One hundred consecutive pneumonectomies after induction therapy for non-small cell lung cancer: An uncertain balance between risks and benefits

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Objective: We sought to assess postoperative outcome after pneumonectomy after neoadjuvant therapy in patients with non-small cell lung cancer.

Methods: This retrospective study included 100 patients treated from January 1989 through December 2003 for a primary lung cancer in whom pneumonectomy had been performed after an induction treatment. Surgical intervention had not been considered initially for the following reasons: N2 disease (stage IIIA, $n = 79$), doubtful resectability (stage IIIB [T4, N0], $n = 19$), and M1 disease (stage IV [T2, N0, M1, solitary brain metastasis], $n = 2$). All patients received a 2-drug platinum-based regimen with a median of 2.5 cycles (range, 2-4 cycles), and 30 had associated radiotherapy (30-45 Gy).

Results: There were 55 right and 45 left resections. Overall 30-day and 90-day mortality rates were 12% and 21%, respectively. At multivariate analysis, one independent prognostic factor entered the model to predict 30-day mortality: postoperative cardiovascular event (relative risk, 45.7; 95% confidence interval, 3.7-226.7; $P = .001$). Four variables predicted 90-day mortality: age of more than 60 years (relative risk, 5.06; 95% confidence interval, 1.47-17.48; $P = .01$), male sex (relative risk, 8.25; 95% confidence interval, 1.01-67.34; $P = .049$), postoperative respiratory event (relative risk, 3.64; 95% confidence interval, 1.14-9.37; $P = .007$), and postoperative cardiovascular event (relative risk, 7.84; 95% confidence interval, 3.12-19.71; $P < .001$). Estimated overall survivals in 90-day survivors were 35% (range, 29%-41%) and 25% (range, 19.3%-30.7%) at 3 and 5 years, respectively. At multivariate analysis, one independent prognostic factor entered the model: pathologic stage III-IV residual disease (relative risk, 1.89; 95% confidence interval, 1.09-3.26; $P = .022$).

Conclusions: Pneumonectomy after induction therapy is a high-risk procedure, the survival benefit of which appears uncertain.

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The treatment of patients with locally advanced non-small lung cancer remains a challenge. The current efforts relate essentially to the evaluation of induction therapy.¹⁻⁵ The purpose of such therapy is (1) to decrease the tumor volume and, in turn, to provide the best chances for a complete resection (R0), leaving no identifiable residual disease, and (2) to control a potentially micrometastatic disease in distant organs. Even if the response to the induction therapy and survival are not rigorously correlated, it seems that improvement in survival is mainly observed in those patients in whom the disease has been downstaged by the preoperative treatment.⁶ However, this long-term benefit is of modest magnitude and could be offset by the cumulated toxicity of combined treatment modalities. We previously reported that surgical intervention after induction therapy was associated with an increased operative risk,⁷ and many reports dealing with that issue have been published. However, only few data are available regarding pneumonectomy,

TABLE 1. Variables predicting 30 day-mortality

Variable	Levels	Crude HR* estimate	95% CI	P value	Adjusted HR estimate	95% CI	P value
Age	≤60 y	1					
	>60 y	3.05	0.83-11.27	.09			
Sex	Male	2.28	0.3-17.69	.43			
	Female	1					
Preoperative RT	Yes	1					
	No	1.34	0.36-4.93	.67			
Resection	Standard	1					
	Extended	1.37	0.30-6.26	.68			
Operation	EPR	1.48	0.45-4.91	.52			
	IPR	1					
Side of resection	Right	2.65	0.72-9.8	.14			
	Left	1					
Bronchial suture reinforcement	Yes	1					
	No	2.43	0.66-8.99	.18			
Pathologic stage	0, I, II	1.04	0.33-3.21	.95			
	III, IV	1					
PO respiratory event	Yes	7.4	2.3-23.2	.001			
	No	1					
PO cardiovascular event	Yes	45.7	5.9-355	<.001	29	3.7-226.7	.001
	No	1			1		
PO surgical complication	Yes	2.4	0.64-8.74	.2			
	No	1					
Blood transfusion	Yes	1					
	No	0.01	0-1.40	.07			
Period of the study	1989-1997	1.04	0.33-3.28	.95			
	1998-2003	1					

