Original Article

Extended resections for the treatment of patients with T4 stage IIIA non-small cell lung cancer (NSCLC) ($T_4N_{0-1}M_0$) with or without cardiopulmonary bypass: a 15-year two-center experience

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Background: Stage IIIA non-small cell lung cancer (NSCLC) is a heterogeneous group of patients, often requiring variable and individualized approaches. The dilemma to operate or not frequently arises, since more than 75% of the cases of NSCLC are diagnosed in advanced stages (IIIA). The main objective of this study was to assess whether the benefits outweigh surgical risks for the $T_4N_{0-1}M_0$ subgroup.

Methods: Data from 857 patients with locally advanced T4 NSCLC were retrospectively collected from two different institutions, between 2002 and 2017. Clinical data that were retrieved and analyzed, included demographics, comorbidities, surgical details, neoadjuvant or/and adjuvant therapy and postoperative complications.

Results: Twelve patients were in the cardiopulmonary bypass (CPB) group and thirty in the non-CPB. The most common types of lung cancer were squamous cell carcinoma (50.0%) and adenocarcinoma (35.7%). The most frequent invasion of the tumor was seen in main pulmonary artery and the superior vena cava. Significantly more patients of the CPB group underwent pneumonectomy as their primary lung resection (P=0.006). In all patients R0 resection was achieved according to histological reports. The overall 5-year survival was 60%, while the median overall survival was 22.5 months. Analysis revealed that patient age (P=0.027), preoperative chronic obstructive pulmonary disease (COPD) (P=0.001), tumor size (4.0 *vs.* 6.0 cm) (P=0.001), postoperative respiratory dysfunction (P=0.001) and postoperative atelectasis (P=0.036) are possible independent variables that are significantly correlated with patient outcome.

Conclusions: We suggest that in patients with stage IIIA/T4 NSCLC, complete resection of the T4 tumor, although challenging, can be performed in highly selected patients. Such an approach seems to result in improved long-term survival. More specific studies on this area of NSCLC probably will further enlighten this field, and may result in even better outcomes, as advanced systemic perioperative approaches such as modern chemotherapy, immunotherapy and improvements in radiation therapy have been incorporated in daily practice.

Keywords: Extended resection; carcinoma; non-small cell lung cancer (NSCLC); cardiopulmonary bypass (CPB)

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Introduction

It is known that stage IIIA non-small cell lung cancer (NSCLC) is a heterogeneous group of patients, often requiring variable and individualized approaches. In particular, for T4 tumors, although a complete resection is really challenging even for experienced thoracic surgeons, it remains unclear if there is a true benefit for the patients. T4 lesions are defined by local invasion of structures, such as the heart, great vessels, esophagus, trachea, carina, recurrent laryngeal nerve, vertebral body, so that they are frequently considered unresectable. Surgical attempts of resecting such tumors require advanced techniques, often including the use of cardiopulmonary bypass (CPB).

The dilemma to operate or not frequently arises, since more than 75% of the cases of NSCLC are diagnosed in advanced stages (IIIA) (1). Patients with locally advanced T4 NSCLC have a poor prognosis with systemic treatments, such as chemotherapy with or without radiation; the achievement of *en bloc* R0 resection seems to be a hopeful strategy, as it may yield a 43% 5-year survival rate (2). However, few surgical series have been reported examining separately the outcome in T4/stage IIIA NSCLC, so that the question of the value of resection of such tumors is not clearly established, for $T4N_{0-1}$ patients (3). Determination of resectability, surgical staging, and extent of pulmonary resection should be made by a multidisciplinary approach. Accordingly, highly selected patients may benefit from multimodal therapy, including surgery (4).

In this study, we retrospectively analyzed the characteristics and the outcomes of patients with clinical stage IIIA ($T_4N_{0-1}M_0$) NSCLC, who underwent an intended curative resection at two different cardiothoracic surgical centers in Europe. The main objectives of this study were to assess whether the benefits outweigh the surgical risks and if CPB was associated with worse outcome.

The study was approved by institutional ethics board of European Interbalkan Medical Center (No. 1287), while all patients had pre-operatively been through an informed-consent process where future publication of data was pre-authorized.

Methods

Patients

Data from 857 patients with locally advanced T4 NSCLC were retrospectively collected from two different institutions between 2002 and 2017. At the Cardiothoracic Department of Interbalkan Medical Center of Thessaloniki (Greece), 29 patients underwent pulmonary resections for T4 NSCLC and by the Thoracic Department of St James University Hospital of Leeds (UK), 13 patients were treated for the same reason, for a total of 42 patients.

Clinical data that were retrieved and analyzed, included demographics (age, gender), comorbidities [chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), myocardial infarction (MI), diabetes, stroke, hypertension, renal dysfunction], tumor characteristics (histology, T status, pathological stage, topography), lymph node invasion (pathological N status), organ invasion (thoracic inlet, superior vena cava, inferior vena cava, trachea, carina, pericardium, intra-pericardial pulmonary artery, left atrium, right atrium, thoracic aorta, esophagus, diaphragm, vertebra), surgical approach, resection type, use of CPB, use of neoadjuvant therapy, use of adjuvant therapy and postoperative complications [atrial fibrillation (AF), MI, stroke, pneumonia, atelectasis, respiratory failure (as defined by prolonged need for non-invasive oxygenation due to desaturation), renal failure (as defined by exceeding the baseline serum creatinine level), reoperation for bleeding].

