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CASE REPORT

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Neoadjuvant immunochemotherapy followed by ex situ lung auto-transplant (Oto procedure) for central lung cancer: A case report with literature review

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Abstract

Sleeve and double-sleeve lobectomies are lung-sparing techniques for treating central lung cancers. However, if the tumour extends to involve the bronchi and vessels, lung auto-transplantation may be an alternative to pneumonectomy. Neoadjuvant therapy after surgery is the most common strategy for patients with extensive central lung cancer. Herein, we report a case of central lung cancer in a patient who underwent immunochemotherapy as neoadjuvant therapy following lung auto-transplantation. A 68-year-old man with stage IIIA non-small cell lung cancer and left upper lobe squamous cell carcinoma underwent neoadjuvant immunochemotherapy. Following partial regression, a multidisciplinary team decided on a back-table procedure with auto-lung transplantation after pneumonectomy to preserve pulmonary function. The patient had an uneventful recovery and was discharged after three weeks with no residual tumour or lymph node metastases. Lung auto-transplantation can be successfully performed in non-lung transplantation centres, potentially broadening treatment options for patients with central lung cancer.

KEYWORDS
central lung cancer, immunochemotherapy, lung auto-transplantation, neoadjuvant therapy, sleeve lobectomy

INTRODUCTION

Treatment of central lung cancer is challenging. Pneumonectomy is the standard for managing advanced central lung cancer; however, it is associated with a high risk of peri- and post-operative mortality. Some surgeons perform sleeve or bronchovascular double-sleeve lobectomy to preserve the lung parenchyma in patients with poor pulmonary function.[1] For certain patients with extensive central lung cancer involving the bronchus and the pulmonary artery, the lung auto-transplantation (Oto procedure) technique after the ex-situ division of the segmental graft has proven to be a feasible operation for minimizing the loss of pulmonary reserve.[2,3] Recently, neoadjuvant immunotherapy (IO) plus chemotherapy has been proven to provide more benefits than neoadjuvant chemotherapy alone.[4] Here, we present the case of a patient with central lung cancer who underwent IO plus chemotherapy, followed by the Oto procedure, and describe the procedure along with its short-term outcomes.

CASE REPORT

A 68-year-old man was diagnosed with non-small cell lung cancer (NSCLC) and left upper lobe squamous cell carcinoma. The tumour exhibited intrapulmonary metastasis and invaded the bronchus and left pulmonary artery (cT4N1M0, stage IIIA, chest computed tomography [CT] and positron

