

Lobectomy with pulmonary artery resection: Morbidity, mortality, and long-term survival

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Objective: We report our experience with 93 consecutive pulmonary artery reconstructions during pulmonary lobectomy with regard to morbidity, mortality, and long-term survival.

Methods: Clinical records of all patients who underwent lobectomy with partial or circumferential pulmonary artery resection in a single institution during an 8-year period were reviewed retrospectively.

Results: Lobectomy with partial (n = 90) or circumferential (n = 3) pulmonary artery resection was carried out in 93 patients. Indications for surgical intervention were non-small cell lung cancer in 87 patients and other malignancy in the remaining 6 patients. Bronchial sleeve resection was associated in 23 patients. Neoadjuvant chemotherapy had been administered in 34 cases because of cN2 disease. Operative mortality was 5.4%. Postoperative complications occurred in 27 (29.0%) patients. All the patients underwent contrast-enhanced computed tomographic scanning 6 to 8 weeks postoperatively, which always showed patency of the pulmonary arteries. In the whole population median and 5-year survivals were 40 months and 39.4%, respectively. Disease-free survival was 41.4% at 5 years. Among patients with non-small cell lung cancer, at univariate analysis, tumor size of less than 3 cm; presence of vascular peritumoral emboli, intratumoral emboli, or both; and dyspnea influenced 5-year survival. Multivariate analysis showed that the size of the primary tumor and the presence of vascular emboli were independent factors of worse outcome.

Conclusions: Lobectomy with arterial sleeve resection has acceptable mortality and no specific complications. Late results in terms of survival are satisfactory.

Pneumonectomy has been the typical treatment for lung cancers with involvement of lobar bronchus, direct invasion of the pulmonary artery (PA), or metastasis to N1 regional lymph nodes. Because of morbidity, mortality, and reduction of quality of life,¹⁻³ some surgeons established the bases of parenchymal sparing resection: bronchoplasty and PA reconstruction.^{4,5} These techniques were also developed to allow resection in patients with limited pulmonary function, contraindicating pneumonectomy.

In the past 2 decades, many authors confirmed the feasibility and efficacy of sleeve bronchial lobectomy.⁶⁻¹⁰ Nevertheless, for many years, PA reconstruction did not seem to be a real alternative to pneumonectomy, and even recently, results were quite discouraging in terms of complications.¹¹ Relatively limited experience is available on large clinical series,¹² and interpretation is difficult because of the heterogeneity of populations and indications for surgical techniques.

The aim of this retrospective study was reporting short- and long-term results of our experience with arterial resec-

tion and reconstructions during pulmonary lobectomy. Univariate and multivariate analyses were carried out to identify predictors of morbidity, mortality, and long-term survival.

MATERIALS AND METHODS

We retrospectively reviewed the clinical records of all the patients who underwent lobectomy with partial or circumferential PA resection in a single institution during an 8-year period (November 2000–March 2008) in the Thoracic Surgery Department, Hôtel-Dieu University Hospital, Paris, France. PA resection was defined as a resection that involved, at least circumferentially, the origin of a segmental artery.

For all the patients, preoperative evaluation included clinical history, physical examination, routine blood tests, electrocardiographic analysis, lung function tests, and perfusion lung scanning. The lung cancer staging protocol included chest radiographic analysis, fiberoptic bronchoscopy, and thoracic, upper abdominal, and cerebral computed tomographic (CT) scans. Isotopic bone scanning was performed in the presence of bone pain, abnormalities in serum calcium or alkaline phosphatase levels, or both.

In case of clinical suspicion of N2 disease (short axis >1 cm at CT scan), mediastinal staging by means of either transbronchial needle aspiration or, more frequently, mediastinoscopic analysis was carried out. In rare cases the disease was staged as N2 on the basis of CT and positron emission tomographic scanning without histologic confirmation because of the presence of bulky homolateral lymph nodes. If N2 disease was confirmed, neoadjuvant chemotherapy was administered. Patients were then considered operable in the presence of a clinical response^{13,14} or stable disease. In case of progressive disease, surgical intervention was denied.

Resection was considered functionally possible if the predictive postoperative forced expiratory volume in 1 second (FEV₁; calculated on the basis of spirometry and isotopic scanning) was greater than 40% of the predicted value and provided that no major hypoxemia (<60 mm Hg) or hypercapnia (>46 mm Hg) existed, whereas it was contraindicated if the predicted postoperative FEV₁ was less than 30%. When FEV₁ values were between 30% and 40%, patients were considered at relatively high risk, and a definitive

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Abbreviations and Acronyms

CT	= computed tomographic
FEV ₁	= forced expiratory volume in 1 second
PA	= pulmonary artery

decision was based on an evaluation including multiple parameters (predictive postoperative FEV₁, Po₂, Pco₂, carbon monoxide transfer factor, age, associated comorbidities and results of exercise tests [ie, stair climbing and 6-minute walking]).

