Risk Factors for Early Mortality and Major Complications Following Pneumonectomy for Non-small Cell Carcinoma of the Lung*

Marc Licker, MD; Anastase Spiliopoulos, MD; Jean-Georges Frey, MD; John Robert, MD; Laurent Höhn, MD; Marc de Perrot, MD; and Jean-Marie Tschopp, MD, FCCP

Study objectives: **To assess the mortality rate and the incidence of cardiopulmonary complications after pneumonectomy for non-small cell lung carcinoma (NSCLC) and to identify possible associated risk factors.**

Design: **Observational study of patients who underwent pneumonectomy. Potential risk factors were analyzed from a local database including all thoracic surgical cases.**

Setting: **A university hospital and a chest medical center.**

Patients and methods: **From January 1, 1990, to April 30, 2000, 193 consecutive pneumonectomies were performed for NSCLC in two affiliated institutions. The following information was recorded: demographic, clinical, functional, and surgical variables; as well as intraoperative and postoperative events. The risk of mortality and cardiopulmonary complications was evaluated using multiple logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs).**

Results: **After undergoing pneumonectomy, all patients were successfully extubated in the operating room and then transferred to a postanesthesia care unit (126 patients) or ICU (67 patients). The 30-day mortality rate was 9.3%, and cardiovascular and/or pulmonary complications occurred in 47% of cases. Coronary artery disease (CAD) was a predictor of 30-day mortality (OR, 2.9; 95% CI, 1.1 to 8.9). Cardiac morbidity (mainly arrhythmias) was significantly related to advanced age (OR, 3.7; 95% CI, 1.6 to 8.6) and pathologic stages III/IV (OR, 1.4; 95% CI, 1.1 to 4.7), whereas continuous epidural analgesia was associated with a reduced incidence of respiratory complications (OR, 0.2; 95% CI, 0.1 to 0.6).**

Conclusions: **Pneumonectomy for lung cancer is a high-risk procedure, the risk for which is significantly related to the presence of CAD and advanced pathologic stages. Importantly, the provision of epidural analgesia contributes to lower the risk of respiratory complications.**

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Key words: epidural analgesia; lung cancer; pneumonectomy; postoperative cardiopulmonary complications

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; ASA = American Society of Anesthesiology; CAD = coronary artery disease; CI = confidence interval; CVP = Center Valaisan de Pneumologie; HUG = Hôpital Universitaire de Genève; NSCLC = non-small cell lung cancer; OR = odds ratio

In the European Community, carcinoma of the lung is now a leading cause of cancer death for both men and women.[1] In Switzerland, approximately 3,200 new cases occur each year, and the majority of patients will die within the first year after receiving the diagnosis. So far, attempts at early detection as well as promises for major advances in treatment have been unrewarding.[2] Unless the operative risk is considered too high, surgical resection remains the only potential curative option for patients with non-small cell lung carcinoma (NSCLC). In clinical stages I and II, 30 to 70% of patients are expected to survive 5 years after surgery, whereas much lower survival rates are achieved in the heterogeneous group of patients who are in clinical stages IIIA and IIIB, who require adjuvant chemotherapy and radiotherapy.[3–5]

*From the Department of Anesthesiology, Pharmacology, and Surgical Intensive Care (Drs. Licker and Höhn), the Unit of Thoracic Surgery (Drs. Spiliopoulos, Robert, and de Perrot), the University Hospital of Geneva, Geneva, Switzerland; and the Chest Medical Center (Drs. Frey and Tschopp), Valais, Switzerland.

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Correspondence to: Marc Licker, MD, Division d'Anesthésiologie, Hopital Universitaire, rue Micheli-Ducrest, CH-1211 Genève 14; e-mail: marc-joseph.licker@hcuge.ch

The choice from among pneumonectomy, lobectomy, or lesser extended resection is determined mainly by the degree of invasion of the mediastinal nodes as well as by the size and localization of the tumor.[6,7] Despite refinements in operative techniques and perioperative medical care, pneumonectomy still carries higher mortality and morbidity rates than lesser resection.[8] Hence, a proper selection of surgical candidates takes into account the balance between the operative risks due to associated diseases and the benefits in terms of increased survival time and quality of life.

