# Surgical treatment of locally advanced T4 non-small cell lung cancer with mechanical circulatory support

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**Abstract:** T4 non-small cell lung cancer (NSCLC) is a very heterogeneous group of locally advanced neoplasm greater than 7 cm or characterized by at the least one of the following: one or more satellite tumor nodules in a different ipsilateral lobe or by the invasion of the trachea, carina, heart, great vessels, vertebral body, oesophagus, or mediastinum. Because of the location and invasion of surrounding structures, controversy exists in surgical resection of T4 tumours which are usually considered unresectable and incurable. For a long time, a radical or extended resection of these tumours, needing a removal of tissues beyond the physical boundaries of a standard lobectomy or pneumonectomy, has been considered as an obstacle. At the same time the introduction of more advanced surgical techniques, often including the use of extracorporeal life support (ECLS), has allowed to extend the limits of conventional surgery increasing the rate of a complete surgical resection. Thanks to increasing experience gained during lung transplantation, more surgeons are now using such methods to obtain a good oxygenation and hemodynamic support during complex resections of the locally advanced tumours. The aim of this paper was to perform a critical review of the state of art of surgical treatment for T4 NSCLC with ECLS. Concerning the two different categories of T4 (tumors reaches heart and great vessels or tumors presenting with carina extension) which more often may need ECLS, we analysed indications, choice of suitable extracorporeal device, short- and long-term results.

**Keywords:** T4 non-small cell lung cancer (T4 NSCLC); locally advanced T4; mechanical circulatory support; extracorporeal life support (ECLS); cardio-pulmonary bypass and extracorporeal membrane oxygenation (CPB and ECMO)

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## Introduction

T4 non-small cell lung cancer (NSCLC) is defined by a diameter larger than 7 cm or by one of the following features: one or more satellite tumor nodules in different ipsilateral lobe; the invasion of the trachea, carina, vertebral body or mediastinal organs (superior vena cava, left atrium, great arteries) (1). T4 NSCLCs invading vital structure such as heart, great vessels, or carina are generally considered unresectable (2) and, usually, their treatment is palliative (supportive care, chemotherapy or radiotherapy alone or in combination) (3,4). However, progress in anaesthesia and surgical techniques has hallowed to redefine the limits of resection and to overcome certain dogmas (5): during the 90s, several studies about extended resection of T4 NSCLC have been published, with encouraging long-term results (6-13).

Mechanical extracorporeal circulatory support (ECLS), such as cardio-pulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO), has become an integral part of these challenging resections (14,15). T4 NSCLC needing complex cardiac resections or reconstructions, replacement of the thoracic aorta, or the common pulmonary artery are approached with cardiac arrest and total circulatory support by using standard CPB (16-18). Conversely, T4 NSCLC with tracheal or carina extension, needing complex tracheal-bronchial surgery, are performed by using ECMO which allows a good oxygenation as well as removal of $CO_2$ and assuring a complete ventilator support (19).

The aim of this article was to perform a critical review of the state of art of surgical treatment for T4 NSCLC with ECLS: we focused on indications, choice of suitable extracorporeal device, short- and long-term results.

## T4 NSCLC involving heart and great vessels

T4 NSCLCs invading vital mediastinal vascular structures are considered at high risk for resection and associated with a poor prognosis (4,20). For these tumours, conventional surgical techniques allow a complete resection rate of only 30–40% (6); complex cardiac resections or reconstructions (open resection of either the left or the right atrium), replacement of the thoracic aorta, or the common pulmonary artery can only be performed by using conventional CPB (15). Historically full CPB has been the most typical form of extracorporeal mechanical gas exchange support for complex thoracic surgery, but his practice during resection of thoracic malignancy has been controversial. Most thoracic surgeons have considered such operations as contraindicated considering the high morbidity and mortality reported (21). The fears of CPB-induced tumor dissemination and the consequent poor prognosis were considered limiting criteria (22). The use of CPB needs central cannulation by standard sternotomy and pericardiotomy. A full systemic heparinization is mandatory before cannulation that usually is planned with a bicaval venous cannulation and an arterial return in the ascending aorta. Systemic hypothermia and cold blood potassium cardioplegia are required to protect myocardium during the time of cardiac arrest, intracardiac resection and reconstruction (23). The complete stability for gas exchange and hemodynamic support is surely the main advantage of CPB: on this way, it allows a complete inspection of infiltrated structure permitting for safe resections margins which can be confirmed by intra-operative frozen section (15). However, CPB requiring full heparinization, potentially increases, bleeding, transfusion requirements, re-operations for hemothorax (24) and can lead to an inflammatory response with the risk of lung injury (25,26). Several studies have reported a possible role of immunosuppression due to the pump and blood transfusion in favouring the enhancement of metastasis (27,28).