HR, Hazard ratio; CI, confidence interval; RT, radiotherapy; EPR, extrapericardial route; IPR, intrapericardial route; PO, postoperative. *Estimates obtained by running the model with one independent variable at a time.

which makes generalizations difficult.^{6,8-19} Most articles reported on small case series^{8-12,14,16,17} with sometimes all kinds of lung resection and without emphasis on those patients who received pneumonectomy.^{6,13,15} Moreover, the usual markers of postoperative mortality (30-day and in-hospital mortality) might reflect the risks of the procedure insufficiently. Indeed, treatment-related mortality should also include all deaths occurring as a direct consequence of a complication or sequel of surgical intervention, whatever the delay from the surgical procedure. In that way, 90-day mortality was used recently to emphasize the risks of right pneumonectomy after neoadjuvant therapy for lung cancer.¹⁸ Thus we conducted this study to assess the risk/benefit ratio of combined therapies, including pneumonectomy, in terms of 30-day and 90-day mortality and long-term survival in patients with non-small cell lung cancer.

Patients and Methods

Patients

The medical records of 100 consecutive patients who underwent pneumonectomy after neoadjuvant therapy for a primary lung cancer were reviewed for the 15-year period ranging from January 1989 through December 2003. Patient charts were identified by

screening of a database into which data were entered prospectively for any patient undergoing surgical intervention for thoracic malignancy at our department.

There were 83 male and 17 female subjects, whose ages ranged from 32 to 76 years (mean, 57 ± 10 years). Surgical intervention had not been considered initially for the following reasons: N2 disease (IIIA, n = 79), doubtful resectability (stage IIIB [T4, N0], n = 19), and M1 disease (stage IV [T2, N0, M1, solitary brain metastasis], n = 2). These 2 patients were previously operated on for their cerebral disease.

All patients received a 2-drug platinum-based regimen. Combination was done with vinorelbine in 46 patients, etoposide in 25 patients, gemcitabine in 15 patients, and paclitaxel in 14 patients. A median of 2.5 cycles (range, 2-4 cycles) was administered. Thirty patients received thoracic radiotherapy with neoadjuvant chemotherapy at doses ranging from 30 to 45 Gy.

Among the 79 patients who were considered initially to have N2 disease, only 25 (31.6%) had pathologically proved mediastinal node involvement. Other cases were staged as cN2 on the basis of computed tomographic (CT) scan findings only. None of these patients had a positron emission tomographic scan because this technology was not available routinely in our city before June 2004. Similarly, the diagnosis of a cT4 N0 disease (n = 19) was established on the basis of bronchoscopic and CT scan findings.

TABLE 2. Variables predicting 90-day mortality

Variable	Levels	Crude HR* estimate	95% CI	P value	Adjusted HR estimate	95% CI	P value
Age	≤60 y	1			1		
	>60 y	6.85	2.02-23.30	.002	5.06	1.47-17.48	.01
Sex	Male	4.5	0.6-32.42	.14	8.25	1.01-67.34	.049
	Female	1			1		
Preoperative RT	Yes	1.11	0.45-2.76	.81			
	No	1					
Resection	Standard	1					
	Extended	1.64	0.55-4.87	.38			
Operation	EPR	1.6	0.65-3.96	.31			
	IPR	1					
Side of resection	Right	1.87	0.76-4.64	.18			
	Left	1					
Bronchial suture reinforcement	Yes	1					
	No	1.73	0.7-4.28	.24			
Pathologic stage	0, I, II	1.13	0.48-2.67	.78			
	III, IV	1					
PO respiratory event	Yes	3.84	1.59-9.29	.003	3.64	1.14-9.37	.007
	No	1			1		
PO cardiovascular event	Yes	6.78	2.84-16.2	<.001	7.84	3.12-19.71	<.001
	No	1			1		
PO surgical complication	Yes	2.27	0.83-6.19	.11			
	No	1					
Blood transfusion	Yes	4.09	1.5-11.2	.006			
	No	1					
Period of the study	1989-1997	1					
	1998-2003	1.04	0.44-2.47	.93			