Unfortunately, most studies do not accurately describe the perioperative complications occurring after pneumonectomy, and existing data are difficult to interpret for several reasons. First, the sample size is often too small to apply a multivariate logistic regression model, and postoperative complications are not clearly defined.[9,10] Second, the study population is heterogenous due to the inclusion of patients with cancer, benign tumors, or infectious processes who undergo various types of lung resections.[8] Third, few studies have included detailed information concerning preoperative characteristics (*ie*, cardiologic testing) and perioperative interventions such as the analgesic regimen.

In the present study, we analyzed a clinical database including all thoracic surgical cases managed by the same medical team and determined the risk factors for perioperative mortality and cardiopulmonary complications in patients with NSCLC who underwent pneumonectomy.

Materials and Methods

Patient Management

From January 1, 1990, to April 30, 2000, 815 consecutive patients underwent thoracic surgery for NSCLC in the following two affiliated institutions: an academic medical center (Hôpital Universitaire de Genève [HUG]; Geneva, Switzerland); and a regional hospital (Center Valaisan de Pneumologie [CVP]; Valais, Switzerland) that covered an area with approximately 450,000 inhabitants. Among the 815 surgical cases, there were 193 pneumonectomies (24%). All patients were operated on by one of three surgeons who specialized in thoracic surgery and were managed by the same team of anesthesiologists and chest physicians.

The preoperative evaluation included a complete history, physical examination, blood cell count, biochemical profile, chest roentgenogram, ECG, pulmonary function tests, and CT scan of the chest and abdomen. When FEV_1 was $< 60\%$ of the predicted value, a differential lung perfusion scan was performed. Patients with borderline spirometric results or impaired exercise tolerance underwent a cardiopulmonary exercise test on a bicycle ergometer. Most surgical candidates were selected to undergo pneumonectomy if the calculated postoperative FEV_1 was ≥ 0.8 L (or 40% of the predicted value) and if the maximal aerobic capacity was $\geq 50\%$ of the predicted value. Transthoracic echocardiography (n = 10), thallium-dipyridamole myocardial scintigraphy (n = 13), or coronary angiogram (n = 1) was performed in patients with risk factors for coronary artery disease (CAD) and in those patients with low functional capacity, according to the guidelines published by the American Heart Association (AHA) and the American College of Cardiology (ACC).[11]

Preoperatively, a thoracic epidural catheter was routinely inserted, except in patients who refuse the placement of the catheter, and in patients with coagulation disorders, acute neurologic problems, local or systemic infections, and technical failures (*ie*, catheter malpositioning or malfunction). Pneumonectomy was performed through a standard posterolateral (n = 21) or anterolateral muscle-sparing thoracotomy (n = 172). Prophylactic antibiotic therapy (*ie*, cefuroxime, 1.5 g per 8 h for 24 h) was administered routinely and, after anesthesia induction (*ie*, thiopental, 4 to 7 mg/kg, and vecuromium, 1 mg/kg), a double-lumen tube was inserted to allow one-lung ventilation. Anesthesia was maintained with inhaled isoflurane, and intraoperative analgesia was provided with repeated doses of IV opiate (fentanyl, 50 to 100 μg) or the epidural administration of local anesthetics and opiate (bupivacaine, 0.25%, and fentanyl, 2 μg/mL). After surgery, all patients were monitored for at least 24 h in the postanesthesia care unit or the ICU to provide them with intensive nursing and respiratory care, with an emphasis being placed on pain control, diaphragmatic breathing, aggressive pulmonary toilet, as well as early mobilization, ambulation, and feeding. IV fluid infusion was limited to compensate for the volume of blood loss with colloids and to replace evaporation loss with 5% glucose in saline solution at a rate of 1 mL/kg/h. Postoperative pain was assessed at rest and during coughing with a visual analog scale, and the analgesic regimen was titrated to keep the visual analog scale at $< 3/10$ using either IV morphine (with a patient-controlled analgesia pump) or a mixture of bupivacaine (0.125%) and fentanyl (2 μg/mL) through the epidural catheter for 2 to 4 days. Chemotherapy was administered to all patients with lymph node involvement, and postoperative radiotherapy was used when the resection border was not tumor-free.

Data Collection and Extraction

Demographic, clinical, surgical, and anesthetic data and perioperative complications were abstracted from an institutional database that included all patients who had undergone thoracic surgery. In addition, nursing charts and medical records (including specialty consultations, anesthesia charts, results of investigations, and hospital discharge letters) were reviewed by two investigators. Staging of the tumor extension was based on the revised TNM classification,[12] and histologic typing was reported according to the World Health Organization.[13] Binary data were obtained by the identification of the presence or absence of relevant comorbidities and perioperative complications.

