment, there was 1 complete response (CR), 6 partial responses (PRs), and 3 stable diseases (SDs). All cases achieved R0 resection, with 6 cases attaining complete pathological remission (CPR) and 2 cases exhibiting major pathological remission (MPR). No operative death occurred within 30 days. Six cases developed perioperative complications, with five cases being mild to moderate in severity, all of which recovered after standardized treatment. Only one instance of severe pulmonary artery embolism was observed, which improved with systemic anticoagulation therapy. The median follow-up time was 9.5 (range, 1.1–54.2) months. One patient had 4R lymph node recurrence (improved after radiotherapy and immunotherapy), and seven patients survived without recurrence.

Conclusions: Lung autotransplantation for advanced central NSCLC after neoadjuvant immuno-chemotherapy is feasible and safe, with maximal preservation of lung function and a high rate of R0 resection. This also demonstrates the advantages of organ preservation strategies. The procedure can be

technically challenging, but lethal complications are uncommon. Overall, outcomes are satisfactory, and patients achieved reasonable survival during the follow-up period.

Keywords: Lung autotransplantation; lung cancer; neoadjuvant immuno-chemotherapy; prognosis; case series

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Introduction

Lung cancer is the leading cause of cancer-related death, with non–small cell lung cancer (NSCLC) accounting for 85% of these cases (1,2). Central NSCLC is usually discovered at an advanced stage, so most patients lose the opportunity for surgery and thus have an extremely poor prognosis. Since Graham and Singer reported the first case of pneumonectomy in 1933 and Thomas reported the first case of sleeve lobectomy in 1947 (3,4), these two surgical methods have gradually become common surgical interventions for the treatment of locally advanced central NSCLC. Pneumonectomy is closely associated with high postoperative morbidity and mortality, but some patients are unable to undergo pneumonectomy due to poor pulmonary function. With the advancement of surgical techniques, sleeve and extended sleeve lobectomy now represent a more suitable approach for central NSCLC, which allows pneumonectomy to be avoided and thus facilitates greater preservation of pulmonary function (5,6).

Although sleeve and extended sleeve lobectomy address the limitation of pneumonectomy, radical resection for central NSCLC with extensive invasion of the main bronchus and pulmonary artery is difficult to perform with these methods. Consequently, the preferred approach for these patients is comprehensive treatment, mainly including chemotherapy, targeted therapy, and immunotherapy. In some patients with central NSCLC, the tumor and its invasive zone regress, and a second chance for radical resection is possible after neoadjuvant treatment (7). However, toward ensuring a negative surgical margin, anastomosis of the bronchus and pulmonary vessels is not possible due to excessive tension. In such cases, lung autotransplantation is a suitable alternative, providing complete resection of the tumor and maximal preservation of pulmonary function. In addition, the emergence of neoadjuvant immunotherapy has improved the survival prognosis of patients with NSCLC.

The feasibility and safety of lung autotransplantation for treating locally advanced central NSCLC following neoadjuvant immuno-chemotherapy remain unclear. To date, few case reports have been documented with a small number of patients related to this condition, offering only limited information. This study aimed to evaluate the feasibility and safety of lung autotransplantation for advanced central NSCLC after neoadjuvant immuno-chemotherapy. We present this article in accordance with the STROBE and AME Case Series reporting checklists (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-501/rc).

Highlight box

Key findings

- Lung autotransplantation following neoadjuvant immuno-chemotherapy for the treatment of advanced central non-small cell lung cancer (NSCLC) is feasible, safe, and associated with survival benefits.

What is known and what is new?

- The emergence of neoadjuvant immuno-chemotherapy has improved the survival prognosis of patients with advanced central NSCLC. Lung autotransplantation is an alternative technique for patients who cannot undergo pneumonectomy or extended sleeve resection.
- In this study, lung autotransplantation for advanced central NSCLC after neoadjuvant immuno-chemotherapy is feasible and safe, with maximal preservation of lung function and a high rate of R0 resection. Patients achieved reasonable survival during the follow-up period.

What is the implication, and what should change now?

- Since our study demonstrated low complications, reasonable survival and the advantages of organ preservation strategies, lung autotransplantation after neoadjuvant immuno-chemotherapy for advanced central NSCLC is an appropriate treatment option for patients who cannot undergo pneumonectomy or extended sleeve resection.