We identified six studies describing surgical treatment for T4 NSCLC adopting CPB (*Table 1*). Studies considering other intra-thoracic malignancies or less than 5 cases have been not included. All studies were retrospective. 3 studies were retrospective series including exclusively patients treating by using CPB (29-34). Three studies reported a second group of patients. In the first one the group was represented by 8 patients suffered from coincidental T1–2 NSCLC and heart disease both treated by using CPB (32), the second and the last one by respectively 355 and 30 patients affected by T4 NSCLC resected without CPB (33,34). A total 71 surgically resected patients for T4 NSCLC with the use of CPB have been reported. For each study, data on the type of lung resection, the surgical procedure associated with lung resection, R0 resection rate, nodal involvement rate, overall morbidity, 30-day mortality and long-term results were obtained (29-34).

### *Elective or unplanned CPB*

In literature, two different setting of use of CPB are reported: planned and unplanned. Elective use of CPB is reported by reference centres, on which the possibility to use CPB is usually evoked during preoperative work-up. Generally, in these centers, CPB is placed during operation when efforts to avoid its use are unsuccessful and it was found that the tumour was otherwise unresectable. Unplanned use of CPB is reported when injuries to major vascular structures (pulmonary artery, superior or inferior vena cava, left or right atrium) occur during a planned lung resection. In these cases, the emergent use of CPB may be life-saving (26).

In the included studies, the use of CPB was planned in 67/71 (94%) cases, while in only 4 cases (6%) the CPB was instituted emergently (33). Interestingly in one series even if the use of CPB was planned in 14 cases, finally, it was used in 12 cases (34).

**Table 1** Studies reported at the least 5 patients undergoing pulmonary resection for NSCLC using CPB

| Studies | Year | N° of NSCLC treated | Lung resection | Procedure/reason for requiring CPB | Planned (P), urgent (U) | R0 | N status | Overall morbidity | 30-day Mortality | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Hasegawa (29) | 2003 | 11/11 | PN: 9; lobectomy: 2 | LA: 4; Ao: 3; PA: 3; respiratory support: 1 | P: 11, U: 0 | 9/11 | N0: 3, N1: 3, N2: 4 | 63% | 0% | 2/11 alive at 34 and 41 months with recurrence |
| de Perrot (30) | 2005 | 7/7 | PN: 4; lobectomy: 2; carinal reconstruction: 1 | Ao: 3; PA + LA: 2; carina: 2 | P: 7, U: 0 | 6/7 | N0: 3, N1: 4 | 42% | 0% | 6/7 alive at 17, 25 and 72 without recurrence and at 8, 13 and 54 with recurrence |
| Ohta (31) | 2005 | 13/16 | PN: 6; lobectomy: 9; partial lung resection: 1 | Ao: 16 | P: 13, U: 0 | 12/16 | N0: 9, N2:4 | 31% | 12.5% | 9/16 alive, median survival: 26 months, 5-year survival: 48.2% |
| Kauffmann* (32) | 2013 | 8/8 | PN: 6; bilobectomy: 1; sleeve lobectomy: 1 | LA: 3; Ao: 2; PA: 3 | P: 8, U: 0 | 8/8 | N0: 4, N1: 3, N2: 1 | 25% | 12.5% | 8/8 died, median survival 13.6 months, 1 long survival at 155 months, 5-year survival: 12.5% |
| Langer* (33) | 2016 | 20/355 | PN: 15; lobectomy: 3; sleeve lobectomy: 1; sleeve bi-lobectomy: 1 | LA: 2; Ao: 5; LA + Ao: 1; PA: 5; PA + LA: 2; SVC + RA: 1; carina: 4 | P: 16, U: 4 | 19/20 | NR | NR | 9% | 5-year survival: 37%, 10-year survival: 28% |
| Filippou* (34) | 2019 | 12/42 | PN: 5; lobectomy: 3; sleeve lobectomy: 1; sleeve pneumonectomy: 1; tracheal resection: 2 | LA: 2; RA: 1; Ao: 3; PA: 4; carina: 2 | P: 12, U: 0 | 12/12 | N0–N1: 12, N2: 0 | 33% | 0% | Overall 5-year survival: 60% |