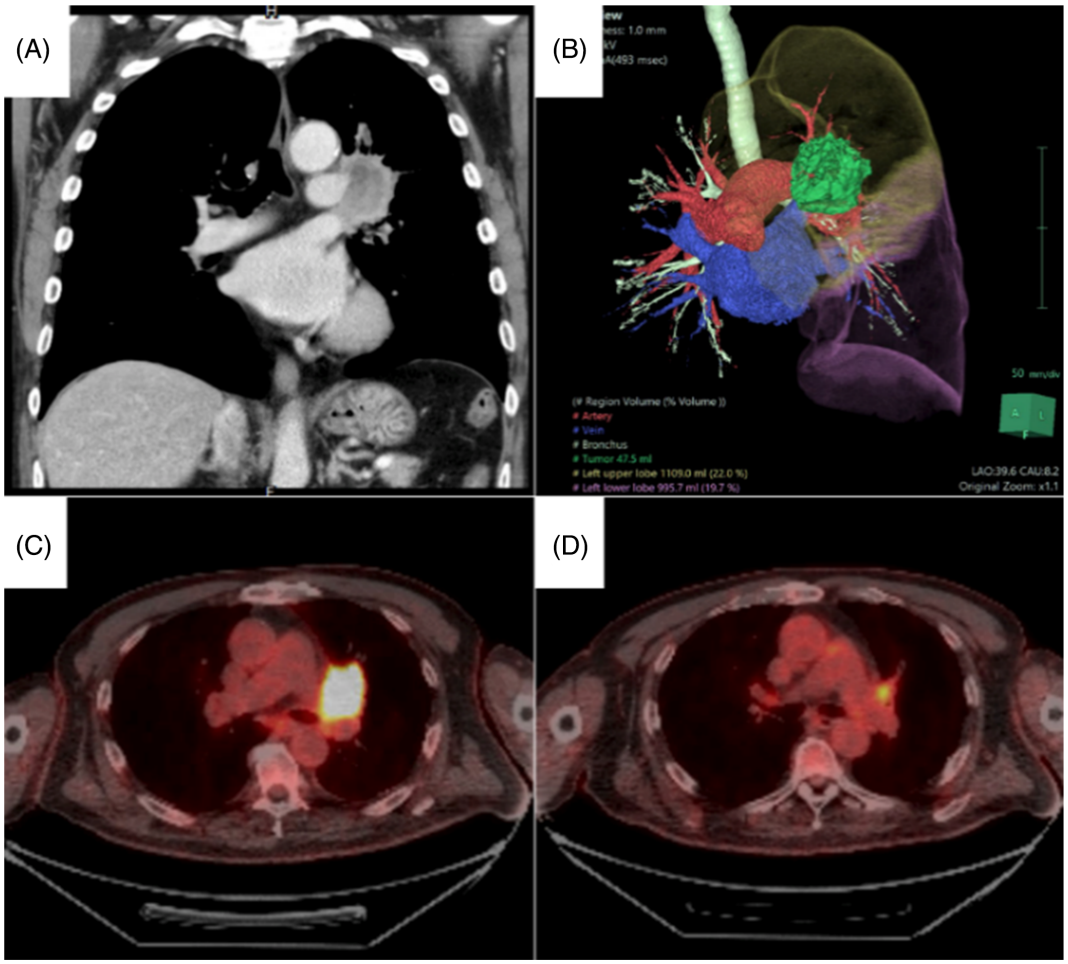

FIGURE 1 Serial examinations before treatment by (A) chest computed tomography (CT). (B) The tumour shows an invasion to the left pulmonary artery and bronchus in the CT reconstruction image. (C, D) The tumour and hilar lymph node exhibit a high standard uptake value (SUV) in the PET/CT scan; the clinical staging was cT4N1M0, stage IIIA.

emission tomography [PET]/CT scan, as shown in Figure 1). Due to the expression of programmed death ligand 1 (PD-L1) at 10–50%, the patient received immunotherapy plus chemotherapy (nivolumab + cisplatin + paclitaxel) as neoadjuvant therapy. After neoadjuvant immunochemotherapy, bronchoscopy showed less prominent endobronchial involvement, and PET/CT revealed the following. The left upper lobe main tumour showed partial regression after neoadjuvant treatment. Chest CT revealed a left upper lobe lung mass (3.2 cm) directly attached to the left pulmonary artery. The pulmonary function test result revealed a forced vital capacity (FVC) of 2.35 L and a forced expiratory volume in 1 s (FEV1) of 1.48 L; the FEV1/FVC ratio was 63%. Thus, we discussed how to avoid left pneumonectomy and preserve more pulmonary function in this case in a multidisciplinary team meeting; subsequently, we decided to perform a back-table procedure with auto-lung transplantation after pneumonectomy for curative resection and basal-segment preservation (Oto procedure).

The patient was placed in the supine position, and a fourth intercostal clamshell incision was initially made. After inferior pulmonary ligament dissection and mediastinal lymph node dissection (IASLC station 5/6/9), the pericardium was opened, and the left main pulmonary artery was clamped and divided. The left superior and inferior pulmonary veins and left main bronchus were excised sequentially. Heparin (5000 U) was administered before clamping the artery and vein, and a left pneumonectomy was performed. Another table was placed in the same room for the back-table preparation. Cooled organ-preserving histidine-tryptophan-ketoglutarate (HTK) solution (2000 mL) was perfused anterogradely, followed by retrogradely using a 16Fr Foley, and the graft was ventilated with an ID 6.0 endotracheal tube during the operation. Dissection of the lymph node IASLC station 7/11 and ex-situ resection of the left upper lobe was performed (Figure 2A,B). The basal bronchus was sutured end-to-end with the left main bronchus via 4-0 PDS. The superior pulmonary vein stump with augmentation of the pericardial patch was anastomosed to the inferior pulmonary vein stump of the graft using 4–0 prolene, and the remaining pulmonary artery to the basal segment was anastomosed to the main pulmonary artery using 4–0 prolene. Subsequently, basal