HR, Hazard ratio; CI, confidence interval; RT, radiotherapy; EPR, extrapericardial route; IPR, intrapericardial route; PO, postoperative. *Estimates obtained by running the model with one independent variable at a time.

Among the 19 patients with cT4 disease, 8 had a pretreatment mediastinoscopy to rule out N2 disease, a nonresectable mediastinal invasion, or both.

Histology was squamous cell carcinoma in 49 patients, adenocarcinoma in 34 patients, and undifferentiated carcinoma in 17 patients. Nine patients had a preoperative mediastinoscopy or a remediastinoscopy to rule out N2 disease.

Adjuvant therapy was performed under the care of referring physicians, and therefore no uniform protocol was used. Adjuvant radiotherapy, chemotherapy, or associated radiochemotherapy was administered in 18, 6, and 14 patients, respectively.

Statistical Analysis

The following variables were considered as potential prognostic factors of 30- and 90-day mortality and survival: age (≤60 vs >60 years), sex, postoperative stage (0, I, and II vs III and IV), type of induction therapy (chemotherapy vs radiochemotherapy), side of resection, type of resection (standard vs extended; intrapericardial vs extrapericardial route), reinforcement of the bronchial suture, postoperative respiratory event (bronchopulmonary obstruction, atelectasis, pneumonia, postpneumectomy edema, adult respiratory distress syndrome, pneumothorax in the remaining lung, or pulmonary embolism), postoperative cardiovascular event (arrhythmias, cardiac failure [whatever the origin], myocardial infar-

tion, deep vein thrombosis, or stroke), postoperative surgical complication (haemothorax, bronchopleural fistula, empyema, or cardiac luxation), perioperative allogeneic blood transfusion, and the period of the study (1989-1997 vs 1998-2003). Survival was estimated by using the product limit method of Kaplan-Meier. Univariate and multivariate analyses were performed by using the Cox proportional hazards regression model to determine factors potentially predicting postoperative mortality (30- and 90-day mortality) and survival. The Cox model was used to incorporate in the same model any explanatory variables with a *P* value of less than .20. Forward stepwise procedure and likelihood ratio tests were used to select the variables with the greatest prognostic value (*P* < .05). Univariate and multiple logistic regression analysis was performed to obtain factors potentially predicting postoperative respiratory event or cardiovascular event and to adjust the odds ratio for each risk factor while controlling for the potential influence of others variables. This statistical analysis was performed with the SPSS V10.0 software package (SPSS Inc, Chicago, Ill).

Results

Surgical Procedure

Two patients were operated on before the completion of the neoadjuvant treatment because of a complication

TABLE 3. Variables predicting postoperative respiratory events

Variable	Levels	Crude OR* estimate	95% CI	P value	Adjusted OR estimate	95% CI	P value
Age	≤60 y	1					
	>60 y	2.45	0.85-7.09	.09			
Sex	Male	1	0.4-4.88	.6			
	Female	1.4					
Preoperative RT	Yes	1.95	0.69-5.49	.20	3.84	1.09-13.55	.04
	No	1			1		
Resection	Standard	1					
	Extended	1.33	0.33-5.40	.69			
Operation	EPR	1.09	0.35-3.40	.88			
	IPR	1					
Side of resection	Right	2.73	0.9-8.29	.08			
	Left	1					
Bronchial suture reinforcement	Yes	1					
	No	3.48	1.06-11.40	.04			
Pathologic stage	0, I, II	1					
	III, IV	1.08	0.40-2.95	.87			
PO cardiovascular event	Yes	4.89	1.69-14.12	.003	4	1.25-12.88	.02
	No	1			1		
PO surgical complication	Yes	1.05	0.46-2.48	.94			
	No	1					
Blood transfusion	Yes	5.18	1.58-17.00	.07	5.59	1.47-21.26	.012
	No	1			1		
Period of the study	1989-1997	1					
	1998-2003	1.62	0.59-4.41	.35			