*, studies presenting a second group of patients affected by NSCLC resected without CPB. NSCLC, non-small cell lung cancer; CPB, cardio-pulmonary bypass; PN, pneumonectomy; LA, left atrium; RA, right atrium; Ao, aorta; PA, pulmonary artery; SVC, superior vena cava.

If a planned use of CPB is associated with a significantly improved survival is argument of debate in literature. Only one study evaluated the prognostic role of planned/unplanned CPB (33): no significant difference in survival was found. Marie Lannelounge group explained this result both for the extensive experience in their center with the use of CPB for lung transplantation and because the potential need for emergent CPB was included in the case planning and operative set-up for all T4 resections (33).

Different results were found by a recent review (including studies from 1990 to 2010) (22): overall 5-year survival was significantly higher in case of planned CPB (54% *vs.* 37%). At multivariate analysis, the authors confirmed that the unplanned CPB was a significant prognostic factor (22). The reasons for these different results could be the following: the review didn't include exclusively T4 NSCLC (but also T1–3); most of the included studies were case report (8/20); only 3/20 studies included more than 5 cases.

According to the results of our review, there are not sufficient data to state that a planned CPB is associated with higher survival if compared to emergent one for the treatment of T4 NSCLC. However, we can state that a detailed mapping of the tumor's extension and a preoperational decision regarding the use of CBP is mandatory. In this scenario, an emergency use of CPB represents a helpful and safety net when the procedure is complicated without affecting survival results.

### *Single or multiple resections/organ type*

Published studies are extremely heterogeneous in terms of kind of lung resection, the type and the number of associated resected organs (*Table 1*). Pneumonectomy was the most common lung resection performed (45/71, 63%), followed by lobectomy (19/71, 27%). In some studies, the invasion was limited to one structure and therefore the surgery was extended to a single organ (29,31,32,34), in others an invasion of several structures required more demolitive surgery (30,33). The most common associated resection was thoracic aorta (32/71, 45%) following by resection of pulmonary artery trunk (15/71, 21%). No ventricular resection has ever been reported in any series. Multiple resections are reported in only 6 patients (8%): the most common association was combined resection of pulmonary artery and left atrium.

Due to the small size of each study, none of them analyzed the impact of resected organ on survival. However, Kauffmann *et al.* (32) described that the invasion of the aorto-pulmonary window could be considered a significant prognostic factor: 3/5 patients died six months after surgery due to local recurrence (32). The authors explained this result due to the fact that in the aorto-pulmonary window resection margins to other vital mediastinal structures are too narrow for effective radical resection, in spite of en bloc resection of cardiovascular structures and pathological R0 status (32).

A recent systematic review reported that the resected organ didn't affect survival (22). However, several limitations were presents in this study, above all the lack of formally evaluation of publication bias. Muralidaran underscores as all included studies were characterized by a strong bias to report uneventful surgical resection rather than those that were complicated. This hypothesis is confirmed by the extremely low reported perioperative mortality rate (0% at 90-day) suggesting that the surgical results presented in the literature may derive from a skewed population (22).

Considering the lack of data concerning survival due to the small size of analyzed studies, the overall picture emerging from literature did not allow us to speculate about the presence or not of significant survival difference based on the specific organ resected during CPB surgery.

### *R0 resection rate*

Long-term outcomes of patients with T4 NSCLC depends primarily on the completeness of resection (R0): any incomplete resection with either a gross (R2) or microscopic (R1) residual tumor is responsible for a significant decrease in survival (35,36). Martini *et al.* reported, in a series of NSCLC invading the mediastinum a 5-year survival rate of 30% and 14% in case of R0 and R1, respectively (6). Similar data have been reported by Fukuse *et al.*: 3-year survival rate of 44% and 0% for R0 and R1, respectively (35). In these above mentioned studies, CPB was not used and the R0 rate was 45% and 37%, respectively. These data confirmed that surgical resection of T4 tumors involving the heart and great vessels can be achieved without CPB with questionable R0 rate.