The diagnosis of CAD was based on a history of myocardial infarction or angina, typical Q waves seen on the ECG, positive result of a stress test, or evidence of coronary artery stenosis on the angiogram. Elevated BP, arrhythmias, and diabetes mellitus requiring medication were considered significant comorbidities. Peripheral artery disease was defined by clinical evidence (*ie*, claudication at exercise and past or current vascular surgery) or arteriography. The diagnosis of COPD was based on the criteria of the American Thoracic Society and on the results of functional tests (*ie*, FEV_1/FVC, $\leq 70\%$ of predicted value).[14] Specific cutoff points were selected to define advanced age (*ie*, ≥ 70 years), obesity (body mass index, ≥ 30), and renal insufficiency (serum creatinine level, > 160 μg/L [corrected for age]). The five-grade classification of the American Society Anesthesiology (ASA) was used as a composite index of a patient's general status.

The following potential intraoperative risk factors also were

considered: duration of surgery; surgical approach (*ie*, anterolateral or posterolateral thoracotomy); extended resection (including adjacent structures); type of analgesia (*ie*, IV opiate or epidural local anesthetic with an opiate); and staging (*ie*, stages I/II and III/IV).

Operative mortality was defined as any death occurring within 30 days of a patient undergoing an operation or within the duration of a hospital stay. Respiratory complications included reintubation, atelectasis, pneumonia, reperfusion edema, and bronchopleural fistula. Cardiovascular complications included arrhythmias, myocardial infarctions, acute heart failure, pulmonary emboli, and strokes. Renal impairment was considered if the serum creatinine level increased $\geq 20\%$ compared with the preoperative value. For time-trends analysis, outcome data were divided into two periods, 1990 to 1995 and 1996 to 2000.

Statistical Analysis

Data are presented as the mean ($\pm$ SD), the median (range), and absolute numbers or percentages. Potential risk factors for an adverse event were identified by univariate and multivariate logistic regression analysis. To avoid overadjustment by using too many variables in the multivariate model, all variables were subjected to univariate analysis in a first step. Factors with a p value < 0.25 were considered as potential risk factors in the forward multivariate model. To avoid multicollinearity, only one variable in a set of variables with a correlation coefficient > 0.5 was used in the multivariate analysis. Outcome (*ie*, death, cardiac complications, or pulmonary complications) was the dependent variable, whereas clinical and surgical variables were the independent variables. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results

General Characteristics

The 193 patients who underwent pneumonectomy had a mean age of 63 ± 8 years and included a majority of smokers (80%) and men (75%). Arterial hypertension (30%), emphysema (29%), mild-to-moderate renal insufficiency (19.2%), peripheral vascular disease (10.4%), and diabetes mellitus (8.8%) were the most frequent associated medical diseases. The diagnosis of CAD was documented in 24 patients (12.4%) based on clinical history and ECG findings (angina, 3 patients; myocardial infarction, 10 patients; angina and myocardial infarction, 2 patients), or additional cardiac testing (10 patients). Among patients with COPD, the median FEV_1 value was 1.5 L (range, 0.7 to 2.8 L) and the median FEV_1/FVC ratio was 55% of the predicted value (range, 45 to 70% of predicted).

Squamous cell carcinoma was the most common histologic type of cancer (69%), followed by adenocarcinoma (22%), large cell carcinoma (3.6%), bronchioloalveolar carcinoma (3.6%), and other carcinomas (1.4%). Pneumonectomy was performed mainly for early disease stages (stage I, 28%; stage II, 26%; stage IIIA, 33%; stage IIIB, 12%; stage IV, 2%).

The surgical procedure lasted 125 ± 27 min, and all patients were successfully extubated in the operating room and then transferred to the postanesthesia care unit (126 patients) or the ICU (67 patients). Only two patients required secondary transfer from the surgical ward to the ICU. Continuous epidural analgesia was provided to 159 patients (82%), and IV patient-controlled analgesia was provided to the remaining 34 patients. Allogenic blood transfusions were administered in 20 patients (11.4%).