Methods

Study design

This study was a multicenter nonconsecutive retrospective case series study. The study was approved by the Ethics Committees of the First Affiliated Hospital of Guangzhou Medical University with an approval of No. 22 (ID: 443-3645) in 2022, the Shanghai General Hospital Affiliated to Shanghai Jiao Tong University School of Medicine with an approval of No. 034227387 in 2024, the First Affiliated Hospital of Zhejiang University School of Medicine with an approval of No. PRO20230117, and the Liaoning Cancer Hospital & Institute with an approval of No. 202205128, and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients

Ten patients who underwent lung autotransplantation from four centers from June 2019 to December 2023 were reviewed, including the First Affiliated Hospital of Guangzhou Medical University, the Shanghai General Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, the First Affiliated Hospital of Zhejiang University School of Medicine and the Liaoning Cancer Hospital & Institute. All patients underwent computed tomography (CT) and positron emission tomography-computed tomography (PET/CT) scans followed by bronchoscopy biopsy and were diagnosed with locally advanced central NSCLC. Before surgery, the ten patients received neoadjuvant immuno-chemotherapy. The treatment regimen was programmed cell death protein 1 (PD-1) inhibitor (nivolumab, sintilimab, toripalimab or pembrolizumab) combined with platinum (carboplatin, cisplatin or nedaplatin) plus paclitaxel. Tumor response assessment after neoadjuvant therapy was based on the Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1. The relevant clinical and pathological data were reviewed to extract data on demographics, clinical Tumor, Node, Metastasis (TNM) stage, tumor location, preoperative neoadjuvant therapy, pathology, surgery, complications, postoperative treatment and follow-up outcomes. The detailed information of the patients was demonstrated in *Table 1*.

Procedure

Seven patients were subjected to thoracotomy through a lateral approach, whereas three patients received hybrid video-assisted thoracoscopic surgery (VATS) utilizing a lateral approach. Among the grafts, one case involved the right upper lobe, three cases the right lower lobe, one case the left lower lobe, and five cases the basal segment, including three cases of the right basal segment and two cases of the left basal segment. All were supported without venoarterial extracorporeal membrane oxygen (ECMO) or cardiopulmonary bypass (CPB). Among the procedures performed in these ten cases, nine cases were performed *ex situ* and one *in situ* without graft perfusion.

After trimming and perfusion was completed (Perfadex solution), the graft was implanted in the chest cavity. The venous and arterial anastomoses are detailed in *Table 2* (*Figure 1*). Right middle and upper lobectomy was performed in case 4. After systemic heparinization (1 mg/kg), the pulmonary artery and vein of the graft were clamped and disconnected, which was followed by trimming *in situ* without perfusion. Venous anastomosis was completed between the inferior pulmonary vein of the graft and the stump of the superior pulmonary vein, and the right basal segmental pulmonary artery was anastomosed to the right superior lobe apical and anterior segmental artery. End-to-end vascular anastomosis was completed continuously with 5-0 Prolene suture.

For airway reconstruction, end-to-end anastomosis of the bronchus and main bronchus stump was performed in eight cases (*Figure 1*), and end-to-side anastomosis of the basal segmental bronchus and tracheal side wall was performed in two cases (*Table 2*). The end-to-end anastomosis of the graft bronchus and the main bronchus was completed continuously using double-ended 3-0 Prolene suture. End-to-side anastomosis was performed using double-ended 4-0 Prolene suture in cases 2 and 4 for both the right basal segmental bronchus and the lateral wall of the trachea.

A lateral tracheal fenestration was performed above the level of the carina using an aortic punch. The size of the tracheal opening was at least 1.0 to 1.5 cm^2, and the opening was entirely on the cartilaginous wall of the trachea or partially included the edge between the cartilaginous and membranous walls (8,9). The bronchus of the graft and tracheal lateral wall were anastomosed using the parachute principle. A double-ended 4-0 Prolene suture was threaded through the cartilage wall of the graft bronchus. Firstly, continuous sutures were placed on the cartilaginous margin and tightened using a nerve hook to invert the airway mucosa. The remaining margin of the membrane wall was then closed with the same suture to allow for adjustment

Table 1 The profile of patients with locally advanced central non-small cell lung cancer who received lung autotransplantation after neoadjuvant immuno-chemotherapy