OR, Odds ratio; CI, confidence interval; RT, radiotherapy; EPR, extrapericardial route; IPR, intrapericardial route; PO, postoperative. *Estimates obtained by running the model with one independent variable at a time.

directly in relation to this medical therapy. They represented 1 pneumothorax and 1 hemoptysis by tumoral necrosis. For the 98 other patients, the surgical intervention was performed from 4 to 8 weeks after the completion of medical therapy.

There were 55 right and 45 left resections. The surgical approaches were a posterolateral thoracotomy in 88 patients, a lateral thoracotomy in 11 patients, and a sternotomy in 1 patient. The intrapericardial route was used in 85 patients. The procedure was extended to one of the following structures: superior vena cava (n = 3), aorta (n = 1), left atrium (n = 2), carina (n = 4), chest wall (n = 1), subclavian artery (n = 1), and esophagus (n = 1).

The main bronchus was stapled in 81 patients and hand sutured in 19 patients (interrupted stitches in 15 and running sutures in 4 patients). The bronchial stump was reinforced in 57 patients with a pedicled parietal pleural flap in 25 patients, mediastinal fatty tissues from the thymic area in 14 patients, a pedicled muscle in 15 patients, and pericardium in 3 patients, with the difference relating to operator preference only. The bronchial stump was covered 48 times on the right side (87%) and 9 times on the left side (20%). Each resection included an ipsilateral mediastinal lymphadenectomy. Complete resection (R0) was achieved in 94 patients.

For the remaining patients, 2 had a macroscopic residual tumor (R2), and 4 had a microscopic residual tumor found on specimen analysis (R1). Postoperative pathologic study of the specimen showed no tumor cells in 8 patients, 10 stage IA tumors, 9 stage IB tumors, 7 stage IIA tumors, 15 stage IIB tumors, 25 stage IIIA tumors, 19 stage IIIB tumors, and 7 stage IV tumors.

Postoperative Mortality

The 30-day mortality rate was 12%. This rate according to the right side/left side distribution was, respectively, 16.4%/6.7% ($P = .14$). Causes of death were as follows: postpneumonectomy edema–adult respiratory distress syndrome (n = 5), bronchial fistula (n = 2), myocardial infarction (n = 1), pulmonary embolism occurring from a superior vena caval graft occlusion (n = 1), acute right cardiac failure (n = 1), hemorrhagic shock (n = 1), and sepsis shock (n = 1). Thirty-day mortality with reference to various variables is shown in Table 1.

The 90-day mortality rate was 21%. This rate according to the right side/left side distribution was, respectively, 25.5%/15.5% ($P = .18$). Ninety-day mortality with reference to various variables is mentioned in Table 2. Causes of the 9 additional deaths were as follows: recurrence disease