Preoperative workup

As per routine, all patients underwent a preoperative evaluation, including staging [chest computed tomography (CT) scan, brain CT, upper abdomen CT and bone scan or brain magnetic resonance imaging (MRI) and positron emission tomography with CT (PET-CT scan)], flexible fiberoptic bronchoscopy, respiratory mechanics tests (spirometry), lung parenchyma function tests [diffusion capacity for carbon monoxide (DL_{CO}), arterial blood gas analysis], cardiopulmonary interaction tests (stair climbing, 6-minute walk, VO_2max), transthoracic echocardiogram, routine biochemical profile and blood tests.

On clinical grounds, a few patients underwent additionally chest MRI, ventilation perfusion lung scintigraphy and vibration response imaging (VRIxp™). Mediastinoscopy or endobronchial ultrasound (EBUS) was performed only in patients with a mediastinal lymph node larger than 1 cm or PET-positive. We excluded in this study patients, who had only chest wall invasion. All selected cases were discussed in a multidisciplinary team meeting involving chest physicians, thoracic surgeons, chest radiologist, clinical and medical oncologists and histopathologists; such setting is available in both centers.

Operative methods

All patients underwent general anesthesia with double lumen tube, except of cases with central airway invasion, where special ventilation techniques, namely jet ventilation, time limited apneic diffusion oxygenation or use of CPB/extracorporeal membrane oxygenation (ECMO). We selected the most appropriate surgical approach according to tumor invasion: median sternotomy, posterolateral thoracotomy, clamshell or hemi clamshell, Dartevelle, Shaw-Paulson and cervical incision. The decision of using CPB was performed in selected patients intraoperatively, with peripheral cannulation sites and beating heart. In cases with invasion of great vessels or atrium, after resection, the affected structure was reconstructed by autologous or heterologous pericardial patch.

All patients were followed up initially at the tertiary center for 6 months. Subsequently, the follow-up protocol was organized by the medical oncologist; outpatient visits were planned every 3 months for the first 2 years and annually thereafter.

Statistical analysis

Statistical analysis was performed using the statistical package IMB SPSS Statistics v.20.0. All results are expressed as medians and ranges or as absolute numbers and percentages. Statistical significance was evaluated using the χ^2 test with P value of less than 0.05. Survival curves were calculated using the Kaplan-Meier method. Univariate comparison was performed using a Cox proportional hazard model. Two post hoc groups, one with CPB and the non-CBP groups were analyzed separately and outcomes were compared.

Results

Patient characteristics

A summary of the demographic and clinical data recorded is listed in *Table 1*. There were 11 female patients (26.2%) among the 42 patients. Twelve patients were in the CPB group and 30 in the non-CPB. The median age was 65.0±12.8 (range, 28–75) years for the CPB group and 63.5±11.8 (range, 24–70) years for the non-CPB group. No statistically significant differences were found for medical comorbidities between the two groups. The median size of the tumor was 4.0±1.9 cm in the non-CPB group and 6.0±2.2 cm in the CPB group. The most common types of lung cancer were squamous cell carcinoma (SCC) (50.0%) and adenocarcinoma (35.7%). The most frequent invasion of the tumor was seen in main pulmonary artery and the superior vena cava.

Surgical details

The most preferable surgical approach was the posterolateral thoracotomy (61.9%). Significantly more patients of the CPB group underwent pneumonectomy as their primary lung resection (P=0.006). The surgical operation was completed in most cases without the usage of the CPB (30 *vs.* 12 patients). For the patients who required CBP, the preferable cannulation site was the right femo-femoral site, with mean duration 45.0±7.0 minutes. The use of the CPB was intraoperatively decided in 14 cases, but only used at the 12 cases (CPB standby in 2 cases). In all patients R0 resection was achieved according to histological reports. A small sample of surgical techniques is presented in *Figures 1-3*.

Postoperative complications

The postoperative outcomes are presented at the *Table 2*. The median length of the in overall hospital stay was similar in the two groups (8.0±4.7 days). The rate of major postoperative complications was different in the two groups. The most frequent observed complications were AF (14.3%) and atelectasis (14.3%). Blood transfusion was significantly higher in the CBP group (P=0.010). Thirty-day mortality was zero in both groups. Most of the patient received adjuvant chemotherapy (76.2%), while fewer received additionally adjuvant radiotherapy (40.5%). Hematogenous tumor dissemination of patients undergoing CPB was not observed.