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Mean ± SD/median (range)
Sex	Male	Male	Female	Male	Male	Male	Male	Male	Male	Male	–
Age (years)	74	62	59	48	73	64	60	56	58	69	62.3±7.6
Histology	Sq	Sq	Ly	Sq	Sq	Sq	Sq	Sq	Sq	Sq	–
cTNM	T2bN2M0	T4N3M0	T2bN2M0	T2bN2M1	T2bN1M0	T4N1M0	T4N2M0	T4N0M0	T4N2M0	T4N0M0	–
cStage	IIIA	IIIC	IIIA	IIIA	IIB	IIIA	IIIB	IIIA	IIIB	IIIA	–
Location	RLL	RUL	LUL	RML	RUL	LUL	RUL	LUL	RUL	RUL	–
Neoadjuvant immunotherapy plus chemotherapy	CBP + PTX + pembrolizumab	CBP + PTX + nivolumab	CBP + PTX + nivolumab	CBP + PTX + nivolumab	NDP + PTX + nivolumab	CBP + PTX + sintilimab	CBP + PTX + sintilimab	CBP + PTX + sintilimab	CDDP + PTX + toripalimab	CBP + PTX + sintilimab	–
Cycle	3	2	3	2	2	2	2	2	3	2	2.3±0.5
Response	CR	PR	PR	PR	SD	PR	PR	SD	PR	SD	–
Interval (days)	24	40	64	36	35	25	21	52	31	22	35.0±13.3
Operation duration (minutes)	393	460	435	505	620	245	285	240	350	420	395.3±113.9
Blood loss (mL)	100	150	200	800	200	50	100	100	50	800	255.0±277.0
Margin	R0	R0	R0	R0	R0	R0	R0	R0	R0	R0	–
Pathological evaluation	CPR	CPR	50% residual viable tumor cells	CPR	CPR	CPR	10% residual viable tumor cells; mediastinal lymph node metastasis	MPR	MPR	CPR	–
ICU stay (days)	1	7	2	5	N	1	1	2	1	1	2.3±2.1
Respiratory support (days)	1	6	N	2	N	N	N	N	N	N	3.0±2.2
Drainage tube stay (days)	5	10	7	10	5	6	18	7	12	30	11.0±7.4
Postoperative hospitalization (days)	8	15	8	11	13	7	19	8	13	34	13.6±7.7
Perioperative mortality	N	N	N	N	N	N	N	N	N	N	–
Perioperative morbidity	Pulmonary artery embolism	Type I respiratory failure	N	Type I respiratory failure	N	N	Pneumonia	Atrial fibrillation	N	Pneumonia	–
Complication grading: mild, moderate, or severe	Severe	Mild	–	Mild	–	–	Moderate	Mild	–	Moderate	–
Vascular/airway anastomotic complications	N	N	N	N	N	N	N	N	N	N	–
Adjuvant therapy	N	CBP + PTX + nivolumab	CBP + PTX + nivolumab	CBP + PTX	NDP + PTX	CBP + PTX + sintilimab	N	CBP + PTX + sintilimab	CDDP + PTX + toripalimab	N	–
Local recurrence	N	N	4R lymph nodes	N	N	N	N	N	N	N	–
Distant recurrence	N	N	N	N	N	N	N	N	N	N	–
Treatment to recurrence	–	–	Radiotherapy + immunotherapy	–	–	–	–	–	–	–	–
Recurrence free survival (months)	23.8	10.8	9.5	54.2	1.6	9.6	1.1	9.4	3.8	4.5	9.5 (1.1–54.2)
Follow up duration (months)	23.8	10.8	19.2	54.2	1.6	9.6	1.1	9.4	3.8	4.5	9.5 (1.1–54.2)
Status	Alive	Alive	Alive	Alive	Deceased	Alive	Deceased	Alive	Alive	Alive	–

SD, standard deviation; Sq, squamous cell carcinoma; Ly, lymphoepithelial carcinoma; cTNM, clinical Tumor, Node, Metastasis; CBP, carboplatin; CDDP, cisplatin; PTX, paclitaxel; NDP, nedaplatin; CR, complete response; PR, partial response; SD, stable disease; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; RML, right middle lobe; ICU, intensive care unit; CPR, complete pathological remission; MPR, major pathological response; N, none.