TABLE 4. Variables predicting postoperative cardiovascular events

Variable	Levels	Crude OR* estimate	95% CI	P value	Adjusted OR estimate	95% CI	P value
Age	≤60 y	1					
	>60 y	2.03	0.79-5.17	.14			
Sex	Male	1.10	0.32-3.75	.88			
	Female	1					
Preoperative RT	Yes	1					
	No	1.49	0.53-4.21	.45			
Resection	Standard	1					
	Extended	3.07	0.92-10.22	.07			
Operation	EPR	1	0.37-3.08	.89			
	IPR	1.07					
Side of resection	Right	1.31	0.52-3.29	.56			
	Left	1					
Bronchial suture reinforcement	Yes	1.86	0.72-4.83	.20			
	No	1					
Pathologic stage	0, I, II	1					
	III, IV	1.06	0.43-2.61	.9			
PO respiratory event	Yes	4.89	1.69-14.12	.003	3.47	1.09-10.95	.03
	No	1			1		
PO surgical complication	Yes	1.40	0.39-5.00	.61			
	No	1					
Blood transfusion	Yes	3.65	1.36-9.79	.01	2.88	0.99-8.40	.05
	No	1			1		
Period of the study	1989-1997	1			1		
	1998-2003	3.16	1.23-8.11	.02	3.18	1.16-8.74	.03

OR, Odds ratio; CI, confidence interval; RT, radiotherapy; EPR, extrapericardial route; IPR, intrapericardial route; PO, postoperative. *Estimates obtained by running the model with one independent variable at a time.

in 4 patients, fungal sepsis shock (*Candida* species) in 1 patient, chronic respiratory failure in 1 patient, and unknown in 3 patients.

The adjuvant therapy did not contribute to the 90-day mortality because among the 21 patients who died within 3 months postoperatively, only one had adjuvant radiotherapy.

Postoperative Respiratory Event

Nineteen patients presented with one or more postoperative respiratory events of very variable gravity without technical and surgical complication. These were represented by bronchopulmonary obstruction (n = 12), atelectasis (n = 6), postpneumectomy edema–adult respiratory distress syndrome (n = 6), pneumothorax in the remaining lung (n = 1), pulmonary embolism (n = 2), and pneumonia (n = 11). Among these 11 cases of pneumonia, there were 3 cases of cytomegalovirus-induced pneumonia, the diagnosis of which had been obtained on the basis of a positive viremia in addition of positive cultures from bronchoalveolar lavage. The relationship between variables and respiratory events is shown in Table 3.

Postoperative Cardiovascular Event

Twenty-five patients experienced one or more cardiovascular events without surgical complication during the postoperative course. These were as follow: arrhythmia (n = 19), cardiac failure (n = 3), myocardial infarction (n = 1), deep vein thrombosis (n = 2), and stroke (n = 2). The relationship between variables and cardiovascular events is shown in Table 4.

Postoperative Surgical Complications

Thirteen patients had a surgical complication. There were 6 hemothoraxes, 6 bronchopleural fistulas, and 1 cardiac luxation. Seven patients required a reoperation: 5 for bronchial fistula, 1 for cardiac luxation, and 1 for hemothorax.

Hemorrhagic Risk

Forty-nine patients were transfused (allogeneic blood transfusion) with, on average, 5 ± 3 cell packs.

Bronchial Fistula

Six patients had an early bronchial fistula. This complication represented 9% versus 2% of the patients who underwent a

TABLE 5. Relationship between variables and 5-year survivals for patients undergoing pneumonectomy after an induction therapy