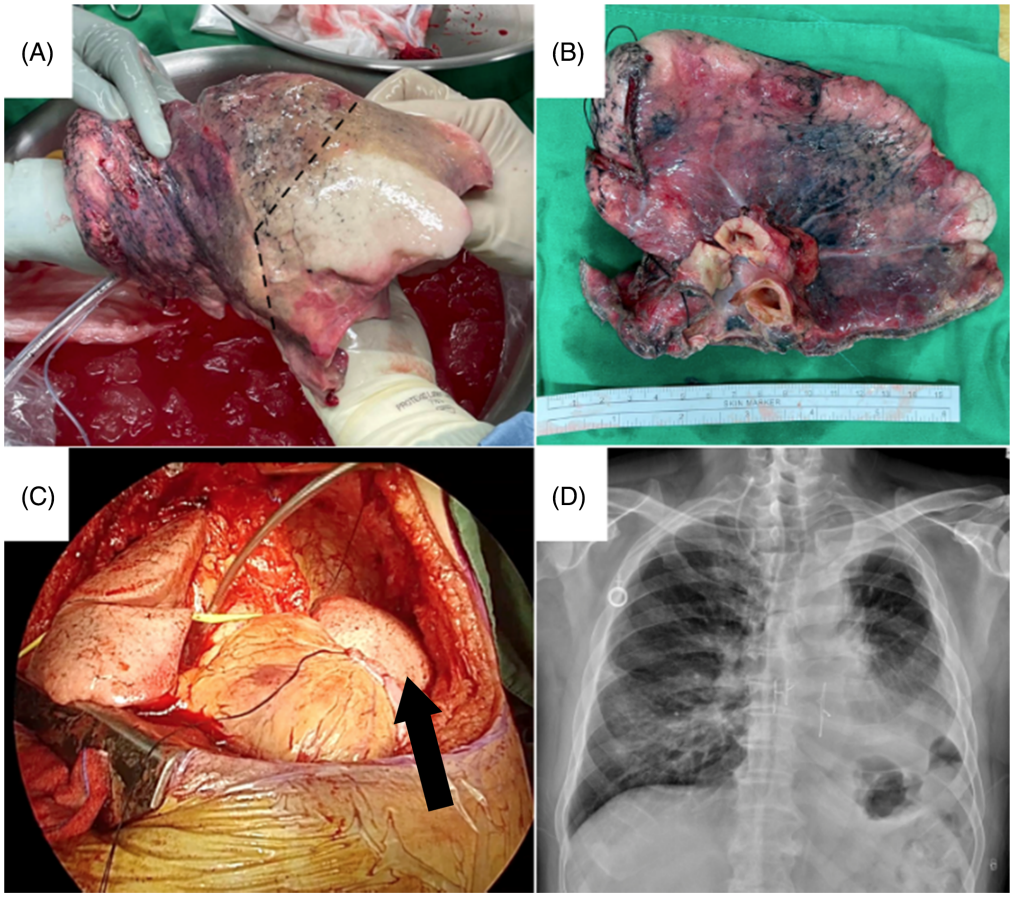

FIGURE 2 Images obtained during the operation. (A) Back-table sleeve resection. (B) Divided LUL lung (tumour part). (C) The arrow shows the full expansion graft. (D) Chest radiography findings at the follow-up 1 month after the operation.

segment auto-transplantation was completed (Figure 2C). Transoesophageal echocardiography was performed to check the air bobble, and intraoperative bronchoscopy was also performed to secure the anastomosis site. The total ischemic time was 205 min. The postoperative course was uneventful, and no ischemia–reperfusion injury or patent vascular anastomosis was noted. The patient was discharged 3 weeks after surgery. The pathological report indicated no residual tumour and no evidence of malignancy in any lymph node.