Table 2 The operation details on patients with lung autotransplantation

Operation details	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Surgical approach	Lateral approach	Hybrid VATS—lateral approach	Hybrid VATS—lateral approach	Hybrid VATS—lateral approach	Lateral approach	Lateral approach	Lateral approach	Lateral approach	Lateral approach	Lateral approach
Re-implanted lung	RUL	Right basal segment	Left basal segment	Right basal segment	RLL	Left basal segment	Right basal segment	LLL	RLL	RLL
Ex situ/in situ	*Ex situ*	*Ex situ*	*Ex situ*	*In situ*	*Ex situ*	*Ex situ*	*Ex situ*	*Ex situ*	*Ex situ*	*Ex situ*
Warm ischemia time (min)	90	95	78	–	85	107	116	89	99	109
Venous anastomosis	Right superior pulmonary vein—left atrial cuff	Right inferior pulmonary vein—right superior pulmonary vein	Left inferior pulmonary vein—left superior pulmonary vein	Right inferior pulmonary vein—right superior pulmonary vein	Right inferior pulmonary vein—right superior pulmonary vein	Left inferior pulmonary vein—left atrium	Right inferior pulmonary vein—left atrium	Left inferior pulmonary vein—left superior pulmonary vein	Right inferior pulmonary vein—left atrium	Right inferior pulmonary vein—left atrium
Arterial anastomosis	Right superior pulmonary artery—right pulmonary trunk	Right basal segmental pulmonary artery—right superior lobe apical and anterior segmental artery	Left basal segmental pulmonary artery—left pulmonary trunk	Right basal segmental pulmonary artery—right superior lobe apical and anterior segmental artery	Right inferior pulmonary artery—right pulmonary trunk	Left inferior pulmonary artery—left pulmonary trunk	Right inferior pulmonary artery—right pulmonary trunk	Left inferior pulmonary artery—left pulmonary trunk	Right inferior pulmonary artery—right pulmonary trunk	Right inferior pulmonary artery—right pulmonary trunk
Airway reconstruction	Right upper lobe bronchus—right main bronchus	Right basal segmental bronchus—lateral wall of the trachea	Left basal segmental bronchus—left main bronchus	Right basal segmental bronchus—lateral wall of the trachea	Right lower lobe bronchus—right main bronchus	Left basal segmental bronchus—left main bronchus	Right basal segmental bronchus—right main bronchus	Left lower lobe bronchus—left main bronchus	Right lower lobe bronchus—right main bronchus	Right lower lobe bronchus—right main bronchus

VATS, video-assisted thoracoscopic surgery; RUL, right upper lobe; RLL, right lower lobe; LLL, left lower lobe.

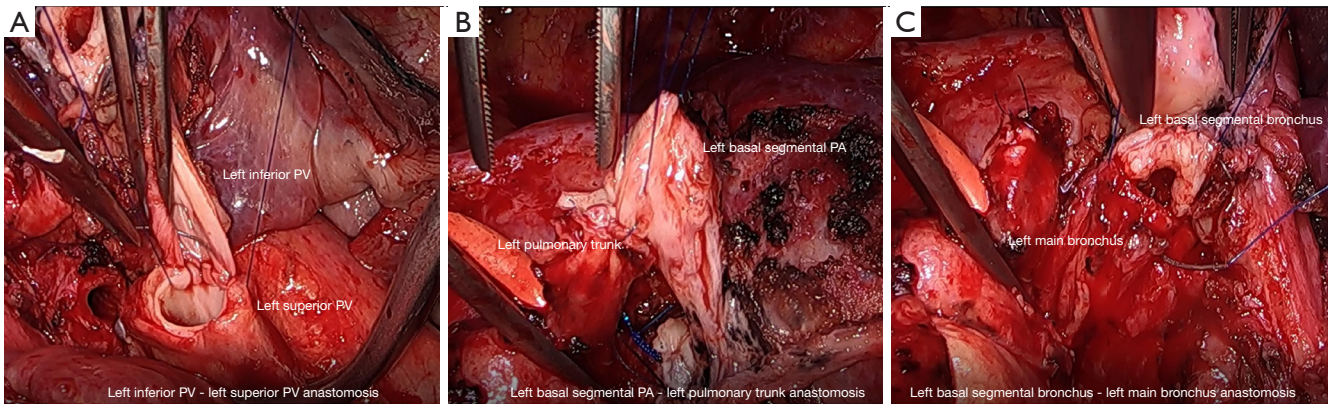

Figure 1 The reconstruction procedure of case 3. (A) Anastomosis of left inferior PV to left superior PV. (B) Anastomosis of left basal segmental PA to left pulmonary trunk. (C) Left basal segmental bronchus and left main bronchus end-to-end anastomosis. PA, pulmonary artery; PV, pulmonary vein.

of the anastomosis and thus prevent imbalance or excessive traction (8). All knots were tied on the outside of the airway. After the anastomosis was completed, an air leak test was performed on the anastomosis with a test pressure of up to 35 mmHg to ensure that there was no air leakage. Finally, the mediastinal pleura was used to cover around the anastomosis.