Variable	No. of observations		95% CI		P value
	(n = 100)	5 y	Lower	Upper	
Age					
≤60 y	49	20.8%	14.2%	27.4%	.18
>60 y	51	18.7%	12.1%	25.3%	
Sex					
Male	83	18.3%	13.3%	23.3%	.69
Female	17	25.4%	13.4%	37.4%	
Preoperative radiotherapy					
Yes	30	37%	27.6%	46.4%	.14
No	70	10.4%	5.9%	14.9%	
Resection					
Standard	87	21.2%	16.1%	26.3%	.05
Extended	13	9.6%	0.7%	19.7%	
Operation					
Extrapericardial route	15	6%	0.3%	11.7%	.44
Intrapericardial route	85	24.1%	18.5%	29.7%	
Side of resection					
Right	55	18.9%	13%	24.8%	.66
Left	45	20.8%	13.6%	28%	
Bronchial suture reinforcement					
Yes	57	26.7%	19.6%	33.2%	.30
No	43	12.5%	7.1%	17.9%	
Pathology stage					
0, I, II	49	26.3%	18.9%	33.7%	.08
III, IV	51	13.3%	7.9%	18.7%	
Postoperative respiratory event					
Yes	19	20.5%	9.5%	31.5%	.07
No	81	20.6%	14.6%	26.6%	
Postoperative cardiovascular event					
Yes	25	9%	0%	18%	.004
No	75	22.4%	17.4%	27.4%	
Postoperative surgical complication					
Yes	13	7%	0%	14%	.03
No	87	21.9%	16.9%	26.9%	
Blood transfusion					
Yes	49	19%	12.6%	25.4%	.08
No	51	21.2%	14.5%	27.9%	
Period of the study					
1989-1997	57	20.3%	14.9%	25.7%	.89
1998-2003	43	23.4%	15%	31.8%	

CI, Confidence interval.

right versus left resection, respectively ($P = .15$). All bronchial fistulas occurred within the first 30 days after the operation. Two (33%) patients died, both from respiratory failure.

Six empyemas occurred in otherwise healthy discharged patients within the first 3 months after the pneumonectomy: 1 was related to esophagopleural fistula, and 2 to were related bronchopleural fistula. The results of esophageal and bronchial fiberoscopies were normal in the remaining 3 patients.

Survival

Survival information was obtained for all patients. At completion of the study, 25 patients were alive, and 75 were dead. The median follow-up for the survivors was 21 months (mean, 39 ± 7 months). Their clinical status was as follow: alive and well (84%) and alive with disease (16%). The cause of death was related to the operation in 16% of cases and to the lung cancer in 49%. Cancer-unrelated deaths accounted for 11% of all deaths.

TABLE 6. Relationship between variables and 5-year survivals in 90-day survivors

Variable	No. of observations		95% CI		P value
	(n = 79)	5 y	Lower	Upper	
Age					
≤60 y	46	22.1%	15.2%	29%	.5
>60 y	33	29.4%	19.2%	39.3%	
Sex					
Male	63	24.2%	17.8%	30.6%	.58
Female	16	27%	14.4%	39.6%	
Preoperative radiotherapy					
Yes	23	48.5%	37.3%	59.7%	.05
No	56	13.1%	7.5%	18.7%	
Resection					
Standard	70	26.4%	20.2%	32.6%	.07
Extended	9	13.8%	1.1%	26.5%	
Operation					
Extrapericardial route	18	8.3%	0.4%	16.2%	.7
Intrapericardial route	61	29.7%	23.1%	36.3%	
Side of resection					
Right	41	25.6%	17.8%	33.4%	.74
Left	38	24.7%	16.4%	33%	
Bronchial suture reinforcement					
Yes	43	35.6%	26.6%	44.6%	.05
No	36	14.9%	8.5%	21.3%	
Pathology stage					
0, I, II	38	34.1%	24.9%	43.3%	.01
III, IV	41	16.6%	10.1%	23.1%	
Postoperative respiratory event					
Yes	11	37%	18.2%	45.8%	.95
No	68	24.6%	18.7%	30.5%	
Postoperative cardiovascular event					
Yes	13	19.1%	2.5%	35.7%	.91
No	66	25.5%	19.5%	31.5%	
Postoperative surgical complication					
Yes	8	12.5%	0.8%	24.2%	.14
No	71	27%	20.8%	33.2%	
Blood transfusion					
Yes	33	28.2%	19.2%	37.2%	.85
No	46	23.5%	16.2%	30.8%	
Period of the study					
1989-1997	45	25.7%	19.1%	32.3%	.88
1998-2003	34	23.4%	19.5%	40.3%	

CI, Confidence value.

The cause of death was not documented in 24% of cases. Among the 41 patients who experienced recurrence of their lung cancer, 32 (78%) had distant metastases, and 9 (22%) had a locoregional recurrence as the first site of recurrence.