Overall survival (OS)

The overall 5-year survival was 60%, while the median OS was 22.5 months (*Figure 4*). Between the two groups there was no statistically significant difference in OS (P=0.353), as presented in *Figure 5*. We tried to identify a possible predictive factor for survival, using the Cox regression analysis by various characteristics and the results are shown on *Table 3*. Analysis revealed that patient age (P=0.027), preoperative COPD (P=0.001), tumor size (4.0 *vs.* 6.0 cm) (P=0.001), postoperative respiratory dysfunction (P=0.001) and postoperative atelectasis (P=0.036) are possible

Table 1 Patient demographics and comorbidities—tumor characteristics

Variables	Total		No CPB or standby		On CPB		P value
	N	%	N	%	N	%	
Demographic							
Patient number	42	100.0	30	71.4	12	28.6	–
Age, years (median)	64.5±12.0		63.5±11.8		65.0±12.8		0.811
Sex							0.464
Male	31	73.8	21	50.0	10	23.8	
Female	11	26.2	9	21.4	2	4.8	
Center							0.007
GR	29	69.0	17	40.5	12	28.6	
UK	13	31.0	13	31.0	0	0.0	
Medical comorbidities							
COPD	14	33.3	9	21.4	5	11.9	0.491
Hypertension	3	7.1	2	4.8	1	2.4	1.000
CAD	2	4.8	2	4.8	0	0.0	1.000
MI	2	4.8	2	4.8	0	0.0	1.000
Diabetes	3	7.1	3	7.1	0	0.0	0.541
Stroke	1	2.4	1	2.4	0	0.0	1.000
Renal dysfunction	0	0.0	0	0.0	0	0.0	–
Smoking	30	71.4	21	50.0	9	21.4	1.000
Tumor characteristics							
Size, cm (median)	4.5±2.0		4.0±1.9		6.0±2.2		0.530
Pathology							
Squamous	21	50.0	18	42.8	3	7.1	0.040
Adenocarcinoma	15	35.7	8	19.0	7	16.7	0.053
Large cell	1	2.4	1	2.4	0	0.0	0.522
Atypical carcinoid	2	4.8	2	4.8	0	0.0	0.359
Adenocystic	2	4.8	1	2.4	1	2.4	0.492
Glomus	1	2.4	0	0.0	1	2.4	0.110
Adjacent anatomic structure invasion							
Thoracic inlet	4	9.5	3	7.1	1	2.4	0.931
SVC	8	19.0	6	14.2	2	4.8	0.804
IVC	0	0.0	0	0.0	0	0.0	–
Trachea	2	4.8	0	0.0	2	4.8	0.022
Carina	6	14.3	4	9.5	2	4.8	0.780
Pericardium	7	16.7	2	4.8	5	11.9	0.006

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total		No CPB or standby		On CPB		P value
	N	%	N	%	N	%	
Pulmonary artery	9	21.4	8	19.0	1	2.4	0.191
Intrapericardial PA	4	9.5	1	2.4	3	7.1	0.031
Left atrium	3	7.1	1	2.4	2	4.8	0.130
Right atrium	1	2.4	0	0.0	1	2.4	0.110
Thoracic aorta	3	7.1	0	0.0	3	7.1	0.004
Esophagus	1	2.4	0	0.0	1	2.4	0.110
Diaphragm	0	0.0	0	0.0	0	0.0	–
Vertebra	2	4.8	2	4.8	0	0.0	0.359
Surgical approach							
Thoracotomy	33	78.6	26	61.9	7	16.7	0.086
Sternotomy	1	2.4	0	0.0	1	2.4	0.110
Cervical	2	4.8	0	0.0	2	4.8	0.022
Clamshell	2	4.8	0	0.0	2	4.8	0.022
Hemi-Clamshell	1	2.4	1	2.4	0	0.0	0.522
Dartevelle	1	2.4	1	2.4	0	0.0	0.522
Shaw-Paulson	2	4.8	2	4.8	0	0.0	0.359
Pulmonary resection							
Lobectomy	14	33.3	11	26.2	3	7.1	0.469
Sleeve lobectomy	8	19.0	7	16.7	1	2.4	0.263
Double sleeve lobectomy	6	14.3	6	14.3	0	0.0	0.094
Pneumonectomy	7	16.7	2	4.8	5	11.9	0.006
Sleeve pneumonectomy	4	9.5	3	7.1	1	2.4	0.868
Resection of trachea	3	7.1	1	2.4	2	4.8	0.130
CBP details							
Cannulation site	–	–	–	–	Femo-femoral		–
Time (min)	–	–	–	–	45.0±7.0		–

CPB, cardiopulmonary bypass; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; MI, myocardial infraction; SVC, superior vena cava; IVC, inferior vena cava; PA, pulmonary artery.

independent variables that are significant correlated with patient outcome (*Figure 6*).

Discussion

This retrospective study was undertaken to quantify outcomes of surgical management of the primary pulmonary tumor in patients with clinical stage IIIA ($T_4N_{0-1}M_0$), using data of two different centers. In order to assess the clinical usefulness of such resections, we attempted to identify patient and tumor factors associated with survival. Such an endeavor might identify parameters that could potentially improve future patient selection. Additionally, we intended to test the hypothesis, that surgical resection with CPB is