In the studies included in the current review, R0 reported rate was extremely high, ranging from 75% to 100% (R1 resection was reported only in 7/71 cases). No data are available concerning the causes of 3 R1 resection in one series (31). In remaining 4 patients, the R1 resection was unexpectedly observed at final histologic examination. All R1 patients were died (median survival: 7 months) (29) or presented local recurrence at follow-up (30). The best 5-year overall survival (60%) was reported by Filippou presenting a 100% R0 rate in a large series of 12 patients (34). Langer *et al.*, in their series of 20 patients characterized by a 95% R0 rate, were the only ones to report surprising 10-year survival values (28%) (33).

These data confirm the importance of R0 resection and the probable role of CPB to allow this providing a widespread and detailed inspection of infiltrated cardiac or vascular structures consenting for safe resections margins.

### *N status*

One feature of T4 NSCLC is the high frequency of lymph node (LN) involvement (50%) (37,38). In 4 evaluated studies a detailed N status was reported: LN involvement was reported in 49% (19/39) of cases and N2 rate was 20% (8/39) (29-32). No cN3 NSCLCs were submitted to surgery in all selected studies (29-34).

A substantial amount of clinical researches investigated the impact of lymph-node status on survival in T4 NSCLC. Doddoli *et al.* reported a difference in median survival of 16 *vs.* 9 months for N0-1 and N2 disease, respectively, in T4 NSCLC invading mediastinal structures (38).

In our critical review, only one study analyzed the impact of nodal status on survival for T4 NSCLC treated with CPB (31). Ohat *et al.* demonstrated that survival outcome was relatively favorable for patients with N0, if compared with N2 or N3 disease (31): median overall survival and 5-year survival were 31 months and 70%, respectively, for N0 disease and 10 months and 17% for the N2 or N3 disease (31). In the remaining studies, although an analysis of survival in relation to LN status was not performed, all authors agree that lung resection on CPB for locally advanced NSCLC should be performed only in well-selected patients with no mediastinal LN metastasis (N0–1) (30,33,34). Hasegawa and Langer did not consider N2 disease as an absolute contraindication for surgery. According to Hasegawa, the decision on surgical treatment of cN2 NSCLC should be taken on case by case, but exclusively in case of a single level cN2 disease (29). According to Langer, patients with N2 disease should be submitted to surgery if they are eligible to lobectomy or otherwise relatively limited operations; on the other hand, patients presenting clinical N3 disease and high-risk N2 disease, such as requiring pneumonectomy or carinal pneumonectomy, should be considered not surgical candidates (33). A systematic review performed by Muralidaran *et al.* found that the nodal status (N0 *vs.* N1–2) was not a prognostic factor in patients submitted to resection under CPB for a NSCLC. However, the authors themselves criticize their result due to both the lack of an adequate sample size affecting the power of the study and the bias of included studies (22).

All these results underscore the importance of accurate diagnosis of mediastinal lymph-node involvement before surgical treatment. The presence of N2 or N3 disease should preclude surgical resection considering the risks of postoperative complications and the low rate of long survival.

### *Overall morbidity and 30-day mortality*

Following routinely lobectomy or pneumonectomy, respiratory complications occur with an incidence of more than 49% (39). In case of additional application of CPB, more frequent and severe pulmonary injury has to be expected. CPB is known to cause lung injury and may be harmful, especially with prolonged use. Furthermore, several CPB-related complications have been reported in addition to non-fatal complications that are common to general thoracic resections and are not necessarily attributable to the use of CPB. Low cardiac output syndrome, reoperation for bleeding, stroke and pulmonary edema are the most common reported (26). Finally, studies reporting concomitant pulmonary resection and cardiac procedure with CPB support showed an increased rate of pulmonary complication and an excessive bleeding (26).

In our analysis, overall morbidity [not reported in one study (33)], ranged from 25% to 63% (29,32). Interestingly 4 out of 5 studies reported an overall morbidity lower than 42%. Overall 30-day mortality, ranged from 0% to 12.5% (29-32,34). In three studies the 30-day mortality reported was 0% (29,30,34).