Follow-up and recurrence

Patients were followed up by telephone, mobile phone, or email every 2 months after surgery to check their condition. At the discretion of the attending physician, patients were scheduled to receive routine bronchoscopy and CT or PET/CT scans every 3 to 6 months postoperatively. Recurrence was determined by the attending physician based on bronchoscopic, radiographic, or pathological examination. Progression-free survival (PFS) is defined as the length of time from surgery until the first recurrence of the tumor. Overall survival (also referred to as follow-up) is defined as the length of time from surgery until the patient's death from any cause.

Statistical analysis

SPSS 25.0 (IBM Corp, Armonk, NY, USA) was used for data processing. Data that fit a normal distribution were expressed as the mean ± standard deviation, and data that fit a nonnormal distribution were presented as the median with range.

Results

From June 2019 to December 2023, ten patients with advanced central NSCLC underwent lung autotransplantation (*Table 1*). All patients received transbronchial biopsy and were diagnosed with malignant tumors. Except for one patient with lymphoepithelial carcinoma, all patients had squamous cell carcinoma and a long history of smoking. The clinical TNM stages of the tumors ranged from IIB to IIIC. All cases received neoadjuvant immuno-chemotherapy before surgery. The average number of cycles was 2.3±0.5 cycles, and the average interval between neoadjuvant treatment and surgery was 35.0±13.3 days. Following treatment, one patient (10%) achieved a complete response (CR), six patients (60%) achieved a partial response (PR), and three patients (30%) achieved a stable disease (SD) according to RECIST v. 1.1 (*Figure 1*).

The operation duration was 395.3±113.9 minutes, and the blood loss was 255.0±277.0 mL. The *ex situ* warm ischemia time was 96.4±11.7 minutes for 9 cases. Four patients underwent intraoperative blood transfusion, mainly red blood cell suspension and frozen plasma. All patients had negative surgical margins (R0), with six achieving complete pathological remission (CPR) and two achieving major pathological remission (MPR) according to the final pathological evaluation. The remaining two cases had poor outcomes, with one case having approximately 50% residual viable tumor cells and the other case having about 10% residual viable tumor cells along with mediastinal lymph

