Pneumonectomy for lung cancer: Contemporary national early morbidity and mortality outcomes

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Objective: The study objective was to determine contemporary early outcomes associated with pneumonectomy for lung cancer and to identify their predictors using a nationally representative general thoracic surgery database (EPITHOR).

Methods: After discarding inconsistent files, a group of 4498 patients who underwent elective pneumonectomy for primary lung cancer between 2003 and 2013 was selected. Logistic regression analysis was performed on variables for mortality and major adverse events. Then, a propensity score analysis was adjusted for imbalances in baseline characteristics between patients with or without neoadjuvant treatment.

Results: Operative mortality was 7.8%. Surgical, cardiovascular, pulmonary, and infectious complications rates were 14.9%, 14.1%, 11.5%, and 2.7%, respectively. None of these complications were predicted by the performance of a neoadjuvant therapy. Operative mortality analysis, adjusted for the propensity scores, identified age greater than 65 years (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.5-2.9; $P < .001$), underweight body mass index category (OR, 2.2; 95% CI, 1.2-4.0; $P = .009$), American Society of Anesthesiologists score of 3 or greater (OR, 2.310; 95% CI, 1.615-3.304; $P < .001$), right laterality of the procedure (OR, 1.8; 95% CI, 1.1-2.4; $P = .011$), performance of an extended pneumonectomy (OR, 1.5; 95% CI, 1.1-2.1; $P = .018$), and absence of systematic lymphadenectomy (OR, 2.9; 95% CI, 1.1-7.8; $P = .027$) as risk predictors. Induction therapy (OR, 0.63; 95% CI, 0.5-0.9; $P = .005$) and overweight body mass index category (OR, 0.60; 95% CI, 0.4-0.9; $P = .033$) were protective factors.

Conclusions: Several risk factors for major adverse early outcomes after pneumonectomy for cancer were identified. Overweight patients and those who received induction therapy had paradoxically lower adjusted risks of mortality. (J Thorac Cardiovasc Surg 2015;149:73-83)

See related commentary on pages 83-4.

Pneumonectomy historically carries significant and, in some cases, prohibitive morbidity and mortality.[1] With epidemiologic changes, advances in patient selection, operative techniques, and postoperative care, these risks are likely to be reduced and need to be updated. The purpose of this study was to determine the contemporary early outcomes associated with pneumonectomy for lung cancer and to identify predictors of these outcomes using a nationally representative general thoracic surgery database (EPITHOR).

MATERIALS AND METHODS

The institutional review board of the French Society of Thoracic and Cardiovascular Surgery approved the study (approval number 2014-2-6-19-0-26-ThPa). Patients' consent was obtained for entry into the database, and patients were aware that these data would be used anonymously for research purposes.

The French National Database EPITHOR

EPITHOR is the French Society of Thoracic and Cardiovascular Surgery general thoracic surgery database. Its characteristics have been described in detail.[2,3] EPITHOR is a government-recognized clinical database, funded in part by the National Cancer Institute (Institut National du Cancer) for data quality monitoring. EPITHOR also is approved by the French National High Authority for Health (Haute Autorité de Santé), a governmental agency designed to improve the quality of patient care and to guarantee equity within the health care system. The software includes functions that allow participating surgeons to benchmark their activity

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Abbreviations and Acronyms

ARDS = acute respiratory distress syndrome
ASA = American Society of Anesthesiologists
BMI = body mass index
CI = confidence interval
COPD = chronic obstructive pulmonary disorder
FEV1 = forced expiratory volume in 1 second
MRC = Medical Research Council
OR = odds ratio
WHO = World Health Organization

against national averages. Quality assessment includes some software utilities for data consistency, alerting to aberrant or contradictory values in some fields, especially for those mandatory items that are required to initialize and close the process. Furthermore, regular, external, onsite audits, initiated in 2010, are carried out to verify the accuracy of data collection.