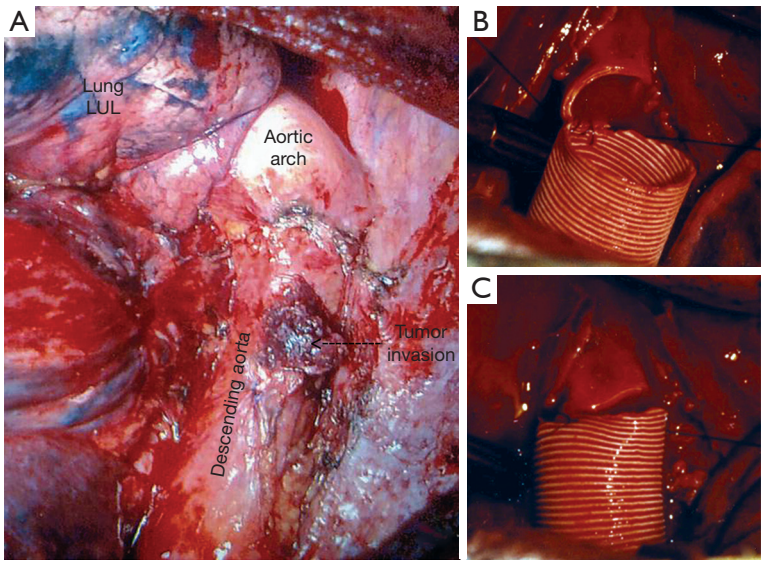

Figure 1 Descending aorta invasion resection and reconstruction with synthetic graft. (A) Tumor invading the wall of descending aorta; (B) the begging of end to end proximal aorta-graft anastomosis; (C) completing of proximal aorta-graft anastomosis. LUL, left upper lobe.

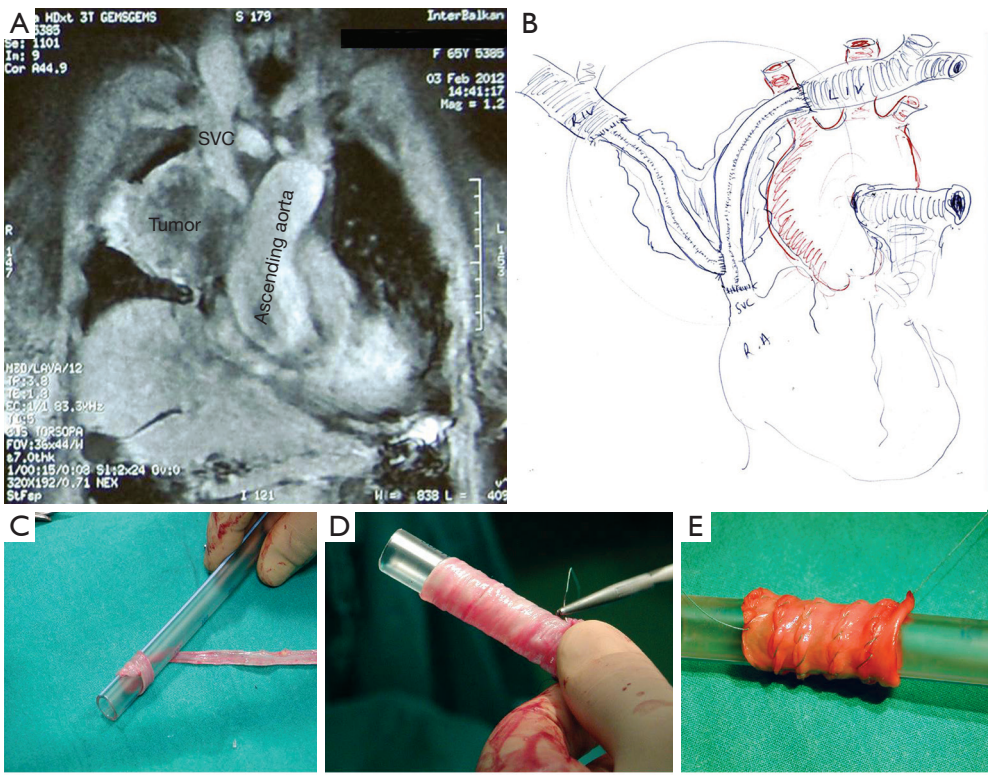

Figure 2 Superior vena cava (SVC) invasion resection and reconstruction with native venous-graft. (A) Tumor invading the SVC (chest MRI—coronal view); (B) handmade sketch of SVC and anonymous reconstruction with native graft constructed by saphenous vein; (C,D,E) stages of native venous-grafts construction by saphenous vein. MRI, magnetic resonance imaging.