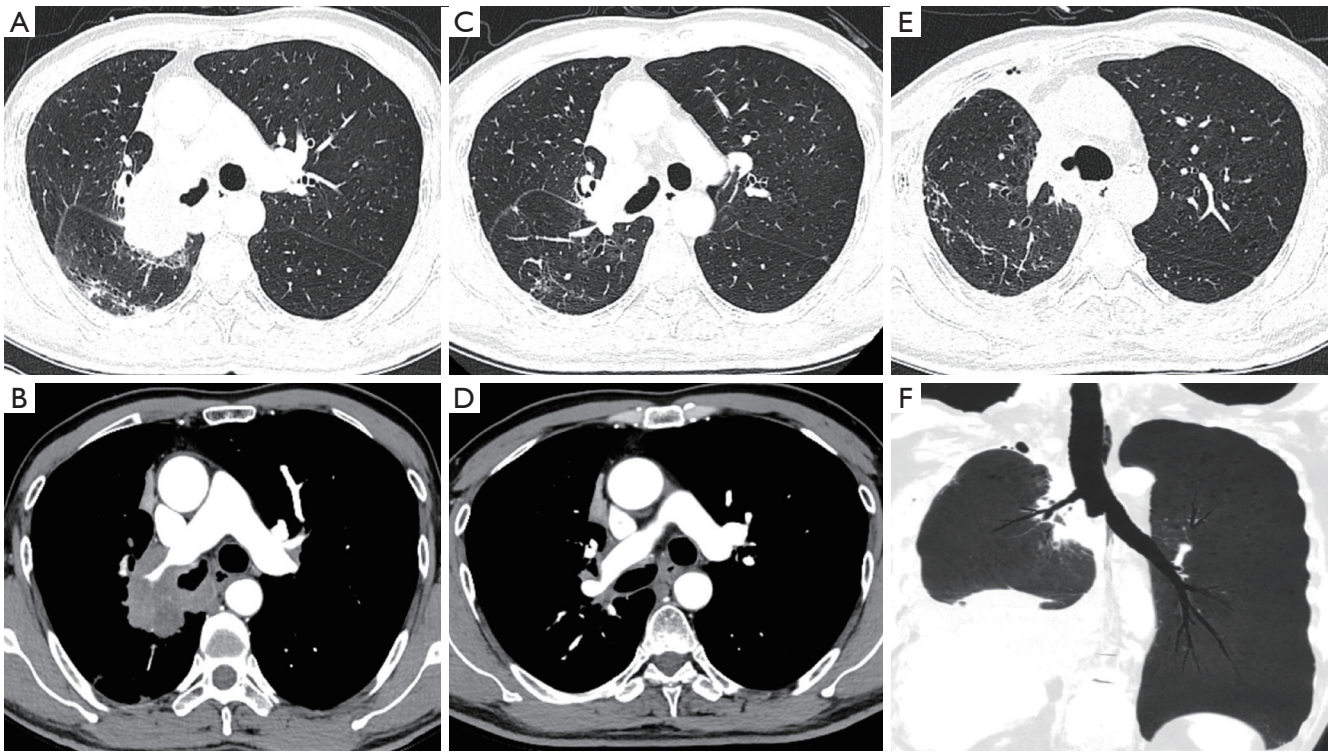

Figure 2 Comparison of the patient before and after neoadjuvant therapy in this study. Before neoadjuvant treatment, CT images revealed a tumor in the right upper lobe, associated with atelectasis, as well as metastasis to bilateral hilar and mediastinal lymph nodes. The tumor also exhibited invasion into the pulmonary arteries and veins (A,B). Following neoadjuvant therapy, subsequent CT scan demonstrated a reduction in the sizes of tumor and hilar and mediastinal lymph node metastases. Additionally, there was an improvement in the invasion of the tumor into the pulmonary vessels (C,D). Postoperative CT scans showed a well-inflated transplanted lung, and the reconstructed airway displayed patent conditions without stenosis (E,F). CT, computed tomography.

node metastasis. Nine patients were transferred to the department of critical care medicine after surgery, three of whom required mechanical ventilation, and the respiratory support time was 3.0±2.2 days. The drainage tube placement duration after surgery was 11.0±7.4 days. The postoperative hospitalization time of nine patients in the intensive care unit was 2.3±2.1 days, and the postoperative hospitalization time of all patients was 13.6±7.7 days. No operative deaths occurred in the perioperative period (within 30 days). Six patients experienced perioperative complications, including type I respiratory failure (2 cases), pneumonia (2 cases), atrial fibrillation (1 case), and pulmonary embolism (1 case). Except for the pulmonary embolism, all were mild to moderate in severity. All six patients recovered with standardized treatment. No vascular or airway anastomotic complications occurred in any patient.

Adjuvant chemotherapy was performed in two cases after surgery, and adjuvant immuno-chemotherapy was performed in five cases. Furthermore, 3 patients did not receive postoperative adjuvant therapy; one due to coronavirus disease 2019 (COVID-19) infection, one due to severe immunological pneumonia, and one refused treatment. The median follow-up time was 9.5 (range, 1.1–54.2) months, and seven patients were alive without anastomotic complications or signs of recurrence (*Figure 2*), except for one patient with station 4R lymph node recurrence, which improved after radiotherapy and immunotherapy. During the follow-up period, two patients passed away: one succumbed to severe immunological pneumonia on day 33 post-operatively, and the other to COVID-19 on day 47 post-operatively.

Discussion

Lung cancer is one of the leading causes of cancer-related death worldwide, posing a serious threat to human health.

Unless distant metastasis occurs, surgical resection is still one of the most effective treatments for patients with NSCLC. However, some patients with advanced central NSCLC are unable to tolerate pneumonectomy due to poor lung function, which limits surgical opportunities. Pneumonectomy has a reported mortality rate of 4.9–8.0% (10-16), and the associated severe postoperative loss of lung function can reduce patients' quality of life. Therefore, pneumonectomy has been used with increasing caution in the treatment of central NSCLC. Sleeve or double-sleeve lobectomy can offer a greater degree of pulmonary parenchyma preservation as much as possible, and its mortality and survival rates are comparable to those of lobectomy, making it the first choice of most thoracic surgeons for avoiding pneumonectomy (17-23). However, some patients with central NSCLC have extensive local tumor invasion, including of the main bronchus and/or pulmonary vessels. In this case, the anastomosis may not be completed due to the length of the resected bronchus and/or pulmonary vessels. Under these challenging conditions, lung autotransplantation may be a more appropriate and feasible alternative (24,25), as it may achieve complete tumor resection and maximize the preservation of pulmonary function. Due to the small sample size of our study, statistical analysis was not performed in our study. According to our study, lung autotransplantation after neoadjuvant immuno-chemotherapy can achieve similar mortality and survival rates as sleeve or double-sleeve lobectomy (18,22,23). In our study, 70% of the patients underwent lung autotransplantation on the right side. Previous reports have indicated that the mortality rate for right-sided pneumonectomy is twice as high as that for the left side, due to bronchopleural fistulas (26,27). Therefore, we believe that lung autotransplantation is more suitable for the right advanced central NSCLC.