Operative Mortality

The 30-day mortality rate was 9.3% and was mainly related to the presence of hemorrhage, pneumonia, bronchopulmonary fistulas, reperfusion lung edema, arrhythmias, and pulmonary emboli (Table 1). Univariate analysis showed a significant association between the 30-day mortality rate and male gender, ASA class 3 and 4, and CAD (Table 2). The ASA classes 3 and 4 were significantly correlated with age of ≥ 70 years ($r = 0.6$), the presence of CAD ($r = 0.5$), and the presence of COPD ($r = 0.4$). In the multivariate logistic regression model, the potential predictors of ASA score (*ie*, age, hypertension, and COPD) were also included, and gender and ASA score became nonsignificant, whereas only the presence of CAD retained significance in predicting the 30-day mortality rate after pneumonectomy (Table 3).

Postoperative Cardiovascular and Respiratory Complications

Cardiovascular and/or pulmonary complications occurred in 47% of all patients who underwent surgery. As shown in Table 4, the most common postoperative nonfatal complications were arrhythmias (25%), pneumonia (7.8%), and bronchopulmonary fistulas (4.7%). The occurrence of respiratory complications was associated with a prolonged duration of hospital stay (19 ± 9 vs 12 ± 2 days in patients without respiratory complications; $p < 0.05$).

There was no association between adverse postoperative outcome and the side on which the operation occurred (*ie*, left or right), the calendar period (*ie*, 1990 to 1995 or 1996 to 2000), the medical center (HUG or CVP), as well as the surgical approach (*ie*, standard posterolateral vs anterolateral thoracotomy), the extent of resection, or the presence of diabetes mellitus, peripheral artery disease, or renal insufficiency.

Cardiac morbidity was higher in elderly patients, whereas respiratory morbidity was associated with ASA classes 3 and 4, extended resection, and IV analgesia (Table 2). After multivariate analysis, cardiac morbidity was significantly related to advanced age and pathologic stages (*ie*, stages III and IV),

Table 1—*Characteristics of 18 Patients Who Died During Their Hospital Stays or Within 30 Days After Undergoing Thoracic Surgery for NSCLC

Year/Patient No./ASA Stage/Age, yr	Preoperative Risk Factors	Cause of Death	Period
1990/1/III/62	CAD, diabetes, HT	Arrythmia, bronchopneumonia	POD 5
1990/2/II/56	None	Pulmonary thromboembolism, arrythmia	POD 15
1991/3/III/57	Obesity	Pulmonary thromboembolism	POD 7
1991/4/III/74	CAD	Ventricular arrythmia	Intraoperative
1991/5/III/66	Lung atelectasis	Bronchopneumonia	POD 2
1993/6/III/67	Diabetes, HT, PAD	Bronchopneumonia, MOF	POD 15
1993/7/II/74	PAD, HT	Bronchopneumonia	POD 5
1993/8/II/59	None	Major hemorrhage	Intraoperative
1995/9/III/73	Diabetes, PAD	Hemorrhage, catheter-related sepsis, MOF	POD 30
1995/10/IV/71	CAD, HT	BPF, sepsis, arrythmia	POD 11
1996/11/III/67	HT	Acute lung injury	POD 20
1997/12/III/66	CAD, PAD, COPD	Bronchopneumonia	POD 25
1997/13/II/59	None	Bronchopneumonia, respiratory failure	POD 6
1998/14/II/56	COPD	Acute lung injury	POD 15
1998/15/III/79	Diabetes, HT, PAD	BPF, empyema, MOF	POD 19
1999/16/III/83	COPD, HT	Major hemorrhage	Intraoperative
1999/17/IV/71	CAD, HT, COPD	Hemorrhage, arrythmia	POD 19
1999/18/III/75	COPD	Bronchopneumonia, MOF, arrythmia	POD 20

*HT = hypertension; BPF = bronchopleural fistula; PAD = peripheral arterial disease; MOF = multiple organ failure; POD = postoperative day.

whereas the absence of epidural analgesia was an independent risk factor for the occurrence of respiratory complications (Table 3). *Post hoc* analysis to detect selection bias in patients receiving or not receiving epidural analgesia revealed comparable age, hemoglobin values, and creatinine values as well as respiratory risk factors, except for a higher prevalence of hypertension and peripheral artery disease among patients with epidural analgesia compared with those receiving an IV opiate (Table 5). According to a multiple regression model, the independent risk factors accounted for an 18% mortality rate, a 22% cardiac morbidity rate, and a 24% respiratory morbidity rate (r^2 determined by multiple regression).