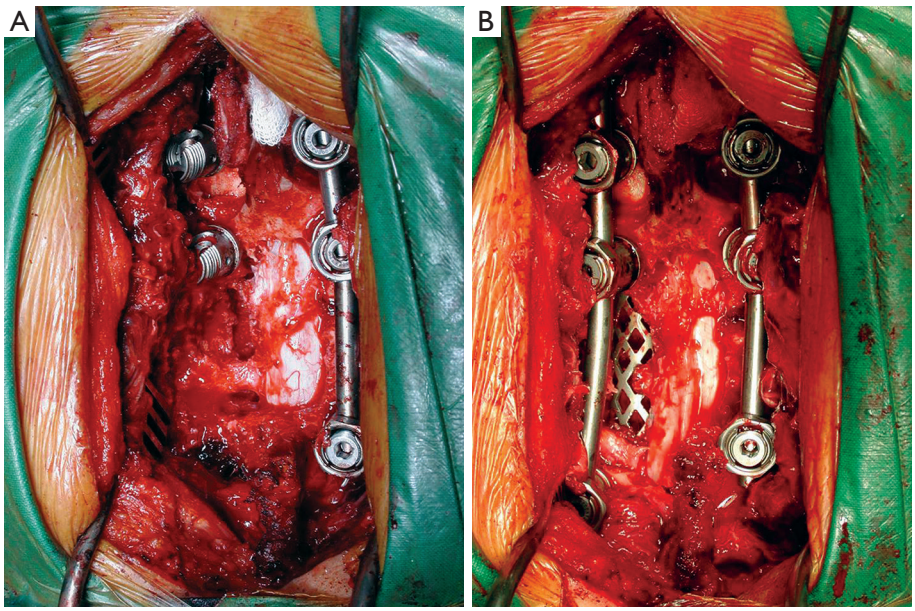

Figure 3 Surgical field after resection of tumor invasion of thoracic spine and spondylodesis.

Table 2 Patient postoperative characteristics

Characteristics	Total		No CPB or standby		On CPB		P value
	N	%	N	%	N	%	
Adjuvant therapy							
Chemotherapy	32	76.2	22	52.4	10	23.8	0.696
Radiotherapy	17	40.5	11	26.2	6	14.3	0.498
In hospital stay (days) median	8.0±4.7		8.0±5.5		8.0±1.5		0.590
Postoperative complications							
AF	6	14.3	3	7.1	3	7.1	0.329
MI	0	0.0	0	0.0	0	0.0	–
Pneumonia	4	9.5	3	7.1	1	2.4	1.000
Respiratory failure	2	4.8	2	4.8	0	0.0	1.000
Atelectasis	6	14.3	5	11.9	1	2.4	0.655
Reoperation	1	2.4	1	2.4	0	0.0	1.000
Pulmonary edema	0	0.0	0	0.0	0	0.0	–
Renal hemodialysis	0	0.0	0	0.0	0	0.0	–
Blood transfusion (units)	1.3±1.1		0.8±1.0		2.4±0.6		0.010
30-day mortality	0	0.0	0	0.0	0	0.0	–

CPB, cardiopulmonary bypass; AF, atrial fibrillation; MI, myocardial infraction.

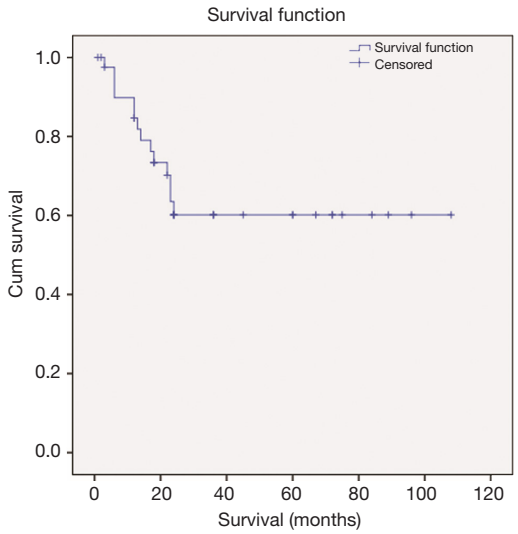

Figure 4 Kaplan-Meier plot for the full group of participants.

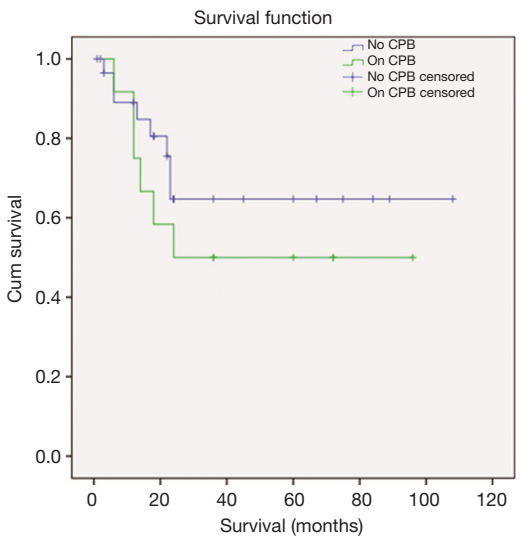

Figure 5 Kaplan-Meier plot for the groups A (no CPB) and B (on CPB). CPB, cardiopulmonary bypass.

Table 3 Cox regression in survival

Variable	P value
Demographic	
Age (years)	0.027
Medical comorbidities	
COPD	0.001
Hypertension	0.999
CAD	0.390
MI	0.390
Diabetes	0.999
Stroke	0.257
Renal dysfunction	–
Smoking	0.244
Tumor characteristics	
Size (cm)	0.001
Pathology	0.288
Adjacent anatomic structure invasion	0.648
Surgical	
Approach	0.124
CPB	0.359
Resection type	0.345
Postoperative	0.017
AF	0.224
Pneumonia	0.085
Respiratory dysfunction	0.001
Atelectasis	0.036
Adjuvant therapy	
Chemotherapy	0.886
Radiotherapy	0.775

COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; MI, myocardial infraction; CPB, cardiopulmonary bypass; AF, atrial fibrillation.

associated with worst perioperative or long-term survival compared to surgical resection without CPB.