In order to downstage the tumor and reduce its size, so that some patients can obtain a second chance for surgery, neoadjuvant therapy is generally recommended for locally advanced NSCLC. However, in some related studies, the results were discouraging and failed to achieve satisfactory radiological and pathological responses in patients treated with neoadjuvant chemotherapy with or without induction radiation therapy (28-30). The emergence of immune checkpoint inhibitors has provided new possibilities in the neoadjuvant treatment of NSCLC. The CheckMate 816 trial reported that neoadjuvant immunotherapy combined with chemotherapy resulted in significantly improved pathological CR (24.0% *vs.* 2.2%; P<0.001) and longer median event-free survival (31.6 *vs.* 20.8 months; P=0.005) compared with neoadjuvant chemotherapy alone (31). Deng *et al.* reported that radical surgery (including lobectomy, pneumonectomy, sleeve lobectomy, and bilobectomy) after immuno-chemotherapy was safe and conferred a survival benefit in patients with initial unresectable stage IIIB NSCLC (32). Neoadjuvant immuno-chemotherapy followed by radical resection has shown good therapeutic effect in initial unresectable locally advanced NSCLC. However, prior to our report, there were no reports on multiple cases of neoadjuvant immuno-chemotherapy followed by lung autotransplantation for locally advanced central NSCLC. The optimal course of neoadjuvant immuno-chemotherapy and interval between the last treatment and surgery have yet to be determined. The expert consensus on neoadjuvant immunotherapy for NSCLC recommends 2 to 4 cycles of neoadjuvant immunotherapy and surgery performed 3 to 6 weeks after the last treatment (33). In our study, the average number of cycles was 2.3±0.5 cycles, and the average interval between neoadjuvant therapy and surgery was 35.0±13.3 days. The cycle and interval of our study are consistent with those recommended by expert consensus. In addition, the neoadjuvant treatment cycles in our study did not exceed 3 cycles, mainly because (I) the operation itself is complicated and difficult, and there are many anastomoses, and (II) neoadjuvant immuno-chemotherapy can lead to intimal fibrosis of blood vessels. In the final pathological assessment, 6 cases showed a CPR and 4 cases an MPR, demonstrating the efficacy of neoadjuvant immuno-chemotherapy in this population. Our study indicates that patients with locally advanced central NSCLC who require lung autotransplantation can benefit from neoadjuvant immuno-chemotherapy. Definitive chemo-radiotherapy followed by immuno-oncology therapy is a novel treatment strategy from which patients can benefit. Compared to lung autotransplantation, definitive chemo-radiotherapy followed by immuno-oncology does not offer a complete cure. This treatment approach may be more suitable for patients with metastatic NSCLC or those who are not candidates for lung autotransplantation.

The operation duration was longer than that in other reports, while the blood loss and postoperative hospital stay were roughly equivalent (24,34,35). This may be due to the fact that blood vessels are more fragile and tissues are more adherent after neoadjuvant immuno-chemotherapy, which can complicate the procedure. Common complications following lung autotransplantation mainly include

pulmonary venous thrombosis, hemorrhage, stenosis of vascular anastomoses, and bronchopleural fistula (35). Among them, the most lethal complication of lung autotransplantation is bronchopleural fistula. No vascular and airway anastomotic complications occurred in our study. Six patients in our study experienced perioperative complications, most of which were mild to moderate. Only one patient developed severe pulmonary embolism, which improved after systemic anticoagulation therapy. The main causes of postoperative pulmonary vascular embolism include improper pulmonary vascular lavage, vascular anastomotic stenosis, vascular distortion or compression, insufficient anticoagulation, and reperfusion injury. Zhang *et al.* reported the use of heparin (50 mg/24 hours) after surgery for 5 consecutive days (35). Shiono *et al.* reported the use of low molecular weight heparin calcium (2,850 IU/24 hours) for 7 days after surgery (36). Adequate anticoagulation therapy after lung autotransplantation is crucial to preventing pulmonary embolism, but the surgeons should be aware of bleeding risk. No operative death occurred within 30 days. Based on the outcomes of our study, the perioperative mortality and morbidity associated with lung autotransplantation following neoadjuvant immuno-chemotherapy are deemed acceptable. Consequently, the safety of performing lung autotransplantation for locally advanced central NSCLC after neoadjuvant immuno-chemotherapy is reliable.