Estimated overall survival rates from the date of the operation and including the operative mortality, as well as any cancer-related and unrelated deaths, were 27.8% (range, 22.9%-32.7%) and 19.8% (range, 15.2%-24.4%) at 3 and 5 years, respectively. Survival with reference to various variables is shown in Table 5. At multivariate analysis, 2

independent prognostic factors entered the model: postoperative cardiovascular event (relative risk [RR], 2.29; 95% confidence interval [CI], 1.35-3.91; $P = .002$) and postoperative surgical complication (RR, 2.13; 95% CI, 1.16-3.91; $P = .015$). Estimated overall survival rates in 90-day survivors were 35% (range, 29%-41%) and 25% (range, 19.3%-30.7%) at 3 and 5 years, respectively. This survival with reference to various variables is shown in Table 6. At multivariate analysis, one independent prognostic factor entered the model: pathologic stage III-IV disease (RR, 1.89; 95% CI, 1.09-3.26; $P = .022$).

Discussion

Thirty-day mortality observed in this series (12%) is in line with internationally reported data on lung cancer surgery in the setting of induction therapy.^{10,12,16,18} It is also in accordance with the risk of pneumonectomy as estimated from nationwide data, including in high-volume hospitals (10.7%), that is considerably higher than those typically reported.²⁰ However, this rate seems higher than what is currently reported after an operation alone by single institutions or multicenter databases,²¹⁻²³ suggesting an increased risk caused by the preoperative oncologic therapy.

Neither 30-day nor 90-day mortality rates improved with time in our experience. Unsurprisingly, the spectrum of major complications included various surgical, as well as medical, complications. However, our results show that surgical complications were not the most determining causes of fatality in contrast with cardiopulmonary complications. Indeed, cardiac and pulmonary events occurring in the absence of a concomitant surgical complication were shown to be strong and independent predictors of mortality. Multivariate analyses suggest that both events were often associated concurrently or sequentially and correlated with allogeneic blood transfusions. Because blood requirements after major operations mainly depend on preoperative hemoglobin levels,²⁴ it might be anticipated that induction therapy and anemia logically increase these needs. This fact is of clinical relevance because data on transfusion therapy have not always been favorable, particularly in the areas of postoperative infection, systemic inflammatory response syndrome, multiple organ failure, and finally mortality. Furthermore, the risk of infection transmission now includes both existing and emerging pathogens. Of note, some patients had a well-documented viral pneumonia, a cause that is not common after surgical intervention alone. This fact also suggests an immunosuppressive side effect induced by the preoperative treatment. Cardiac events appeared to be more frequent in the recent period of the study. One might hypothesize that such complications strongly depend on the preoperative cardiac status, and this observation becomes consistent with the constant aging of the surgical population and its related comorbidities.

Even if it did not reach statistical significance, there was an obvious difference according to the side of the procedure, with a 2-fold increase of the operative risk for right pneumonectomy. The same excess of 30-day mortality after right pneumonectomy after induction therapy has been already reported by Sloan Kettering Memorial¹⁸ and might be explained by a magnification of the higher risk of bronchial fistula and respiratory failure of right-sided procedures over left-sided ones performed without any preoperative treatment.²⁵ Of concern is also the fact that the mortality rate considered on a 90-day basis was about twice as high as that observed within the first 30 postoperative days. Our 90-day

mortality rate was very similar to that reported for right pneumonectomy after induction therapy by Martin and colleagues.¹⁸ The majority of the 90-day deaths (57%) were related to postoperative complications. Nevertheless, 1 of 5 patients dies from the initial tumor disease. Generally this was represented by brain metastasis (75%). This concerned patients in the beginning period of our study (1989-1997) who did not have a routine brain CT scan performed as part of the pretherapeutic workup. These patients had cerebral edema during the early postoperative course related to undiagnosed brain metastases. Also, the incidence of sudden deaths with unknown origin in otherwise healthy discharged patients was substantial (14%). In our opinion, some of them might have been due to pulmonary embolism, which is a frequent cause of acute fatality after lung resection.²⁶ This might support the use of vitamin K antagonist in the long run.