Operations were carried out after achievement of general anesthesia with double-lumen endobronchial intubation. Access to the thoracic cavity was achieved through a standard posterolateral thoracotomy. If necessary, arterial sleeve resection was carried out when possible and not only in the case of respiratory impairment contraindicating pneumonectomy. A tangential arterial resection with direct sutures was carried out when possible (residual arterial caliber, $\geq 50\%$). Otherwise, application of an autologous pericardial patch or circumferential resection was performed. Suturing was carried out with double continuous 5-0 polypropylene sutures. Just before tying, the clamp was removed.

Margins were checked intraoperatively by using frozen sections. Full nodal dissection was carried out in all cases. If bronchial and arterial suture lines were in close proximity to each other and in every case of associated bronchoplasty, a pedicled flap (pleural and, much more frequently, intercostal muscle) was interposed between the 2 structures.

We did not usually administer heparin sodium during the operation, but each patient received perioperative antithrombotic prophylaxis with low-molecular-weight heparin at preventive doses.

Pain control was achieved in most cases by means of intrathecal morphine administration (at the end of the operation), followed by continuous patient-controlled intravenous analgesia with morphinics. Intravenous propacetamol was also administered. Supplemental subcutaneous morphinics were administered to achieve a numeric analog at a constant score (range, 1–10) of less than 4 at rest.

A policy of early extubation was systematically adopted. In the postoperative period a policy of high suspicion of cardiorespiratory complication was adopted. In case of suspicion of postoperative pneumonia, a sample for bacteriology was obtained by means of protected distal brushing before institution of any antibiotic treatment.¹⁵

All the patients underwent contrast-enhanced CT scanning 6 to 8 weeks postoperatively. Adjuvant radiotherapy or chemotherapy was performed under the care of referring physicians, and therefore no uniform protocol was used.

Retrospective recording of presurgical data included demographic information, medical comorbidities, side and location, spirometric data, and possible use of induction therapy. With respect to surgical and pathologic data, we collected data about the extent of resection, the pathologic staging, the completeness of resection, and postoperative morbidity and mortality. Possible postoperative treatments were also recorded.

Operative mortality was calculated by taking into account all the deaths occurring within 30 days from the operation or during the hospitalization. Correlation between mortality and potential risk factors was assessed by using the χ^2 or Fisher's exact tests for categorical variables and the *U* test for continuous variables. Factors associated with morbidity or mortality were entered into a logistic regression analysis.

Follow-up information was obtained by means of direct telephone interview with patients or, in case of deaths, with families. Referring physicians were also contacted to confirm data obtained by means of patient or family interviews. Overall survival rates (including non-cancer-related deaths) and disease-free survival were calculated by using the Kaplan–Meier method and compared with the log-rank test. All the clinical and pathologic variables with a possible effect on survival were entered in a multivariate anal-

ysis (Cox proportional hazard model) to identify independent prognostic factors.

Informed consent was obtained from all the patients or relatives (in case of deceased patients), and investigations were conducted according to the Declaration of Helsinki principles. The study was carried out according to the French laws on biomedical research.

RESULTS

Between February 2001 and February 2008, 4530 major lung resections were performed by our team: 584 pneumonectomies, 3732 lobectomies, and 214 sleeve lobectomies. Among the sleeve lobectomies, there were 121 bronchial sleeve lobectomies, 23 bronchovascular sleeve lobectomies, and 70 lobectomies with PA resection. These last 93 patients represent the population of this study.

Preoperative Data

There were 70 (75.3%) men and 23 (24.7%) women; mean age was 64.6 ± 8.7 years. Thirty-two patients were older than 70 years, and 87.1% were smokers. Comorbidities were present in 59 (63.4%) patients, and in particular, 21.5% had a history of a previous neoplasm. Twenty patients had a history of cardiovascular disease (coronary artery disease, $n = 12$; arrhythmia requiring specific treatment, $n = 6$; cerebrovascular disease, $n = 1$; obstructive arteriopathy of the lower limbs, $n = 1$).