The limited number of patients with potentially operable stage IIIA disease is a main reason why current evidence for this topic is generally limited to small single-institution studies (*Table 4*). T4 tumors that invade the heart, great vessels, thoracic vertebrae, or esophagus comprise a heterogeneous group of locally invasive lung cancers. Current National Comprehensive Cancer Network guidelines do not recommend surgery for T4 extension with N_{2-3} disease (stage IIIB). However, biopsy-proven $T4N_{0-1}$ (stage IIIA) may be operable (5). Localized tumors with invasion of the aorta, pulmonary artery, left atrium, thoracic vertebrae, or esophagus represent only small subset of T4 disease.

Randomized data providing proof of a survival advantage in patients undergoing extended resections for these

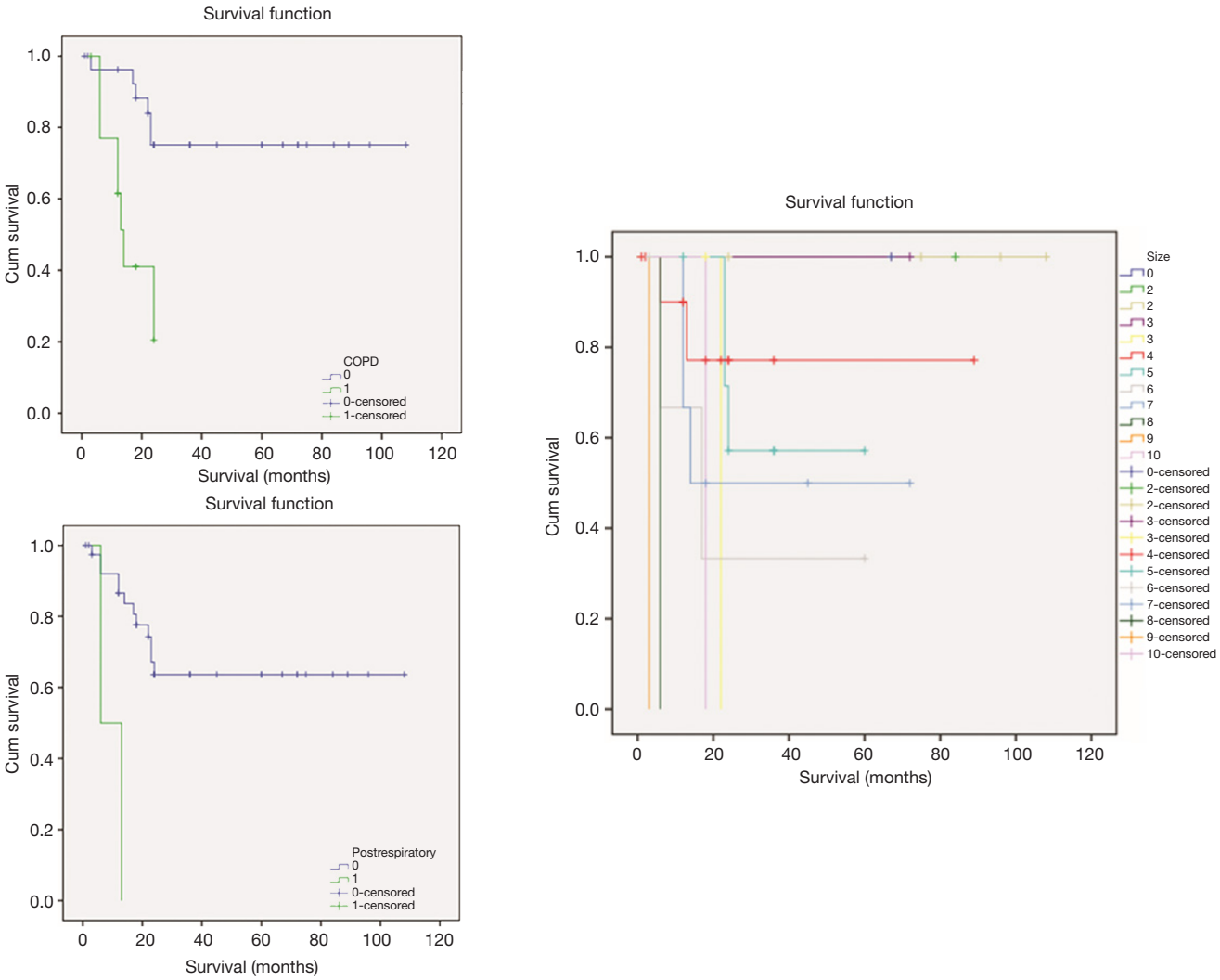

Figure 6 Cox proportional-hazards model (independent variables that are significant correlated with patient outcome). COPD, chronic obstructive pulmonary disease.

neoplasms are lacking. However, accumulated published experience seems to support the merits of a surgical approach on individualizing basis (5). We found, in agreement with literature (6), that the surgical approach was an appropriate therapeutic option in our selected patients, as the median OS was 22.5 months, and the overall 5-year survival was 60%.