Discussion

Previous investigations[15–17] have shown that readily accessible clinical and functional markers are useful to predict complications after thoracic surgery. In our cohort of 193 patients who underwent pneumonectomy for NSCLC, we identified CAD as the main risk factor of 30-day operative mortality, whereas aging (*ie*, $\geq$ 70 years) and advanced cancer stages (*ie*, stages III and IV) were markers of nonfatal cardiac complications such as arrhythmias. Importantly, continuous epidural analgesia contributed to minimize the risk of pulmonary morbidity. These results were obtained in two affiliated hospitals where practice was consultant-led and protocol-driven.

Operative Mortality and Cardiovascular Complications

Modern perioperative mortality following pneumonectomy varies greatly, ranging from 3.0 to 25% in published series.[8,10,18,19] Besides patient comorbidities and lung cancer extension, the volume of surgical cases, the specialization of the medical team, patient selection bias, and the definition of outcome may account for variations in both mortality and morbidity data. Better results are achieved with specialized thoracic surgeons (vs general surgeons) and in institutions with high caseloads.[20,21] Complication rates also can be influenced by variable threshold for excluding high-risk patients. For example, in Japan, the low 30-day mortality rate (3.2%) is associated with a low proportion of pneumonectomies (8.3%), suggesting that elderly patients and patients with comorbidities possibly are kept from undergoing curative resection, undergo less extensive procedures, or receive nonsurgical treatments.[22]

In our local database, pneumonectomy represented a large proportion (24%) of all lung resections for cancer, and 30% of the surgical population was $>$ 70 years of age. The 9.3% operative mortality rate included any death that occurred within the hospital stay or 30 days following surgery. Reporting only in-hospital deaths would have underestimated the true mortality rate derived from the accepted 30-day standard.

Operative mortality was related mainly to hemorrhage, pneumonia, or multiple organ failure and occurred more frequently among the elderly, men,

Table 2—*Univariate Analysis of Potential Risk Factors for Operative Mortality and Cardiac and Respiratory Morbidity

Variables	Patients, No.	30-d Mortality			Cardiac Morbidity			Respiratory Morbidity		
		%	RR (95% CI)	p Value	%	RR (95% CI)	p Value	%	RR (95% CI)	p Value
Age, yr										
≥ 70	58	13.8	1.9 (0.8–4.5)	0.18	46.6	2.3 (1.5–3.6)	0.0004	13.8	0.8 (0.4–1.8)	0.83
< 70	135	7.4			20.0			16.3		
Gender										
Male	154	11.7		0.027	30.5	1.7 (0.8–3.5)	0.16	16.9	1.6 (0.6–4.4)	0.46
Female	39	0.0			17.9			10.3		
Hypertension										
Yes	58	13.8	1.9 (0.8–4.5)	0.18	36.2	1.5 (0.9–2.3)	0.12	15.5	1.0 (0.5–2.0)	1.0
No	135	7.4			24.4			15.6		
CAD										
Yes	24	20.8	2.7 (1.1–6.9)	0.054	37.5	1.4 (0.8–2.5)	0.33	16.7	1.1 (0.4–2.8)	0.77
No	169	7.7			26.6			15.4		
Bronchoemphysema										
Yes	56	14.3	2.0 (0.8–4.7)	0.17	35.7	1.4 (0.9–2.3)	0.16	17.9	1.2 (0.6–2.4)	0.66
No	137	7.3			24.8			14.6		
Smoking										
Yes	155	10.3	2.0 (0.5–8.2)	0.53	28.4	1.1 (0.6–1.9)	1.0	16.8	1.6 (0.6–4.3)	0.46
No	38	5.3			26.3			10.5		
Body mass index										
≥ 30	18	11.1	1.6 (0.9–3.4)	0.32	44.4	1.5 (0.7–2.8)	0.21	15.5	0.9 (0.4–1.9)	0.92
< 30	161	8.7			25.5			16.1		0.56
ASA score										
3/4	86	15.1	3.2 (1.2–8.7)	0.023	31.4	1.2 (0.8–2.0)	0.42	20.9	1.9 (0.9–3.7)	0.074
1/2	107	4.7			25.2			11.2		
Carcinologic staging										
III/IV	90	12.2	1.9 (0.7–7.4)	0.22	32.4	1.5 (0.9–2.3)	0.15	18.9	1.3 (0.3–4.6)	0.32
I/II	102	6.9			22.2			12.7		
Duration of surgery, min										
≥ 120	117	10.2	1.4 (0.4–4.7)	0.84	30.0	1.2 (0.6–1.9)	0.43	15.4	0.9 (0.4–2.4)	0.97
< 120	76	7.9			26.8			15.8		
Extended resection										
Yes	20	10.0	1.1 (0.4–2.4)	0.970	30.0	1.1 (0.3–2.3)	0.77	23.3	1.9 (1.1–4.6)	0.044
No	173	9.2			27.8			7.5		
Epidural analgesia										
Yes	159	8.2	0.7 (0.2–1.9)	0.50	28.3	1.2 (0.6–2.2)	0.83	11.3	0.3 (0.2–0.6)	0.003
No	34	11.8			24.2			36.4		
Year of surgery										
1990–1995	106	9.4	1.0 (0.4–2.5)	1.0	30.2	1.2 (0.7–1.9)	0.52	11.3	0.5 (0.3–1.1)	0.11
1996–2000	87	9.2			25.3			20.7		
Hospital site										
HUG	145	10.3	1.7 (0.5–5.5)	0.57	30.3	1.5 (0.8–2.7)	0.27	14.5	0.8 (0.4–1.6)	0.49
CVP	48	6.3			20.8			18.8		