Eighty-six patients presented with symptoms related to lung tumors, whereas lung cancer was discovered on chest radiographic analysis performed for other reasons in the remaining 7 patients. Of note, 21 patients had effort dyspnea (Medical Research Council Dyspnea Scale ≥ 2).

Mean preoperative FEV₁ was $83.3\% \pm 21.0\%$; 47 (50.5%) patients had an FEV₁ of less than 80%. Induction treatments were carried out in 34 patients (30 receiving chemotherapy and 4 receiving chemoradiotherapy).

The main indication for preoperative induction therapy was N2 disease (21 patients). Induction therapy was administered because of cT4 disease (which was considered potentially resectable) in 7 patients and in 4 patients in whom resectability was in doubt. Two further patients had preoperative chemotherapy because of metastatic disease (isolated brain metastasis treated with surgical intervention and radiotherapy).

All chemotherapy protocols were platinum based. The associated drugs, doses, and schedules were extremely variable because patients were referred by different pulmonologists and oncologists. Imaging re-evaluation after induction therapy showed no complete response. Partial or minor responses were observed in 27 (79.4%) of 34 patients. Disease stability was observed in 7 cases.

Surgical and Pathologic Data

Fifty-six upper left, 17 upper right, and 11 lower left lobectomies and 9 bilobectomies (7 upper medium and 2 medium lower) were carried out. PA tangential resection and direct

TABLE 1. Pathologic features

Oncologic features	No.	%	Mean	Median
T size			4.19 cm	4 cm
Vascular neoplastic emboli	32	36.8		
p Stage				
I	T1 N0 M0 = 4; T2 N0 M0 = 13	17	19.5	
II	T0 N1 M0 = 1; T1 N1 M0 = 4; T2 N1 M0 = 22; T3 N0 M0 = 3	30	34.5	
IIIA	T1 N2 M0 = 2; T2 N2 M0 = 10; T3 N1 M0 = 11	23	26.4	
IIIB	T1-2 N3 M0 = 0; T3 N2-3 M0 = 2; T4 N1-3 M0 = 9	11	12.6	
IV	T1-4 N1-3 M1 = 6	6	6.9	

suturing were performed in 88 (94.6%) patients. The repair was accomplished with an autologous pericardial patch in 2 further patients and a circumferential resection and end-to-end anastomosis in the remaining 3 patients. Bronchial sleeve resection was associated in 23 patients.

Histologic examination showed 87 cases of non-small cell lung cancer: squamous cell cancers, adenocarcinomas, and large cell carcinomas in 46, 34, and 6 patients, respectively. The remaining patient with a prechemotherapy diagnosis of large cell carcinoma had a pathologic complete response. Pathologic staging is reported in Table 1.

Among the remaining 6 patients, 5 had a solitary pulmonary metastasis (of colonic [n = 3], breast [n = 1], and thyroid [n=1] cancer), and 1 had pulmonary mucosa-associated lymphoid tissue lymphoma.

Postoperative Outcome

There were no intraoperative deaths. Postoperative mortality was 5.4% (n = 5). Three deaths occurred after right lobectomy (2 with bronchoplasty), and 2 occurred after left lobectomy. Postoperative pneumonia and acute respiratory distress (with no infection identified) were responsible for 3 deaths. In 2 further patients acute myocardial infarction followed by intractable cardiogenic shock was the cause of death.

Among evaluated factors (Tables 2 and 3), the following were associated at univariate analysis with postoperative death: age ($P = .043$), cardiovascular disease ($P = .007$),

previous neoplasm ($P = .030$), p stage ($P = .002$), smoking ($P = .020$), and FEV₁ ($P = .035$). Multivariate analysis showed that only cardiovascular disease ($P = .022$) and FEV₁ ($P = .039$) were independent predictors of postoperative mortality. No statistical difference was found with respect to possibly associated bronchoplasty or the extent of resection (lobectomy or bilobectomy).

Other complications (not responsible for deaths) occurred in 27 (29.0%) further patients and were in some instances associated: postoperative pneumonia (n = 12), supraventricular arrhythmias (n = 5), persistent air leak without evident bronchopleural fistula (n = 5), respiratory failure (n = 5), atelectasia without pneumonia (n = 3), acute pericarditis (n = 1), and delirium (n = 1).

At univariate analysis, systemic hypertension ($P = .044$), a history of pulmonary embolism ($P = .038$), and cardiovascular disease ($P = .008$) were associated with the occurrence of postoperative complications, with only the latter remaining significant at multivariate analysis ($P = .006$).