DISCUSSION

Approximately 20%–25% of patients diagnosed with NSCLC present with a resectable disease. Neoadjuvant therapy with nivolumab plus chemotherapy in these patients, along with PD-L1 expression, suggests significantly longer event-free survival and a higher percentage of a pathological complete response than chemotherapy alone.[4] In our patient, the tumour extensively invaded the bronchus and artery; therefore, we decided to administer neoadjuvant immunochemotherapy. The results of the pathological report showing a complete response (ypT0N0) were consistent with the description in the previous study. In patients with central lung cancer with PD-L1 positive expression, neoadjuvant immunochemotherapy followed by surgery may be an option to achieve a complete response and avoid pneumonectomy to preserve pulmonary function.

Lung auto-transplantation techniques can be divided into two types: in situ and ex-situ. Re-implantation without graft removal or perfusion was performed in situ. However, in certain cases, in vivo surgery is not feasible because of extensive infiltration, tumour size, or extensive involvement of the vessels of the upper lobe; ex-situ surgery may be an alternative.[5] Taira et al. found that ex-situ bench surgery could be performed easily with a favourable field to avoid excessive bleeding and to minimize tumour manipulation on a back table.[6] In the ex-situ procedure, organ ischemia followed by reperfusion can result in cascading cellular damages; therefore, an appropriate perfusate to minimize ischemia–reperfusion injury is required. A low potassium solution has a lower incidence of graft failure, shows improved PaO_2/FiO_2, and lower duration of mechanical ventilation than the Euro-Collins (EC) solution.[7–9] In another animal experimental study, the histidine-tryptophan-ketoglutarate (HTK) perfusion group had a significantly lower degree of lung injury than the EC perfusion

TABLE 1 Summary of recent studies on lung autotransplantation.

Author/year	Case number	Histology	Staging	Neoadjuvant	Perfusate type	Ischemia and operation time	Pathology report	Follow-up duration
Zhang/2000[12]	In situ: 1 (R) Ex situ: 3 (R: 1, L: 2)	SCC: 3 ASC: 1	N/A	C/T: 2	Heparin solution (12,500 U/500 mL)	Operation time: 300–480 min	In situ: pT3N1: 1 Ex situ: pT3N1: 2 pT3N2: 1	13–31 months
Jiang/2008[13]	In situ: 7	SCC: 5 ASC: 2	N/A	N/A	20°C Heparin solution (12,500 U/500 mL)	Ischemia time: mean 153.1 min Operation time: mean 240.3 min	SCC: pT3N2: 3 pT4N2: 2 ASC: pT3N2: 2	2–73 months
Oto/2012[2]	Ex situ: 1 (R)	SCC	cT4N1	N/A	Low-potassium dextran glucose solution	Ischemia time: 120 min	N/A	19 months
Watanabe/2015[14]	Ex situ: 1 (R)	ADC	cT4N1	N/A	Extracellular phosphate-buffered solution	Ischemia time: 249 min Operation time: 799 min	pT4N0	6 months
Emmanouilides/2015[15]	In situ: 9 (R: 3, L: 6) Ex situ: 6 (R: 2, L: 4)	In situ: SCC: 5 ADC: 2 Low-grade: 1 LCLC: 1 Ex situ: SCC: 3 ADC: 2 Low-grade: 1	N/A	N/A	0.2 mg% PGE1 mixed saline	Ischemia time: 55–80 min	In situ: pT2N1: 1 pT2N2: 4 pT3N1: 2 pT3N2: 2 Ex situ: pT2N1: 1 pT2N2: 1 pT3N1: 3 pT3N2: 1	6–60 months
Karube/2016[16]	Ex situ: 1 (R)	ADC	cT2aN1	N/A	Low-potassium phosphate-buffered Dextran glucose solution (EP-TU solution)	Operation time: 359 min	pT2aN2	9 months
Tanaka/2019[3]	Ex situ: 5 (R:2, L:3)	SCC: 3 ADC: 2	cT4N1:3, cT1bN2:1, cT2aN2M1b:1	CCRT: 4	Low-potassium dextran glucose solution	Ischemia time: 73–135 min	N/A	42.7–84.1 months
Mo/2020[17]	In situ: 1 (L) Ex situ: 2 (L)	SCC: 3	cT4N0: 3	N/A	4°C normal saline	Ischemia time: 67–97 min Operation time: 285–415 min	N/A	18–24 months
He/2021[11]	In situ: 2 (R)	SCC: 1 ACC: 1	cT3N0: 2	SCC: paclitaxel + nivolumab	N/A	Operation time: SCC: 358 min ACC: 280 min	SCC: pCR ACC: pT1bN0	9 months