Langer *et al.* didn't find any significant difference in 30-day mortality between patients undergoing resection with CPB and those without CPB (33). Any CPB-related complications have been reported in three studies (30,32,34). Hasegawa reported only two patients complicated by respectively a cerebral infarction and a cardiac low-output syndrome for several days (29). Ohta reported 3 pleural bleeding after operations, but no critical complications with an intensive care unit stay less than 3 days for each patient (31). In the series of Langer only one patient presented a pulmonary oedema but, interestingly, the red blood cell transfusion rate was comparable in patients operated for a T4 NSCLC by using or not CPB (33).

All these evidences support the fact that resection of T4

NSCLC, although challenging, can be performed under CPB without a major increase in pulmonary and/or in CPB-related complications.

### *Long-term results*

This critical review demonstrates a published survival benefit in the field of the surgical resection of stage T4 NSCLC under CPB.

In the evaluated studies, the reported 5-year survival rate ranged from 37% to 60%. Filippou *et al.* reported the best 5-year survival of 60% (34). Ohta *et al.* reported a reassuring 48% 5-year survival in T4 NSCLC presenting with infiltration of descending thoracic aorta (31). Marie Lanneloungue group reported the best long-term results with a 28% 10-year survival (33). In this latter series of 375 patients of which 20 required CPB for resection there was no difference without or with CPB in overall survival (40% *vs.* 37%, respectively) or disease free survival (33% for both). In the same manner, the above mentioned 5-year survival rate are similar to those reported for other T4 NSCLC resected without CPB: 31% 5-year survival for vena cava resection (40), 14% 5-year survival for left atrium resections (41) and 28% 5-year survival for central pulmonary artery resection (42). Finally, these reporting data are extremely encouraging if compared to 23–37% global 5-year survival commonly reported in the literature for patients with pT3 disease (43) or to 6–8% 5-year survival for T4 treated exclusively with systemic therapy (32). These data underscore that CPB can be a safe and important tool in thoracic oncologic surgery allowing good long-term survival after a extremely challenging surgery.

### *Summary*

Considering these limited series, no definitive conclusions can be drawn based on the heterogeneity of the studied population, but several general considerations are possible:

- ❖ Over the past few years, resection of T4 NSCLC using CPB has been more frequently reported.
- ❖ R0 resection rate is extremely high (75–100%), probably because CPB allows a complete inspection of infiltrated mediastinal structures allowing for safe resections margins.
- ❖ Lymph-node involvement is a significant prognostic factor in T4 NSCLC. Therefore, surgery should be proposed in highly selected patients (T4 N1–0); in cases of N2 or N3 disease considering the low satisfactory rates of long-term survival a case-by-case selection is needed.
- ❖ In experimented surgical centers, T4 NSCLC can be treated using CPB with an acceptable overall morbidity and 30-day mortality.
- ❖ Satisfactory long-term result can be obtained (5-year survival rate 37–60%, 10-year survival rate: 28%).

## T4 NSCLC needing complex trachea-bronchial resection

ECMO represents the ECLS of choice for the treatment of T4 NSCLC presenting with carinal extension or needing complex tracheobronchial reconstruction. In these cases, hemodynamic stability or cardiac arrest is not required and a good oxygenation in addition to removal of $CO_2$ and a complete ventilator support could entirely be assured by ECMO (18).

ECMO involves the use of a centrifugal pump to drive blood from the patient through an externalized membrane oxygenator system for carbon dioxide and oxygen exchange before returning to the patient. Two different form of ECMO are available: veno-arterial (VA) and veno-venous (VV). In addition to assisting in gas exchange, VA ECMO can augment cardiac output. According to the specific indications, these techniques assistance may be introduced peripherally or centrally (44,45). Differently from CPB, ECMO requires minimal amount of heparinization (46). In addition, several technological benefits derive from the use of ECMO such as the miniaturization of circuits requiring lower priming volumes, limited air/blood contact by closed circuits without cardiotomy suction/reservoir, and improved biocompatibility of material used in circuit components making them suitable for long term use (47). This letter benefit allows maintaining ECMO post-operatively in case of acute lung injury of the contralateral lung with consecutive pneumonia and acute respiratory distress syndrome (ARDS), conditions commonly reported after oncological resections performed with CPB (15). From an oncological point of view, a potential prevention of tumour cell spread is expected by using ECMO considering that during jet ventilation a intrathoracic dissemination of mucosal tumor cells due to a mechanical exfoliation is theoretically possible. Unlike CPB, ECMO is a closed circulatory system without reservoir suction, therefore tumour cells from the operative field cannot be reintroduced into the vascular system (48).