Long-term Outcome

No patient was lost at follow-up. Mean and median follow-ups were 28.1 and 24 months, respectively. At completion of the study (April 2008), 48 (51.6%) patients were alive, and 45 (48.4%) were dead. For the whole population, median survival was 40 months; 3- and 5-year overall survivals were 59.6% and 39.4%, respectively.

TABLE 2. Univariate analysis in perioperative morbidity, mortality, and long-term survival with respect to pretherapeutic clinical data

Features	Perioperative morbidity	P value	Perioperative mortality	P value	5-y Survival	P value
Sex		.109		.361		.888
Age		.088		.043		.594
Active smoker (yes/no)		.267		.020		.281
Comorbidity		.467		.394		.423
Previous neoplasm		.574		.030		.353
COPD		.187		.476		.923
Dyspnea		.251		.074		.029
FEV ₁		.352		.035		NS
Hypertension		.044		.620		.887
Pulmonary hypertension		.116		.799		.359
Cardiovascular disease		.008		.007		.661
Deep venous thrombosis		.116		.895		.942
Pulmonary embolism		.038		.846		.439

COPD, Chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second.

TABLE 3. Univariate analyses in perioperative morbidity, mortality, and long-term survival with respect to treatment and pathologic data

Features	Perioperative morbidity	P value	Perioperative mortality	P value	5-y Survival	P value
Histology		.872		.546		.118
pT		.514		.097		.094
T size		.868		.283		.027
pN		.718		.434		.995
pM		.637		.747		.839
Vascular neoplastic emboli		.076		.053		.006
p Stage		.250		.005		.806
Neoadjuvant therapy		.262		.551		.844
Adjuvant therapy		—		—		.230
Lung resection		.743		.163		.426
Bronchoplasty		.210		.361		.260

No recurrence occurred among patients treated for isolated pulmonary metastasis. Four patients with isolated local recurrence of non–small cell lung cancer were managed with completion pneumonectomy; a patient with tracheal recurrence was managed with laser induction chemotherapy and tracheal resection. Twelve further patients presented with both local (mediastinal adenopathies or multiple pulmonary nodules) and extrathoracic recurrence and were managed by means of chemotherapy, which was in 3 instances associated with thoracic radiotherapy. Median time to local recurrence was 34 months. The type of parenchymal sparing procedure (arterial vs bronchovascular) was not associated with the rate of local recurrence.

Twenty-five patients presented with extrathoracic recurrence with a median time of 42 months. These recurrences were managed with chemotherapy, which was associated with surgical intervention in 2 patients (isolated metachronous adrenal and cerebellar metastasis).

Overall, among the late deaths ($n = 45$), 5 were due to intercurrent causes (pneumonia, $n = 3$; myocardial infarction, $n = 1$; small cell lung cancer, $n = 1$), and the remaining 40 were attributable to recurrent disease.

With respect to long-term outcome, multivariate analyses were performed only in patients with non–small cell lung cancer ($n = 87/93$), who had median and 5-year survivals of 38 months and 34.9% (95% confidence interval, 22.8%–49.2%), respectively.

No difference in terms of long-term outcome was observed with respect to sex, age, smoking habit, respiratory functional parameters, and different comorbidities. Patients with pretreatment effort dyspnea had worse outcomes compared with those of the remaining patients (5-year survival of 18.7% vs 39.3%, $P = .029$; Table 2).

A trend toward better outcome was observed in patients with T1–2 tumors compared with T3–4 lesions (5-year survival of 37.3% vs 32.9%, $P = .094$). Patients with tumors of less than 3 cm had significantly better 5-year survival than the remaining patients (47.9% vs 26.1%, $P = .027$; Figure 1).

We did not find significant differences with respect to histologic type, nodal status (N0 vs N+, $P = .930$) or the possibly

associated bronchoplasty ($P = .260$). The presence of peritumoral, intratumoral, or both neoplastic vascular emboli was associated with worse 5-year survival (23.6% vs 43.1%, $P = .0068$; Figure 2). Neither the presence of nodal metastasis nor the stage of disease influenced prognosis (Table 3).

At multivariate analysis, the T factor and the presence of vascular emboli were independent factors of worse outcome ($P = .039$ and $.026$, respectively).

DISCUSSION

In the present study we report evidence that arterial reconstruction for lung cancer is a valuable procedure with acceptable figures of postoperative morbidity and mortality and satisfactory results on long-term survival.