The value of CPB has been reported for thoracic malignancies invading the heart or great vessels (7,8). CPB was used to resect tumor invading the aortic arch, the descending aorta, the pulmonary artery bifurcation, the left atrium, and the carina. However, few authors have reported their experience with CPB in lung cancer (9,10). In these studies authors confirmed the safety of CPB for NSCLC invading the great vessels and/or the left atrium in well-selected cases (7 patients in each of them), but they did not report long-term survival. Within the limitations of the small numbers of our subjects and no data related to the cause of deaths, we found no difference on (I) postoperative complications, (II) 30-day mortality and (III) the OS between the 12 patients underwent CBP and the 30 patients that weren't. To our experience, CPB was not associated with cancer dissemination. Our working hypothesis is that the application of adjuvant chemotherapy played a role in suppressing possible recurrences.

Long-term outcome of patients with locally advanced lung cancer depends primarily on the completeness of

Table 4 Review of publication for extended lung resections

Publication year	Author	Country	No. patient	Period	
				From	To
1971	Charles P. Bailey	USA	2	–	–
1991	Takayuki Shirakusa	Japan	12	–	–
1993	Maeda	Japan	42	–	–
1994	Ryosuke Tsuchiya	Japan	101	1962	1991
1994	Nael Martini	USA	44	1974	1984
1994	Thomas	France	15	1981	1991
1994	Roviaro	–	28	1983	1992
1995	Dartevelle	France	14	–	–
1995	Jakob R. Izbicki	Germany	94	1987	1990
1995	Tatsuo Fukuse	Japan	42	1976	1993
1996	Dartevelle and Macchiarini	–	60	–	–
1996	Pitz	The Netherlands	70	1977	1993
1997	Fukuse	Japan	42	1976	1993
1999	Takao Takahashi	Japan	49	1980	1996
1999	Walter Klepetko	Austria	7	1991	1996
1999	Mitchell	USA	135	1962	1999
2000	Spaggiari	France	25	1983	1996
2001	Mitchell	USA	60	1973	1998
2001	Victor A. Tarasov	Russia	50	–	–
2001	Oda	Japan	24	1981	1999
2001	Bernard A	France	77	1990	1998
2002	Mezzetti	Italy	27	1979	1999
2002	Spaggiari	France	93	1985	2000
2002	Ara A. Vaporciyan	USA	19	–	–
2002	Porhanov	Russia	151	1979	2002
2003	Cordula C.M. Pitz	The Netherlands	89	–	–
2003	Seiki Hasegawa	Japan	11	–	–
2003	Pitz	The Netherlands	89	1977	1993
2004	Spaggiari	Italy	15	1963	2000
2004	John G. Byrne	USA	14	–	–
2004	Ratto	Italy	19	1996	2004
2004	Bobbio	Italy	23	1982	2001
2005	Regnard	France	65	1983	2002
2005	Shargall	Canada	15	1988	2003

Table 4 (*continued*)

Table 4 (*continued*)

Publication year	Author	Country	No. patient	Period	
				From	To
2005	Lorenzo Spaggiari	Italy	15	–	–
2005	Mitsunori Ohta	Japan	16	–	–
2006	Macchiarini	Spain	50	2000	2006
2006	Roviaro	Italy	53	1983	2004
2006	De Perrot	France	119	1981	2004
2008	Rea	Italy	49	1982	2005
2008	Francesco Petrella	Italy	21	–	–
2008	Bedrettin Yıldızeli	France	271	–	–
2009	Wu	China	46	2000	2006
2010	Wang	China	48	1996	2008
2013	Lorenzo Spaggiari	Italy	125	1998	2010
2014	Geraud Galvaing	–	19	2004	2012
2016	Waldemar Schreiner1	Germany	9	–	–
2016	Langer	France	373	1980	2013

resection (R0). Data reported a series of lung cancer invading the mediastinum, and observed that the 5-year survival rate was 30%, if the tumor was completely resected, whereas it was only 14%, if it was incompletely resected (11). Others made similar observations in a series of lung cancers invading the heart or great vessels, with a 5-year survival of 40%, if the tumor was completely resected and much lower if the tumor was incompletely resected (12). In another study, the completeness of surgical resection in NSCLC stage IV invading the pulmonary sulcus and spine was a statistically significant predictor for 5-year survival; patients with an R0 resection have a 69% survival compared with 0% when the resection was incomplete (13). We suggest that a detailed mapping of the lung tumor extension and a preoperational decision regarding the use of CBP, give the best results. Of the 14 patients scheduled to undergo CBP, we eventually canceled only two, as it was not necessary. We succeed in all patients complete resection of the tumor. Postoperative complications were reasonable and the 30-day mortality was zero. Additionally, in agreement with the literature (14,15), the use of CPB does not appear to increase the risk of cancer dissemination as none of our patients had evidence of intrathoracic disease 5 years after the procedure. If the tumor extent remains a problem, in a subgroup of patients re-implantation or auto-transplantation techniques can be considered for cases in which is technically feasible, as extensive pulmonary resection can thus be performed, while minimizing the loss of pulmonary reserve (16,17).