TABLE 1 (Continued)

Author/year	Case number	Histology	Staging	Neoadjuvant	Perfusate type	Ischemia and operation time	Pathology report	Follow-up duration
Brito/2021[18]	Ex situ: 1 (R)	SCC	cT2bN1	N/A	Perfadex	Ischemia time: 210 min	pT3N1	N/A
Taira/2022[6]	Ex situ: 1 (L)	ADC	cT4N1	CCRT	ET-Kyoto solution	N/A	pT4N0	18 months
Current case	Ex situ: 1 (L)	SCC	cT4N1	Cisplatin + Paclitaxel + Nivolumab	HTK solution	Ischemia time: 205 min Operation time: 557 min	pCR	3 months

Abbreviations: ACC, adenoid cystic carcinoma; ADC, adenocarcinoma; ASC, adenosquamous carcinoma; C/T, chemotherapy; CCRT, concurrent chemoradiotherapy; LCLC, large cell lung carcinoma; pCR, pathological complete response; SCC, squamous cell carcinoma.

group.[10] In our case, we chose HTK as the preservation solution, and no organ ischemia or reperfusion injury was observed during the whole hospital course.

In Taiwan, organ transplantation operations are performed in hospitals with organ transplantation centres. These centres are equipped with the necessary facilities and specialized medical teams to handle complicated operations. However, in this case, we believe that the procedure and post-operative care could have been managed in a non-dedicated lung transplantation centre, and non-specialized centres may still effectively handle such complex medical processes with the appropriate resources and expertise. We summarize the results of recent studies on lung auto-transplantation procedures in Table 1, including procedure type, cancer type, staging, perfusate, operation time, and follow-up time. Squamous cell carcinoma was the most common type in those cohorts. He et al. also presented a case that underwent neoadjuvant immunotherapy with a pathological complete response (pCR).[11] Ischemia and operation time were similar to those in other reports; the patient was followed-up at the outpatient department. The bronchoscope, after 2 months of surgery, showed no stricture or obstruction, and the chest radiography revealed good lung expansion. The lung function test indicated a FVC of 1.98L, FEV1 of 1.40L, and a FEV1/FVC ratio of 71%.

We reported the case of central lung cancer in a patient who underwent neoadjuvant immunochemotherapy followed by lung auto-transplantation surgery and was followed-up for 3 months after the operation. Neoadjuvant immunochemotherapy reduced the size of the tumour, rendering it resectable, and presented pCR. Lung auto-transplantation did not require immunosuppressants. This presents the possibility that this procedure can be successfully performed in a non-lung transplantation centre, given that sufficient post-operative care is provided.

AUTHOR CONTRIBUTIONS

Conception and design of study: Po-Keng Su, Shun-Mao Yang. *Acquisition of data (laboratory or clinical)*: Po-Keng Su, Chen-Chieh Lin, Szu-Yen Hu, Ming-Hsien Lin, Chun-Yu Wu, Shun-Mao Yang. *Data analysis and/or interpretation*: Po-Keng Su, Shun-Mao Yang. *Drafting of manuscript and/or critical revision*: Po-Keng Su, Chen-Chieh Lin, Szu-Yen Hu, Ming-Hsien Lin, Chun-Yu Wu, Shun-Mao Yang, Takahiro Oto. *Approval of final version of manuscript*: Po-Keng Su, Chen-Chieh Lin, Szu-Yen Hu, Ming-Hsien Lin, Chun-Yu Wu, Shun-Mao Yang, Takahiro Oto.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

We will provide the data.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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