The history of the last 50 years showed an increasing interest in limited resections, more recently associated with the

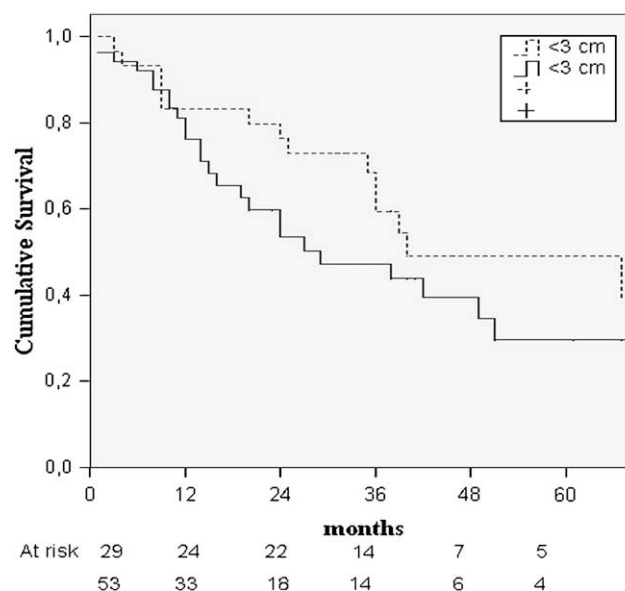


FIGURE 1. Survival according to tumor size in patients with non–small cell lung cancer. Patients with tumors smaller than 3 cm had significantly ($P = .027$) better 5-year survival than the remaining patients (47.9% [95% confidence interval, 25.8%–68.0%] vs 26.1% [95% confidence interval, 13.6%–44.2%]).

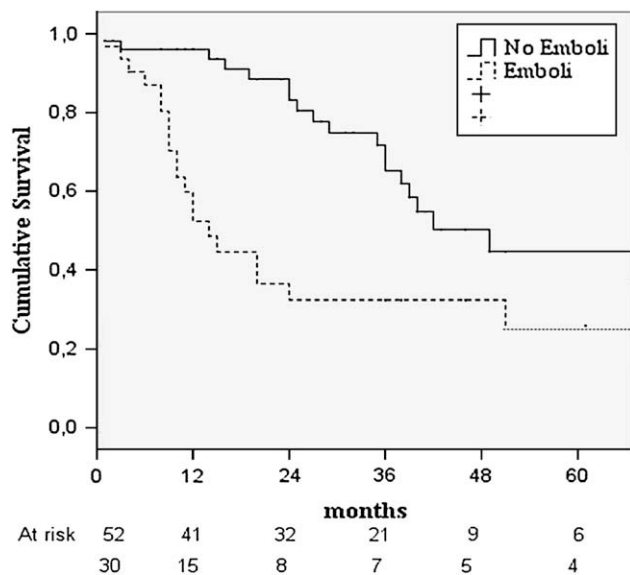


FIGURE 2. Survival according to peritumoral and intratumoral vascular emboli in patients with non-small cell lung cancer. The presence of peritumoral, intratumoral, or both neoplastic vascular emboli was associated with significantly ($P = .0068$) worse 5-year survival (23.6% [95% confidence interval, 10.6%–44.4%] vs 43.1% [95% confidence interval, 26.7%–61.2%]).

multimodality approach, to avoid functional amputation and risks on short- and long-term outcomes of pneumonectomy. In 1947 a report by Price Thomas⁴ on bronchoplasty and in 1986 a report by Vogt-Moykopf⁵ on arterioplasty showed their feasibility.

Even though bronchoplasty is accepted and performed in many centers, PA reconstruction is not. Relatively few works were published, and this distrust shows that doubts about surgical technique and morbidity,¹² as well as functional and oncologic results, probably still persist.

In our experience and in agreement with others,^{16,17} arterial resection and reconstruction were performed more frequently for left-sided tumors (72% of patients) and for the squamous histotype (49.5% of patients). This is obviously explained by the proximal character of the tumors and the different anatomy of PAs on the right and left sides, respectively. In most cases PA involvement was partial, and partial resection and reconstruction (possibly with pericardial patch) was sufficient to deal radically with the disease, whereas circumferential resection with an end-to-end anastomosis was carried out in only 3 patients. These data confirm previous reports on smaller series dealing with probably similar patients^{16,17}; comparison with the experience of Rendina and colleagues¹⁸ is not possible because of different inclusion criteria in their study (only patch reconstruction and circumferential resections were evaluated).