*RR = relative risk.

and patients in ASA classes 3 or 4. After adjustment for concomitant diseases, only the presence of CAD was considered to be an independent risk factor. Myocardial ischemia or infarction was not directly implicated in operative death, however, the presence of CAD in 5 of 18 nonsurvivors could have impaired the cardiac adaptation during acute hypovolemia, sepsis, or reperfusion edema and, thereby, could have contributed to a fatal outcome.

In the remaining 19 coronary patients, the time course of surgery was uneventful, except for one case of nonfatal myocardial infarction. The low incidence of serious adverse cardiac events, besides arrhythmias, could be explained by the application of AHA/ACC guidelines,[11] a low prevalence (12.4%) of CAD among surgical candidates, as well as by appropriate perioperative control of factors like pain, hypovolemia or hypervolemia, anemia, and hypercoagulation. Based on the AHA/ACC guidelines,[11] thoracic surgery is classified as an intermediate-risk procedure, and preoperative cardiologic testing is selectively performed in patients with clinical markers of CAD

Table 3—*Multivariate Analysis of Potential Risk Factors for Major Complications*

Risk Factors	Coefficient	OR	95% CI	p Value
Mortality				
Constant	−5.27			
CAD	1.06	2.9	1.1–8.9	0.042
Cardiac morbidity				
Constant	−1.99			
Age ≥ 70 yr	1.31	3.7	1.6–8.6	0.003
Stage III and IV	0.88	1.4	1.1–4.7	0.032
Respiratory morbidity				
Constant	−1.29			
No epidural analgesia	−1.52	0.2	0.1–0.6	0.001
ASA class 3 and 4	0.84	2.3	0.98–5.5	0.056

Table 5—*Characteristics of Patients With and Without Epidural Analgesia**

Parameters	Epidural (n = 159)	No Epidural (n = 34)
Age, yr	63 (8)	62 (9)
Body mass index	24.9 (3.2)	24.0 (3.1)
Creatinine, μg/L	89 (12)	81 (8)
FEV_1, L	2.2 (0.5)	2.4 (0.5)
Hypertension	32.7†	17.6
Diabetes	9.4	5.9
CAD	11.9	14.7
PAD	11.9*	2.9
COPD	28.9	26.5
Duration of surgery, min	125 (26)	127 (29)

*Values given as mean (SD) or %. See legend of Table 1 for abbreviations not used in the text.
†$p < 0.05$.

(*ie*, diabetes, vascular disease, and angina pectoris) and in those patients with poor exercise tolerance. Such a selective screening approach was helpful in identifying patients who required more intensive perioperative care (*ie*, β-blockers and echocardiography) or myocardial revascularization and to exclude those with poor ventricular function and/or severe CAD who were not amenable to percutaneous angioplasty, since the operative risk outweighed the potential benefits of cancer resection.[11,23]

Supraventricular arrhythmia was the most frequent complication (25%) and was related to increasing age and advanced pathologic stages. Known causative factors are intracardiac conduction abnormalities associated with aging, impaired cardiac autonomic control due to extensive surgical dissection as well as triggering factors like pain, hypoxemia, and right heart overload.[24] Fortunately, postoperative arrhythmias do not appear to have a negative impact on short-term mortality rates if they are promptly reversed, whereas recurrent or chronic arrhythmia is a marker of poor outcome, suggesting advanced lung cancer stages.[25]