Patient Population and Clinical Variables

From March 2003 to March 2013, 39,130 patients were registered in EPITHOR with the main diagnosis of primary lung cancer. We selected those 4820 patients (12.3%) who underwent an elective pneumonectomy. Completion pneumonectomies were not included (N = 389). After discarding data fields with too many inconsistent or missing values and patients with unknown information on variables otherwise suitable for study, a group of 4498 patients was selected for further analysis. Twenty baseline variables per patient were analyzed and are shown in Table 1. Twelve patient-related variables were recorded: age, gender, body mass index (BMI) categories, American Society of Anesthesiologists (ASA) scores, World Health Organization (WHO) performance status, Medical Research Council (MRC) dyspnea score, and number of comorbid diseases. The number of comorbid diseases per patient was thus considered a categoric variable because recent consistent data based on EPITHOR suggested the superiority of this variable on the types of individual comorbidities in a predictive model for operative mortality.[3] Forced expiratory volume in 1 second (FEV1) values were recorded as percentages of predicted values. Patients with chronic obstructive pulmonary disease included those with emphysema, chronic bronchitis, or an FEV1/forced vital capacity ratio of less than 70%. The presence of chronic lung infection as the consequence of an obstructive bronchial tumor was also recorded. Tobacco consumption within 5 weeks before surgery defined the active smoker category. Alcohol dependence or abuse was diagnosed on the basis of excessive habitual drinking or characteristic withdrawal syndrome. The 5 treatment-related variables were side of the procedure (left or right), standard or extended resections to the carina or the chest or mediastinal structures, technique of lymphadenectomy (systematic dissection vs sampling or none), duration of the procedure, and performance of a neoadjuvant therapy. The 3 disease-related variables included tumor histology (adenocarcinoma vs other types); pathologic staging in accordance with the International Association for the Study of Lung Cancer classification,[4] which was presented as consisting of 3 categories to encompass the modifications of subgroup classification during the study period (early I-II, locally advanced III, metastatic IV); and completeness of the resection.

Outcome Definition

The primary end point was operative mortality defined as any death within 30 days after the operation or later if the patient was still in the hospital. Secondary end points were pulmonary, cardiovascular, infectious, and surgical complications. Pulmonary complications included atelectasis requiring bronchial aspiration by fibroscopy, confirmed or suspected pneumonia, and respiratory failure requiring invasive (acute respiratory distress syndrome [ARDS]) or noninvasive mechanical ventilation. Cardiovascular complications included deep venous thrombosis and pulmonary embolism, atrial fibrillation, stroke, acute coronary events, and acute heart failure. Infectious complications included septicemia, isolated fever unrelated to pneumonia or to any specific surgical complication, and urinary tract infections. Surgical complications included vocal cord palsy, bronchial fistula, hemothorax, chylothorax, empyema, and wound abscess.

Statistical Analysis

Descriptive data were expressed as counts and percentages for qualitative variables, and as means and (±) standard deviations for continuous variables. To handle missing data, multiple imputations were performed from the original dataset, using IBM SPSS statistics version 20 (generation of 5 imputations) (IBM SPSS Inc, Chicago, Ill). Then, we performed a propensity score analysis to adjust for imbalances in baseline characteristics between patients with and without induction treatment. We developed a logistic regression model to derive a propensity score for induction treatment; the variables included in the model are detailed in the Online Data Supplement. This logistic regression model was used to estimate a propensity score for each patient, corresponding to the probability of receiving an induction treatment, given the patient's characteristics.[5,6] A graph of propensity scores in the 2 groups of patients was produced (induction therapy vs control) (Figure 1). The matching was performed using greedy matching (1:1 nearest neighbor).[7] Datasets have been treated as a multiple imputation dataset in which missing values have been replaced with imputed values. Multivariable logistic regression analyses were performed to determine variables that might predict, on the one hand, the primary outcome (occurrence of death) and, on the other hand, the secondary outcome (occurrence of pulmonary, cardiovascular, infectious, and surgical complications). These analyses were performed on each imputed dataset. The final result was produced fusing results after multiple imputation (multiple imputation algorithms) (http://pic.dhe.ibm.com/infocenter/spssstat/v21r0m0/index.jsp?topic=%2Fcom.ibm.spss.statistics.help%2Falg_mi-pooling_rubin.htm). The variables relevant to the models were selected from the univariate analyses (chi-square tests for qualitative variables and Student t tests for continuous variables), provided that they were associated with the outcome to explain with a P value of .10 or less, and from their clinical relevance. The final models displayed adjusted odds ratios (ORs), including 95% confidence intervals (CIs). Statistical analyses were performed using IBM SPSS Statistics software version 20 (IBM SPSS Inc) and SAS 9.2 (SAS Institute Inc, Cary, NC). The statistical significance level was set at $P < .05$ in a 2-sided test.

RESULTS

The proportion of pneumonectomies among all surgeries performed for a primary lung cancer and registered in the EPITHOR database during the study period averaged 12.3%. In 12 months, this proportion decreased from 18.9% to 9.1% during the study period.

Overall observed operative mortality was 7.8% (N = 351), including a 30-day mortality rate of 5.7% (N = 256), and decreased in 12 months from 9.1% to 6.9% during the study period. Independent predictors of mortality at multivariate analysis (Table 2) were underweight BMI category, male gender, age more than 65 years, ASA score 3 or greater, number of comorbidities 3 or greater, and right-sided and