Our figures of perioperative morbidity and mortality (29.0% and 5.4%, respectively) could seem relatively high, at least if compared with current figures in standard lobecto-

mies, but one should consider that patients undergoing arterial resection have an increased postoperative risk because of locally more advanced disease. Literature data are quite variable, with values of mortality and morbidity ranging from 0% to 17% and 7% to 40%,^{11,12,16} respectively, probably reflecting the heterogeneity of studied populations and perioperative treatments. In our experience no death or major complications were per se related to the arterial resection (no major bleeding, pulmonary infarction, or bronchovascular fistula), although all these complications have been reported in this setting.^{5,11,17} In agreement with others,¹⁶ we think that careful handling of the vessel and preservation of a sufficient lumen, together with the use of a pedicled flap, especially in the case of contact between arterial and bronchial sutures, are the key measures to eliminate these complications. Postoperative pneumonia and myocardial infarction were the leading causes of death, and statistical analysis showed, as previously reported,^{19,20} that histories of cardiovascular disease ($P = .022$) and low FEV₁ ($P = .039$) were independent risk factors of death. In particular, postoperative pneumonia was responsible for 3 postoperative deaths. In agreement with other European reports, our team has previously reported that postoperative pneumonia was a relatively frequent complication of major lung resection and represented the leading cause of postoperative death.¹⁵ We also demonstrated that these pneumonias were sustained by germs responsible for initial (preoperative) bronchial colonizations.¹⁵ More recently, we showed that the adoption of a new antibioprophyllaxis by amoxicillin-clavulanic acid, targeting these germs more specifically than the previously used second-generation cephalosporin, resulted in a significant decrease in postoperative pneumonia.²¹

On the other hand, in the present series 2 deaths were due to myocardial infarction. We hope that this complication, which occurred relatively early in our experience, will be avoided in the future thanks to the current management of concomitant coronary artery disease, including, in cases not susceptible to percutaneous revascularization, the use of β -blockers and the nondiscontinuation of platelet aggregation inhibitors.

We did not specifically study the late functional status of our patients or perform late pulmonary angiograms. On the other hand, all the patients had contrast-enhanced CT scans 6 to 8 weeks postoperatively, and in no case could we detect a defect of patency of the PA distal to reconstruction, although the accuracy of this evaluation is not absolute.

Relatively few data are available in the literature concerning the long-term outcome of patients treated with arterial resection and reconstruction.^{16,22,23} In the recent (2007) meta-analysis by Ma and colleagues,¹² who reviewed recent studies on parenchymal sparing techniques, 152 patients from 5 studies were identified. The 5-year survival rate was 38.7%, a value close to our 34.9%. Obviously these comparisons are difficult because of differences in terms

of characteristics of studied populations, surgical techniques, and adjuvant treatments. In our experience multivariate analysis showed that the size of the primary tumor and the presence of vascular emboli were independent factors of worse outcome, whereas nodal status failed to be identified as a prognostic factor at either univariate or multivariate analysis. It is difficult to compare this result with the results of previous studies because in most series a limited number of patients treated with angioplastic procedures are often studied together with patients undergoing simple bronchoplastic procedures. There are no data on the effect of nodal involvement on survival in the recent article by Cerfolio and Bryant,¹⁶ and the correlation was not studied in the above-cited metanalysis.¹² In our opinion, as already suggested for other advanced primary tumors,^{24,25} in this subset of patients with non-small cell lung cancer, the prognosis was determined by the tumor itself rather than by the nodal disease. Furthermore, patients with N+ disease were more likely to receive adjuvant or neoadjuvant treatments, with a probable positive effect on outcome. On the other hand, in agreement with others,²⁶ we found that the presence of vascular emboli was an independent negative prognostic factor explained by the already occurred initial steps of hematogenous spreading of the disease.

Our study showed that truly local recurrences were rare and could be managed with completion pneumonectomy; this strongly reinforces the idea that arterioplasty with possibly associated bronchoplasty allows one to radically control the disease. Furthermore, most locoregional recurrences occurred at the mediastinal level and were often associated with systemic metastases. It is evident that initial pneumonectomy would have not prevented this kind of evolution.

Undoubtedly, the retrospective methodology of the study and the mix of tumor histology, stage, and preoperative and postoperative management represent the main limitations of this study. However, PA resection and reconstruction is, in our experience, a relatively safe procedure, with acceptable values of operative morbidity and mortality. Because this procedure leads to clear margins of resection and spare lung parenchyma, we recommend, on the basis of our outcome data, to evaluate its feasibility when possible and when indicated in an effort to avoid pneumonectomy.

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