Table 4—*Mortality and Morbidity Rates After Pneumonectomy*

Variables	Rate, %
30-d mortality rate	
HUG	10.3
CVP	6.3
Cardiovascular complications	
Arrhythmias	24.9
Heart failure	0.5
Myocardial infarction	0.5
Stroke	1
Pulmonary emboli	2.6
Pulmonary complications	
Bronchopneumonia	7.8
Atelectasis	2.6
Bronchopleural fistula	4.7
Re-intubation	2.1
Prolonged chest drainage (≥ 7 days)	2.6
Reperfusion edema	2.1
Renal dysfunction	
Elevation of plasma creatinine (≥ 20%)	2.6

Respiratory Complications

Importantly, fewer respiratory complications occurred in patients receiving continuous epidural analgesia (70%) compared with those treated with IV morphine, despite equal analgesic control. The prevention of atelectasis and secondary infections has been attributed to better preservation of the functional residual volume, efficient mucociliary clearance, and alleviation of the inhibitory reflexes acting on the diaphragm in patients with epidural analgesia.[26–28] In addition, less opiate-induced nausea and sedation are thought to facilitate deep-breathing maneuvers and the collaboration with respiratory therapists.

In our nonrandomized study, the choice of the analgesic regimen was not influenced by preoperative comorbidities. Patient-controlled analgesia with morphine was applied in a minority of patients (18%) who did not qualify for epidural analgesia because of contraindications, technical failure, or patient refusal of therapy. Assuming similar characteristics in the two subgroups, a power analysis shows that we had an 80% chance of detecting a reduction in respiratory complications from 35 to 11% with an α two-tailed set at 0.05.

Although the results of a meta-analysis[29] support the benefits of epidural pain control after noncardiac surgery, no randomized controlled trial has yet compared the efficiency/safety of two equal analgesic techniques (*ie*, IV patient-controlled analgesia vs epidural opiates and local anesthetics) after major

lung resection. Such a study may never be undertaken in the highest risk patients (*ie*, those with severe emphysema undergoing pneumonectomy) for ethical reasons, because of the clinical judgment of the investigators, and due to the unwillingness of the patients to be randomized. In this particular context, it is wise to rely on observational studies since they may give results similar to those of randomized trials when data analysis is adjusted for identifiable differences.[30] In clinical practice, a prospective database including all patients admitted to the hospital for lung surgery is a valuable tool for identifying prognostic risk factors and for guiding an optimal (or least harmful) medical strategy through implementation and evaluation of new health-care interventions.[31]

In contrast with other authors,[24,32,33] we found that advanced age, right-sided surgical procedures, and low FEV_1 were not predictive of operative death or pulmonary complications. These discrepancies likely were explained by the cautious selection of our surgical candidates and by the application of multiregression analysis that identified risk factors unrelated to chronologic age. Indeed, modern health care and better socioeconomic conditions have largely contributed to increased life expectancy, resulting in a growing number of elderly persons who are free of major organ failure and who may safely undergo surgery. On the other hand, regardless of the side operated on, we excluded patients with calculated postoperative $FEV_1 < 40\%$ and those with a maximal oxygen uptake of $< 50\%$ who were at high risk for acute respiratory failure, incapacitating dyspnea, and cardiac complications.[34] Alternatively, a risk stratification assessment of the diffusing capacity of the lung for carbon monoxide could have been used to detect patients who were unable to tolerate lung amputation.[35]

Limitations

A major limitation of our study is that all listed predictors accounted for $< 25\%$ of postoperative complications. Hence, the main part of risk factors remains random or unknown. They are partly related to the individual skills and experience of the members of the medical team as well as to undetected patient illnesses.[36] Several potential predictors of complications were not sufficiently examined and would include the following: renal dysfunction; completion pneumonectomy; surgical techniques (*ie*, muscle-sparing thoracotomy); or the amount of IV fluids. Hence, the determination of other meaningful risk factors will require further analysis in large, multicenter, observational studies to achieve sufficient statistical power.

In conclusion, the analysis of a two-center prospective database was useful to identify variables associated with early complications following pneumonectomy for NSCLC. Advanced age (*ie*, ≥ 70 years) and extended disease stages (*ie*, stages III and IV) were predictive of cardiac arrhythmias. Our data emphasize the importance of preoperative screening for CAD to decrease operative mortality and the benefits of epidural analgesia to lower the incidence of pulmonary complications.

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