Ex situ reimplantation technique, in central lung tumors

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Background: The parenchyma-sparing resection is most often performed in patients with impaired preoperative lung or cardiovascular function who would not be able to tolerate a pneumonectomy.

Methods: Our experience on the *ex situ* reimplantation procedure and the outcome of patients with lung malignancies, who underwent upper or upper-middle lobectomy, with reimplantation of the lower lobe was reported.

Results: We present 9 patients mean age 62.6+16.2 years (7 males/2 females) underwent *ex situ* reimplantation due to extensive lung tumor of upper lobes. The surgical technique precludes IV heparinization and then radical pneumonectomy. The entire lung was immersed in Ringer's solution (temperature 4 degrees centigrade) and bench surgery was performed. The involved upper (or upper-middle) lobes with involved lymph nodes were resected, thus leaving the healthy lower lobe of the lung. Pneumoplegia solution, named "Papworth pneumoplegia", was administered (1,473 mL) through catheterization of the pulmonary artery and vein stumps (ante grade and retrograde) along with 250 mL of prostaglandin E1. Re-implantation of the lower lobe was performed (I) on the right side, implantation involved the anastomosis of lower pulmonary vein in the site of the cuff of left atrium, followed by suturing the stump of the intermedius pulmonary artery to the right main pulmonary artery and finally the bronchial stumps—intermedius bronchus to the right main bronchus; (II) on the left side the pulmonary vein was anastomosed first, followed by the bronchial stumps and finally by the pulmonary artery. The graft ischemia time was 70.2+8.4 minutes ranged between 55 and 80 minutes.

Conclusions: Re-implantation or auto-transplantation should be considered as a safe option for the appropriate patient with lung cancer. The *ex situ* separation of the cancerous lobes is technically feasible and allows extensive pulmonary resection while minimizing the loss of pulmonary reserve. Based on our work, the major factors that play a role for the survival of initially resected and then re-implanted lung graft, are: (I) the ischemia time of the re-implanted lobe; (II) the proper use of pneumoplegia solutions, along with prostaglandin E1 and heparin; (III) the occurrence of pulmonary vein thrombosis; and (IV) the bronchial anastomosis.

Keywords: Non-small lung cancer; re-implantation; bench surgery; auto-transplantation; *ex situ*

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Introduction

Non-small-cell lung cancer confined to the lung is best treated with pulmonary resection, if possible (1). Centrally placed tumors can involve structures that preclude an isolated lobectomy and require a more extended resection meaning pneumonectomy. The parenchyma-sparing resection is most often performed in patients with impaired preoperative lung or cardiovascular function who would not be able to tolerate a pneumonectomy. Because it is considered a more complex procedure and a relevant incidence of bronchial complications has been reported (2) it has not been applied widely.

In the present study, we retrospectively analyzed our experiences of the reimplantation technique in the treatment of central lung tumours of the upper lobe (stage III). We described the procedure of *ex situ* reimplantation technique without adding selection bias. The objective of the present retrospective analysis was to characterize the indications, patient demographics, morbidity, mortality, and late outcomes over time in patients who underwent this kind of reimplantation technique.

Material and methods of *ex-situ* technique of lung reimplantation

We present 9 patients mean age 62.6+16.2 years (7 males/2 females) underwent *ex situ* reimplantation due to extensive lung tumor of upper lobes during a period of 20 years [1993-2014].

In these patients due to extensive infiltration (patient 1) or due to tumor size (patients 2,3,4) or due to the extensive involvement of the lymphatics of the upper bronchi (patients 6,8), or of the vessels of the upper lobe (patients 5,7,9) any kind of lobectomy or *in vivo* lobe surgery showed unfeasible (*Figure 1*). In such cases, the decision by the surgeon was the *ex situ* reimplantation technique (*Table 1*).

After heparinization, a radical pneumonectomy was first performed. The pulmonary artery and the lower pulmonary veins were severed and legated, provisioning for a long enough stump of the pulmonary veins attached to the lung. Subsequently, the entire lung was immersed in Ringer's solution (temperature 4 degrees centigrade) and bench surgery was performed. The involved upper (or upper-middle) lobes with involved lymph nodes were resected, thus leaving the healthy lower lobe of the lung. The origins of the pulmonary vessels and the bronchus were prepared.

Pneumoplegia solution, named "Papworth pneumoplegia", was administered (1,473 mL) through catheterization of the pulmonary artery and vein stumps (ante grade and retrograde) along with 250 mL of prostaglandin E1. Preparation of prostaglandin was made by adding of 0.5 mg of PGE1 in 10 mL of normal saline (NS) solution (3). After shaking of this solution 40 mL more of NS were added. Finally, a 200 mL solution in NS was prepared in order to achieve a concentration of 0.2 mg% of PGE1 (*Figures 2,3*).