Miniaturized extracorporeal circulatory systems like

**Table 2** Studies reported at the least 5 patients undergoing pulmonary resection for NSCLC using ECMO

| Studies | Year | No. of NSCLC treated | T4 NSCLC | Lung resection | Other procedure | ECMO type | R0 | N status | Morbidity | 30-day mortality | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lang (49) | 2011 | 7/9 | 7/7 | Carina: 3; PN: 2; sleeve PN: 1; UBL + carina sleeve: 1 | Ao: 2, PA: 1 | Central: 4, peripheral: 3 | 6/7 | N0: 2, N1: 1, N2: 3, Nx: 1 | Overall: 57%, ECMO: lymphatic fistula left groin | 0% | 6/7 alive, 1 dead at 11 months, 2/6 recurrence at 18 and 20 months, 3-yr survival: 57% |
| Lang (50) | 2015 | 7/10 | 6/7 | Carina: 3; sleeve PN: 1; UBL + carina sleeve: 1; LUL + broncovascular sleeve: 1 | PA: 1 | Central: 3, peripheral: 2 | 5/6 | N0: 2, N1: 1, N2: 2, Nx: 1 | Overall: 50%, ECMO: 0% | 0% | 3/6 alive, 2 dead at 37 and at 61 months for tumour recurrence, 1 dead at 20 months for COPD exacerbation, 5-yr survival: 66% |
| Redwan (51) | 2015 | 6/9 | 2/6 | Lobectomy: 1; sleeve PN: 1 | PA: 1 | Veno-venous: 2 | NR | N0: 2 | Overall: 50%, ECMO: 0% | 0% | |

NSCLC, non-small cell lung cancer; ECMO, extracorporeal membrane oxygenation; PN, pneumonectomy; UBL, upper bilobectomy; LUL, left upper lobectomy; Ao, aorta; PA, pulmonary artery; COPD, chronic obstructive pulmonary disease.

ECMO have a significantly lower impact than CPB in causing the transient immunosuppression associated with open-heart surgery preventing the spread or the growth of hidden cancer cells (48). Surgically, there are several practical advantages of intraoperative ECMO. First, no disturbing lines or tube obstruct the operative field unlike advanced conventional ventilation techniques. Second, the patient's hemodynamics remains completely stable during the entire surgical procedure and the possibility to move the heart maximally represents a condition that is not offered by any other type of intraoperative ventilation support system except CPB (49).

At our review, only 3 retrospective studies reporting their experience with ECMO for resection of T4 NSCLC (including at least 5 cases) have been published (*Table 2*). A total of 28 patients are reported in these series: 20 of them were affected by NSCLC and only 15 were affected by T4 NSCLC. The most common surgical procedures performed were complex trachea-bronchial resection involving carina (more than 60%). The 3 published studies reported the experience of two surgical teams: the Viennese group, that described the adoption of VA ECMO (49,50), and the German one, that mostly adopted the VV ECMO (51).

### *Viennese group experience and VA ECMO*

This group has reported his experience with intraoperative VA ECMO in bronchial resection procedure associated (49) or not to descending aorta resection (50). In 2011, Lang *et al.* reported a series of 7 cases of T4 NSCLC: in 5 of them, ECMO was necessary to perform complex tracheobronchial reconstructions, while in the other 2 cases ECMO was used to perform descending aorta resections (49). In 2014, the same group reported a series of 6 patients submitted to a complex tracheal-bronchial resection for a T4 NSCLC by using VA ECMO (50). In this series 5 of 6 patients were the same those reported in 2011 while the last one was a patient submitted to a left upper lobectomy (LUL) with bronco vascular sleeve.

In their experience VA ECMO support was considered a safe approach and an alternative to CPB for complex tracheo-bronchial resections, thus avoiding the disadvantages of CPB (49,50). Based on this experience, ECMO should be used in performing resection of great vessels too, except open resection of either the left or right atrium, resection of the aortic arch, and central resection of the pulmonary trunk which should be performed with conventional CPB support (49,50).