This study has the obvious limitations of a retrospective study because of data collection. We mixed preoperative, intraoperative, and postoperative variables in the analysis to identify potential predictors of mortality. It might be objected that some potentially pertinent variables were missing, such as spirometric data. However, our selection criteria for pneumonectomy have been rather standardized during the period and led to a very homogeneous surgical cohort from this point of view. It would have been also of great interest to incorporate cardiac and respiratory exercise stress testing findings, as well as comorbidity scores, or any other clinically relevant markers as documented by the current literature. Unfortunately, the modalities of such tests and scores appeared or changed radically along the period, resulting in a high amount of missing data and rendering the analysis unsound. Obviously, postoperative variables are not available at the moment of the patient selection for surgical intervention. However, we opted deliberately for a very pragmatic approach that evaluated also what kind of early postoperative events might have been predictive of delayed complications.

Despite controversial results of available randomized trials,^{2,3} combined strategies with induction therapy are currently applied worldwide for the management of patients with advanced-stage NSCLC to improve survival. Indeed, all our patients presented with a locally advanced or metastatic disease, even if this statement was documented pathologically in only one third of the patients before the induction treatment. The indication and modalities of the induction therapy were decided by the multidisciplinary oncologic committee of our institution with the following rationales: (1) even if there are contradictory data in the literature regarding the value of induction therapy in stage IIIA disease, any patient with resectable N2 disease is considered a candidate for induction therapy, except if he or she accepts to be enrolled in a clinical trial; (2) any T4 N0

tumor suspected to be completely resectable is referred to surgical intervention with or without induction chemotherapy or radiochemotherapy; and (3) because there are no clear guidelines for the treatment of patients with stage IV disease, particularly in the setting of a completely resected single brain metastasis, the treatment discussion remains open. We opted to consider that the disease had been downstaged by the neurosurgeon and that the treatment of the lung cancer had to be based on the residual disease, provided that N2 involvement had been ruled out by the use of mediastinoscopy. We postulated that the overall prognosis of the highly selected population of patients with lung cancer presenting with a resectable primary lung tumor and an apparently solitary brain metastasis was at the same level as that of patients presenting with a locally advanced disease in whom the problem is the presence of a disseminated micrometastatic disease in almost all the cases.

Of interest is the fact that our patients experienced very similar 3- and 5-year survival rates as those seen in currently available studies with multimodal therapies for NSCLC. The substantial overall 5-year survival rate (19.8%) we observed reflects patient selection comparable with that reported worldwide.^{1,7,13,18,27,28} To the best of our knowledge, however, this is the first report that deals specifically with the results of pneumonectomy in that setting. In turn, few data are available to analyze our results comprehensively. The risk/benefit ratio associated with the procedure is difficult to assess. The fact that the occurrence of postoperative complications was the single prognosticator of long-term survival at the multivariate analysis performed on the whole series of patients highlights the necessity to consider first the toxicity of combined modalities. Interestingly, the multivariate analysis limited to the 90-day survivors disclosed downstaging as the sole prognosticator of long-term survival in accordance with the results of recent prospective trials.^{6,29,30} Thus our results strongly suggest that postinduction restaging is of paramount importance to avoid pneumonectomy in nonresponders.

Conclusion

Pneumonectomy after induction therapy is a high-risk procedure, the survival benefit of which appears uncertain. This observation leads to consideration of alternative therapeutic options, such as radiotherapy or bronchial, arterial, or both sleeve lobectomies whenever technically possible, especially in patients with a right-sided disease for whom the risk to die within 90 days after surgical intervention is at the same level as the hope of cure.

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