Reimplantation of the lower lobe was performed as described below.

In the right side (*Figure 4*), implantation involved the anastomosis of lower pulmonary vein in the site of the cuff of left atrium using prolene 4-0, followed by suturing the stump of the intermedius pulmonary artery to the right main pulmonary artery, using prolene 5-0. The bronchial stumps—intermedius bronchus to the right main bronchus—were stitched together with prolene 4-0m, at the end of the procedure. On the left side (*Figure 5*), the sequence differed; the pulmonary vein was anastomosed first, followed by the bronchial stumps (*Figure 6*) and finally

Figure 1 CT of the thorax findings and bronchoscopy findings.

Table 1 Anthropometric characteristics, staging and histological type of the disease, surgical technical details, and follow up data for the 9 patients underwent *ex situ* lung lobe reimplantation surgery procedure

No.	Age	Gender	Histology	Involvement	TNM after operation	Ischemic time of the lung (min)	Follow-up duration (months)	Post treatment
1	27	M	Low grade	LUL	T_3N_2Mo	65	Dead-60	Chemo
2	75	F	Adeno	RUL-RML	T_3N_1Mo	80	Dead-12	Chemo
3	72	M	Squamous carcinoma	RUL	T_3N_1Mo	55	Alive-24	Chemo
4	70	M	Squamous carcinoma	LUL	T_3N_1Mo	62	Alive-36	Chemo
5	72	M	Squamous carcinoma	LUL	T_2N_1Mo	70	Alive-24	Radiation
6	70	M	Adeno	LUL	T_3N_2Mo	75	Alive-60	Chemo
7	65	M	Squamous	RUL	T_2N_1Mo	70	Alive-24	Chemo
8	44	M	Bronchoalveolar	RUL+RML	T_3N_2Mo	80	Alive-12	Chemo
9	69	F	Adeno	LUL	T_2N_0Mo	75	Alive-6	Chemo + Radiation

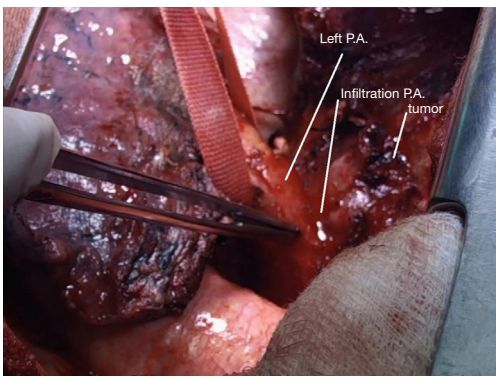

Figure 2 Intraoperative findings of the patient No.1, showed extensive infiltration of pulmonary artery by a lung tumor. In such cases, the decision by the surgeon was the *ex situ* re-implantation technique.

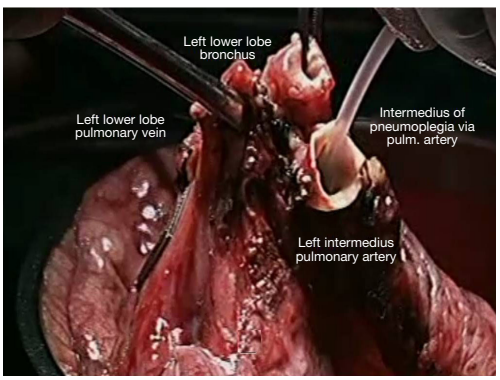

Figure 3 The left lower lobe is showed out of the thorax into the "surgical bowl"—the meaning of bench surgery—just before the re-implantation procedure begins. Also, the antegrade administration of pneumoplegia solution, named "Papworth pneumoplegia", is showed through catheterization of the pulmonary artery, along with prostaglandin E1.

by the pulmonary artery (*Figure* 7). This is due to the different anatomical relation of the artery to the bronchus left and right (*Figures 8*,*9*).

Results

In all cases of *ex-situ* reimplantation, extracorporeal circulation hardware was readily available; in fact, in 3 cases (patients No.1, 3, 7) it was employed due to hemodynamic instability. In two of those cases a femoral-femoral partial bypassing performed. In the other one patient we used extracorporeal membrane oxygenator (ECMO) with partial bypass; a special venous catheter inserted along to the length of the lumen of inferior vena cava.

The graft ischemia time was 70.2+8.4 hours ranged between 55 and 80 minutes (*Table 1*).

There were no significant postoperative problems during X-ray examination at 1st day and bronchoscopy reevaluation at the 7th day. Long term follow up ranged from 6 to 60 months (*Table 1*).