### *German group experience and VV ECMO*

The German group reported their institutional experience with intraoperative VV ECMO during thoracic surgical resection. A total of 9 patients were reported, of which 6 presented a NSCLC but only 2 of them were classified as T4. In reporting their experience, they summarized three different scenarios based on clinical setting and the planned surgical procedures (51):

(I) Patients with previous extensive contralateral pulmonary resection including pneumonectomy. In these cases, a planned anatomical resection with radical LN dissection could be difficult both if they are operated using short intermittent apnoeic phases and due to the limited surgical exposure. To overcome this problem the authors reported the use in their cohort of apnoeic phases up to 45 minutes under low flow VV ECMO in combinations with apnoeic oxygenation in performing anatomical segmentectomy with radical lymph-node dissection in 3 patients with previous pneumonectomy.

(II) Patients having severely compromised pulmonary function, severe emphysema and preoperative hypercapnia. In these patients, conventional ventilation may be problematic due to hyperinflation and bronchial obstruction. In this setting, a single site cannulation low-flow VV ECMO offers sufficient intraoperative support assuring 'protective' single lung ventilation and avoiding additional trauma to the ventilated pathological lung due to intraoperative high –pressure single lung ventilation. In their series, they reported one patient affected by a T4 NSCLC that was submitted to an extended right lower lobectomy with angioplasty of right pulmonary artery, re-implantation of the middle lobe bronchus and en bloc segmentectomy (SII) by using VV ECMO.

(III) Necessity to perform a left-sided carinal pneumonectomy. In this case, ECMO procedure is justified by authors by the needing to avoid cross-field or jet ventilation in the right lung that normally is complex due to the bronchial anatomy. The authors report one patient in their series affected by a T4N0 NSCLC submitted to left-sided pneumonectomy with carinal sleeve resection by using VV ECMO. According to the authors, ECLS support leads, by avoiding cross-field ventilation, to an optimal surgical exposure and sufficient gas exchange throughout the entire procedure.

### *R0 resection*

In case of complex tracheobronchial resections, a complete resection with negative margins documented during surgery by frozen section is mandatory. A positive margin should be accepted only if further resection is precluded by excessive risk imposed on the planned airway reconstruction (52,53). On the other side, the distance considered a safe limit between proximal tracheal and distal main bronchial margins is 4 cm. This should not be exceeded if anastomotic tension is to be minimized (54), considering that anastomotic dehiscence represents one of the main cause of morbidity (11–17%) and mortality (44%) (55).

In the evaluated studies, R0 resection rate reported by Austrian groups was high (more than 83%) in the two series. No data about resection margins are reported by the German group (51). The high rate of R0 resection reported in these series can be obtained exclusively with a careful patient selection and rigorous diagnostic work-up. Airway endoscopy is crucial, allowing to correctly identify the degree and extension of carinal infiltration, to histologically confirm the presence of cancer by target biopsies and to check the feasibility of the procedure and a tension-free anastomosis by random biopsies, 1 or 2 centimetres above and below the visible tumour (56).

### *N status*

Malignant tumors involving the carina and/or distal trachea without lymphatic or systemic metastasis are uncommon but not rare (57). Most of these patients are diagnosed at an advanced stage precluding surgical resection. Instead, in patients with localized diseases, local management is an effective treatment with survival benefit (57).

In reviewed studies, N status was an important selection criteria. Only patients cN0 were directly submitted to surgery. Globally, considering only the second series of Lang and the series of Redwan, the cN0 rate was 87% (7/8) (50,51); only 1 patient was cN2 and, after chemo-radiation induction therapy, final pathology diagnosis was pTxNx. However, in Austrian series preoperative evaluation and clinical staging included a non-invasive mediastinal staging. As consequence, a high rate of N+ (3/6, 50%; N1: 1; N2: 2) was detected at final pathologic examination. One of these patients died at 61 months due to tumor recurrence while the remaining two were alive without recurrence respectively at 143 months (N1) and 111 months (N2) (50). Obviously, considering the small size of patients reported in each series, no study analyzed the impact of nodal status on survival for T4 NSCLC treated with ECMO.