It is important to identify prognostic factors to help select optimal surgical candidates. In that regard, there have been few publications with inconclusive results. In one study patient gender, *EGFR* mutation, N factor, and M factor showed no statistically significant effect on survival. However, not having SCC and being in the M-better group were significantly associated with improved survival (6). Others, in univariate analysis reported that smaller tumor size, fewer pack-years of cigarettes smoked, female sex, lower T factor, N factor, and overall pathologic stage were associated with improved survival, but only female gender remained an independent predictor of survival in multivariate analysis (18). We were able to identify patient age, preoperative history of COPD, tumor size, postoperative respiratory dysfunction and postoperative atelectasis are possible independent variables correlating with patient outcome. Among them, preoperative COPD, tumor size and postoperative respiratory dysfunctions can strongly influence the OS.

There are several limitations of this study. First, because of the retrospective nature of this study, the results are based on a highly selected group of patients, so that inherent biases cannot be excluded. Second, as the incidence of this entity is low, it was difficult to make conclusions about certain subgroups, such as different histology or to distinguish outcomes achieved in patients with different sites of lung invasion. Despite these serious limitations, dome guidance helping patient selection for this kind of surgical procedure can be discerned.

In conclusion, we suggest that in patients with stage IIIA ($T_4N_{0-1}M_0$) NSCLC, the complete resection of the T_4 tumor, although challenging, can be performed in highly selected patients. Such an approach seems to result in improved long-term survival. More specific studies on this area of NSCLC probably will further enlighten this field, and may result in even better outcomes incorporating advanced systemic perioperative approaches such as modern chemotherapy, immunotherapy and improvements in radiation therapy.

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None.

Footnote

Conflicts of Interest: 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 approved by institutional ethics board of European Interbalkan Medical Center (No. 1287), while all patients had pre-operatively been through an informed-consent process where future publication of data was pre-authorized.

References

1. Varela G, Thomas PA. Surgical management of advanced non-small cell lung cancer. J Thorac Dis 2014;6 Suppl 2:S217-23.
2. Langer NB, Mercier O, Fabre D, et al. Outcomes After Resection of T4 Non-Small Cell Lung Cancer Using Cardiopulmonary Bypass. Ann Thorac Surg 2016;102:902-10.
3. Dartevelle PG, Mitilian D, Fadel E. Extended surgery for T4 lung cancer: a 30 years' experience. Gen Thorac Cardiovasc Surg 2017;65:321-8.
4. Galvaing G, Chadeyras JB, Merle P, et al. Extended resection of non-small cell lung cancer invading the left atrium, is it worth the risk? Chin Clin Oncol 2015;4:43.
5. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
6. Chikaishi Y, Shinohara S, Kuwata T, et al. Complete resection of the primary lesion improves survival of certain patients with stage IV non-small cell lung cancer. J Thorac Dis 2017;9:5278-87.
7. Vaporciyan AA, Rice D, Correa AM, et al. Resection of advanced thoracic malignancies requiring cardiopulmonary bypass. Eur J Cardiothorac Surg 2002;22:47-52.
8. Byrne JG, Leacche M, Agnihotri AK, et al. The use of cardiopulmonary bypass during resection of locally advanced thoracic malignancies: a 10-year two-center experience. Chest 2004;125:1581-6.
9. Tsuchiya R, Asamura H, Kondo H, et al. Extended resection of the left atrium, great vessels, or both for lung cancer. Ann Thorac Surg 1994;57:960-5.
10. de Perrot M, Fadel E, Mussot S, et al. Resection of locally advanced (T4) non-small cell lung cancer with cardiopulmonary bypass. Ann Thorac Surg 2005;79:1691-6; discussion 1697.
11. Martini N, Yellin A, Ginsberg RJ, et al. Management of non-small cell lung cancer with direct mediastinal involvement. Ann Thorac Surg 1994;58:1447-51.
12. Fukuse T, Wada H, Hitomi S. Extended operation for non-small cell lung cancer invading great vessels and left atrium. Eur J Cardiothorac Surg 1997;11:664-9.
13. Collaud S, Waddell TK, Yasufuku K, et al. Long-term outcome after en bloc resection of non-small-cell lung cancer invading the pulmonary sulcus and spine. J Thorac Oncol 2013;8:1538-44.
14. Klepetko W, Wisser W, Bîrsan T, et al. T4 lung tumors with infiltration of the thoracic aorta: is an operation reasonable? Ann Thorac Surg 1999;67:340-4.
15. Horita K, Higuchi S, Nakayama Y, et al. An updated report of a case of lung cancer resected using cardiopulmonary bypass. Thorac Cardiovasc Surg 1997;45:100-1.
16. Tryfon S, Zarogoulidis P, Tsavlis D, et al. Ex situ

reimplantation technique, in central lung tumors. Ann Transl Med 2015;3:178.
17. Emmanouilides C, Tryfon S, Baka S, et al. Operation for preservation of lung parenchyma in central lung cancer--in vivo and ex situ reimplantation techniques. Anticancer Res 2015;35:1675-81.
18. Finley DJ, Yoshizawa A, Travis W, et al. Predictors of outcomes after surgical treatment of synchronous primary lung cancers. J Thorac Oncol 2010;5:197-205.

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