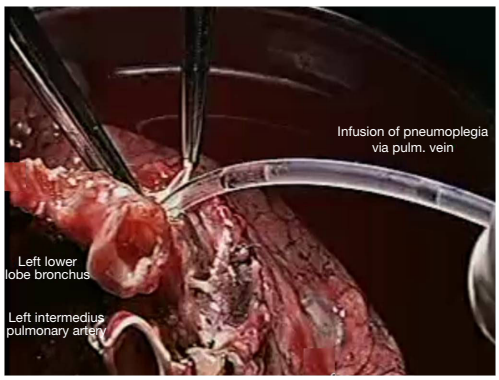

Figure 4 The left lower lobe is showed out of the thorax during the retrograde administration of pneumoplegia solution, along with prostaglandin E1 through catheterization of the pulmonary veins. The administration of this solution is necessary to be infused through pulmonary artery and veins in order to "close the loop" of lung lobe vessels and to maximize the protection of these structures from thrombosis.

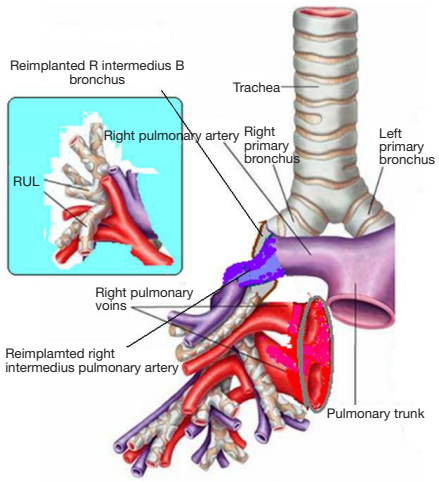

Figure 5 Schematic depiction of the re-implantation technique of the right lower lobe. This technique involved the anastomosis of lower pulmonary vein in the site of the cuff of left atrium, followed by suturing the stump of the intermedius pulmonary artery to the right main pulmonary artery. The bronchial stumps—intermedius bronchus to the right main bronchus—were stitched together at the end of the procedure.

Discussion

In some patients who underwent reimplantation surgery, the upper lobectomy or the upper-middle bilobectomy may have more or specific anatomic difficulties increasing the risk of complications. The resection of this kind of tumors can be considered at bench surgery, followed by reimplantation of the remaining healthy lower lobe with bronchial, arterial or venous reconstruction. This *ex situ* procedure runs with or without circulatory blood pump (CBP) or with ECMO depending on the heamodynamic stability of the patient after the pneumonectomy.

Appropriate lung preservation may provide less ischemic damage and sufficient time to perform the pathological examination of the bronchial and arterial surgical margins. In

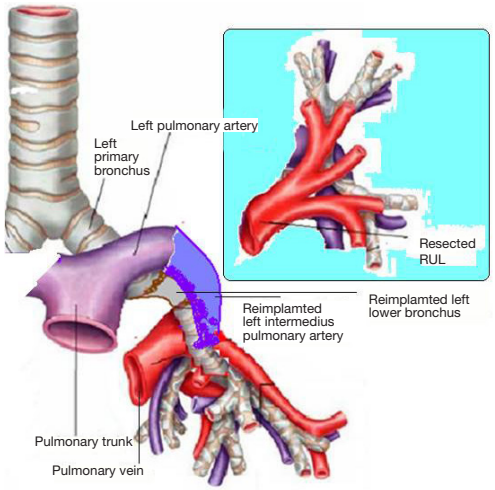

Figure 6 Schematic depiction of the re-implantation technique of the left lower lobe. In this technique the sequence of anastomosis differed to that from the right lung; the pulmonary vein was anastomosed first, followed by the bronchial stumps and finally by the pulmonary artery.

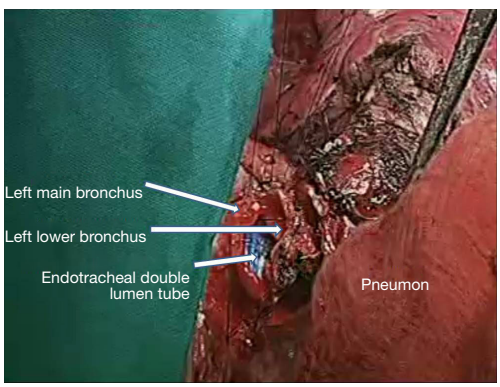

Figure 7 Intraoperative anastomoses of the left lower bronchus to the left main bronchus. The double lumen endotracheal tube was showed through the main left bronchus.