Thus far, two methods of lung autotransplantation have been reported: *ex situ* and *in situ*. In our study, except for one case that was *in situ* without perfusion, the rest were *ex situ* with perfusion. The *ex situ* warm ischemia time was 96.4±11.7 minutes. Warm ischemia time is preferably controlled between 65–120 minutes (37). There is no consensus on whether graft perfusion is essential for either approach. When the following criteria are met, the *in situ* method without perfusion can be selected: (I) the tumor can be resected and removed from graft lung; (II) the graft requires no complex shaping or reconstruction; and (III) reconstruction of pulmonary vessels can be completed within 2 hours (38). Airway reconstruction is the key to the success of lung autotransplantation. In this study, in addition to using end-to-end anastomosis method to reconstruct the airway, we also employed the end-to-side anastomosis method to reconnect the transplanted basal segmental bronchus and the tracheal lateral wall. Yamamoto *et al.* previously reported that adjusting the diameter difference between the main bronchus and the transplanted bronchus is technically difficult, due to issues related to hypertonia (39). Anastomosis of the graft bronchus to the tracheal lateral wall allows for a tension-free anastomosis. The diameter of the fenestration on the side wall of the trachea can be freely adjusted according to the diameter of the graft bronchus. Compared with end-to-end anastomosis with mismatched tube diameters, an anastomosis in which the graft bronchus is connected to the side wall of the trachea is less prone to stenosis. In addition, when the main bronchus and/or carina are invaded by tumors, end-to-side anastomosis of the graft bronchus and trachea is the only method that can be used to reconstruct the airway. End-to-side anastomosis was used to reconstruct the airway in two patients in this study. Bronchoscopy was performed regularly during postoperative follow-up, the airway was patent, and the anastomosis was free of stenosis. After the bronchial and vascular anastomoses are completed, the mediastinal pleural flap and prepericardial fat are used to wrap the anastomosis, which can increase the blood supply to the anastomosis and effectively prevent anastomotic complications (40). No patient developed airway anastomotic complications during follow-up.

The median follow-up time was 9.5 (range, 1.1–54.2) months, and seven patients were alive without anastomotic complications nor signs of recurrence, except for 1 patient with station 4R lymph node recurrence. The patient with lymph node recurrence improved and is still alive after receiving radiation and immunotherapy. Regarding recurrence, we posit that regular monitoring (bronchoscopy and CT or PET/CT scans) for early detection followed by standardized therapeutic interventions is efficacious. Two patients died from COVID-19 and severe immunological pneumonia, respectively. The latter case highlights the importance of being vigilant for the development of immunological pneumonia following neoadjuvant immunotherapy and the necessity for timely intervention. The deceased patient died of COVID-19. According to our research, neoadjuvant immuno-chemotherapy followed by lung autotransplantation is beneficial to the survival of patients with advanced central NSCLC.

Several limitations to this study should be mentioned. Although data were extracted from a prospectively maintained database, this study was retrospective in design and subject to data collection bias. Despite the increased clinical use of neoadjuvant immuno-chemotherapy followed by radical surgery for patients with locally advanced central NSCLC, experience with lung autotransplantation in this setting is still extremely lacking. This study included a relatively small number of patients, and more patients are

needed in the future to elucidate the long-term survival and oncological outcomes of lung autotransplantation after neoadjuvant immuno-chemotherapy.

Conclusions

We report the first retrospective series study on lung autotransplantation following neoadjuvant immuno-chemotherapy for advanced central NSCLC. Although the surgery was technically challenging, no short- or medium-term fatal complications were observed postoperatively, and the patients achieved reasonable postoperative survival. This suggests that lung autotransplantation for advanced central NSCLC after neoadjuvant immuno-chemotherapy is feasible and safe and can provide maximal preservation of lung function.

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Footnote

Reporting Checklist: The authors have completed the STROBE and AME Case Series reporting checklists. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-501/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-501/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of the First Affiliated Hospital of Guangzhou Medical University with an approval of No. 22 (ID: 443-3645) in 2022, the Shanghai General Hospital Affiliated to Shanghai Jiao Tong University School of Medicine with an approval of No. 034227387 in 2024, the First Affiliated Hospital of Zhejiang University School of Medicine with an approval of No. PRO20230117, and the Liaoning Cancer Hospital & Institute with an approval of No. 202205128, and individual consent for this retrospective analysis was waived.

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