However, in literature is clear the meaning of LN involvement in case of carinal resection for NSCLC. Mitchell *et al.* reported long-term results of 60 carinal resection for NSCLC, and showed that patients without nodal involvement (N0) or with limited involvement (N1) had substantially better survival than did patients who had involvement of mediastinal (N2/N3) nodes (48% *vs.* 12%, respectively). These results are comparable to survival data reported by Maeda *et al.* (58) and particularly Dartevelle and Macchiarini. In the latter series, the authors reported a 43% estimated 5-year survival with a significant survival advantage in patients without mediastinal nodal involvement (P=0.02) (7).

These literature data and data reporting in reviewed series underscore as patient selection is crucial. Invasive mediastinal nodal staging by mediastinoscopy or endobronchial ultra sound (EBUS) guided transbronchial needle biopsy (TBNA) is imperative to exclude an N2 disease or to propose induction chemotherapy and further restaging in this subgroup of patients (56). Mediastinoscopy should be performed at the same time of scheduled surgery to prevent mediastinal scarring that could reduce tracheal mobility (55).

### *Overall morbidity and 30-day mortality*

Tracheobronchial resections are challenging surgical procedures for resection of cancer involving lung, lower trachea, carina and tracheobronchial angle. In particular, tracheal sleeve pneumonectomy (TSP) represents one of the most challenging procedures in thoracic surgery due to the necessity to provide adequate ventilation on the remaining lung after distal trachea resection during tracheobronchial reconstruction (56). After a carina resection complication may occur in the postoperative period despite cautious patient selection and a careful surgical procedure (57). After carina resection for NSCLC the mortality rate ranges between 3% to 20% with an overall morbidity rate of 11% to 50% (57). ARDS occurs in more than 20% of TSP with a mortality rate of 50% to 100% (57). Anastomotic dehiscence is the second most important complication. It occurs from 11% to 17% and it is mostly related to tension, faulty anastomotic technique or intraoperative devascularisation with subsequent ischemia (55).

The perioperative outcomes reported by reviewed studies are encouraging. Despite the fact that all operations were technically challenging, no 30-day mortality was reported (49-51). None of the patients affected by T4 NSCLC developed an ARDS or needed prolonged ECMO support in postoperative period. None of reported patients experimented anastomotic dehiscence. Overall morbidity ranged from 50% to 57%. The only complication directly related to the use of ECMO was observed in the first series reported by Lang. It was a lymphatic fistula in the left side of the groin, which required surgical revision. Neither bleeding or thrombo-embolic complications nor air embolism or other technical pitfalls related to the use of ECMO were observed in the remaining patients. All these data support the fact that ECMO can be used without increasing morbidity in high–volume specialized centres with clinical experience in ECLS.

### *Long-term results*

In literature, for carefully selected patients submitted to carinal resections and TSP, 5-year survival ranges from 19% to 44% (18,59). The 3 evaluated studies mainly focused on the technical aspects of intraoperative use of ECMO and oncological outcomes are reported exclusively by two studied of Austrian group (49,50). The long term results reported by Lang are difficult to interpret considering the different histology of NSCLC and the adjuvant therapies. The overall 3-year survival reported in first series was 57%, the overall 5-year survival reported in the second one was 66%. Considering only the 5 patients submitted to complex tracheal-bronchial resection included in both series the reported 5-year survival in 2014 was 80%. Survival rate are similar to those reported by series of tracheal-bronchial resection performed without ECMO support (18,59).

### *Summary*

- ❖ For T4 NSCLC presenting with carina extension or needing complex tracheobronchial reconstruction, oxygenation and hemodynamic stabilization can be provided as well by ECMO even if his use remains exceptional and reported in a small number of patients.
- ❖ According to Austrian experience VA ECMO should be considered such as a safe alternative to CPB in performing complex tracheobronchial reconstruction or resection of great vessels.
- ❖ According to German experience, VV ECMO should be considered as partial or complete lung support in

particular setting (patients having severely compromised pulmonary function, previous pneumonectomy or during left sided carinal resection), avoiding the possible complications associated with other forms of ECLS such as CPB or VA ECMO.

- ❖ The high rate of R0 resection can be obtained exclusively with a careful patient selection and rigorous diagnostic work-up as confirmed by reviewed series.
- ❖ LN involvement is a main prognostic factor in any type of complex tracheobronchial resection; it should be investigated with a rigorous invasive mediastinal staging before surgery.
- ❖ Neither increased morbidity/mortality nor a reduced survival rate should be expected if ECMO support is performed in centers with extensive experience and practice.

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