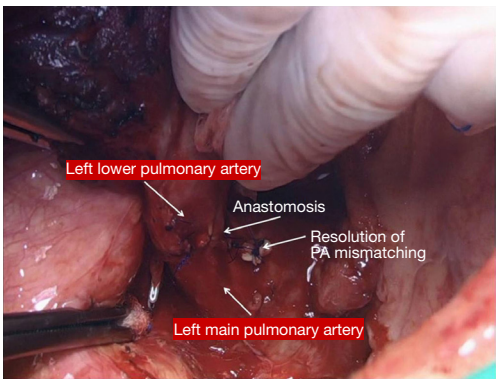

Figure 8 Intraoperative anastomoses of the left lower artery to the left main pulmonary artery. This is the last anatomical anastomosis of the left side re-implantation technique. In this figure also the surgical resolution of the mismatching between the diameters of the lumen of the left lower pulmonary artery to the one of the left main pulmonary artery is showed.

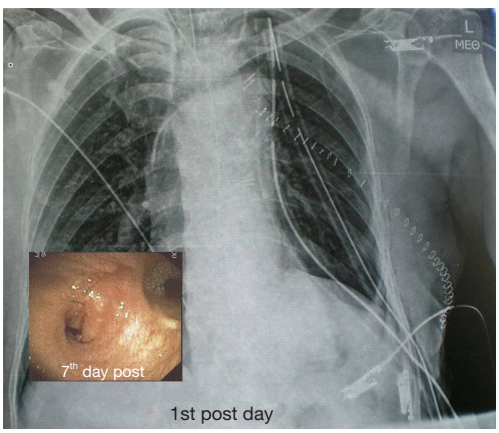

Figure 9 Post surgery evaluation (1st day) with bronchoscopy and chest X-ray.

addition, in agreement with others (4) we believe that the *ex situ* segmental graft resection may be safer and easier than the similar technique of in situ resection. It can be performed with a favorable visual field without excessive bleeding and tumor manipulation, as the cancerous lung is completely removed from the patient's body and can be easier inspected and treated.

The major factors that play a role for the survival of initially resected and then re-implanted lung graft, are: (I) the ischemia time of the re-implanted lobe; (II) proper use of pneumoplegia solutions, use of prostaglandin E1, heparin; (III) the occurrence of pulmonary vein thrombosis; (IV) the bronchial anastomosis.

The ischemia time of the re-implanted lobe

We know that the prevalence of ischemia reperfusion injury to the re-implanted lobe increased geometrically after one hour of ischemia (5). In fact, the average reported ischemic time was from 153 min (6) to 120 min (7). These data are in accordance with the complications that described. In our cases the ischemic time ranges from 65 to 80 min (8). It is important that surgeons are well-trained in order to achieve the lowest time possible.

Proper use of pneumoplegia solutions, use of prostaglandin E1, heparin

All authors noted the importance of preventing ischemia–reperfusion injury with the lung preservation solution. Proper lung preservation was recommended in cases in which the warm ischemic time would exceed 1 h (9).

Some authors suggested the use of cold low-potassium dextran glucose lung preservation solution for ante grade followed by retrograde pulmonary arterial flushes. In our technique the resected lung was immersed in Ringer's solution (temperature 4 degrees centigrade) and then infused with Papworth pneumoplegia with prostaglandin E1. This process was the same as in lung transplantation (10).

The occurrence of pulmonary vein thrombosis

Known factors predisposing to pulmonary vein thrombosis are the decreased blood outflow into the resected lobe, stenosis or angulation of the anastomosis, vascular compression, inadequate anticoagulant therapy and the lung ischemia-reperfusion syndrome.

Vascular complications associated with reconstruction, although uncommon, may further diminish if systemic and local heparinization is performed during flow interruption. Anticoagulant therapy for patients who have received pulmonary artery reconstruction remains controversial (11,12). It was suggested that 3,125 U of intraoperative heparin should be safe and it is unnecessary to use any more anticoagulation postoperatively (13). We used intravenous application of heparin (300 U/kg body weight per day) as a standard therapeutic regimen in all patients for 5 days after surgery and we observed no thrombosis.

The bronchial anastomosis

Pulmonary complications such as deficient healing of

bronchus are to be expected in this type of patients (14). Higher frequency of sputum retention due to disruption of ciliary clearance secondary to bronchial circular suture also characterizes this type of major surgery, requiring intense respiratory physiotherapy.

For these reasons, postoperatively, all patients were transferred to our intensive care unit (ICU) and were treated by inhalation of racemic epinephrine to minimize mucosal edema followed by aggressive physiotherapy to achieve adequate drainage of bronchial secretions. Early mobilization of the patient was started as soon as possible.

In conclusion, auto-transplantation should be considered as a safe option for the appropriate patient with lung cancer (15). The *ex situ* separation of the cancerous lobes is technically feasible and allows extensive pulmonary resection while minimizing the loss of pulmonary reserve (16). The required surgical expertise, lung preservation techniques and the time shortening of the lung graft ischemia significantly decrease the morbidity and mortality rates and render this procedure preferable to pneumonectomy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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