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)

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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 ($\pm$) 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

TABLE 1. Patients' characteristics

Variables	Overall population N = 4498	Induction therapy Yes (n = 1236)	Induction therapy No (n = 3262)	P value —
Age (y, mean ± SD)	61.6 ± 9.9	59.7 ± 8.7	62.4 ± 10.1	**<.001**
Age >65 y	1604 (35.7%)	327 (26.5%)	1277 (39.1)	**<.001**
Age ≤65 y	2894 (64.3%)	909 (73.5%)	1985 (58.3%)	
Sex				
Male	3653 (81.2%)	998 (80.7%)	2655 (81.4%)	.62
Female	845 (18.8%)	238 (19.3%)	607 (18.6%)	
BMI	25.0 ± 4.3	24.9 ± 4.3	25.0 ± 4.3	.69
Normal (BMI 18.5-24.9 kg/m^{-2})	2205 (49%)	600 (48.5%)	1605 (49.2%)	.32
Underweight (BMI <18.5 kg/m^{-2})	193 (4.3%)	64 (5.2%)	129 (4.0%)	
Overweight (BMI 25-29.9 kg/m^{-2})	1554 (34.5%)	419 (33.9%)	1135 (34.8%)	
Obesity (BMI ≥30 kg/m^{-2})	546 (12.1%)	153 (12.4%)	393 (12.0%)	
WHO performance status ≤2				
<2	3999 (88.9%)	1097 (88.8%)	2902 (89.0%)	.243
≥2	499 (11.1%)	139 (11.2%)	360 (11.0%)	
No. of comorbidities				
<3	4276 (95.1%)	1198 (96.9%)	3078 (94.4%)	**<.001**
≥3	222 (4.9%)	38 (3.1%)	184 (5.6%)	
Active smokers				
Yes	1489 (33.1%)	419 (33.9%)	1070 (32.8%)	.49
No	3009 (66.9%)	817 (66.1%)	2192 (67.2%)	
Alcohol dependence/abuse				
Yes	245 (5.4%)	60 (4.9%)	185 (5.7)	.28
No	4253 (94.6%)	1176 (95.1%)	3077 (94.3%)	
ASA score				
<3	3275 (72.8%)	884 (71.5%)	2391 (73.3%)	.231
≥3	1223 (27.2%)	352 (28.5%)	871 (26.7%)	
MRC dyspnea score				
<2	3801 (84.5%)	1080 (87.4%)	2721 (83.4%)	**.004**
≥2	687 (15.5%)	156 (12.6%)	541 (16.6%)	
Presence of COPD				
Yes	937 (20.8%)	250 (20.2%)	687 (21.1%)	.54
No	3561 (79.2%)	986 (79.8%)	2575 (78.9%)	
Chronic lung infection				
Yes	92 (2%)	15 (1.2%)	77 (2.4)	**.02**
No	4406 (98%)	1221 (98.8%)	3185 (97.6%)	
FEV1 % predictive (mean ± SD)	64.1% ± 0.3%	63.9% ± 0.7%	64.1% ± 0.4%	.753
≥80	1123 (25.0%)	313 (25.3%)	810 (24.8%)	.446
60-79	1200 (26.7%)	315 (25.5%)	885 (27.1%)	
40-59	1641 (36.5%)	443 (35.9%)	1197 (36.7%)	
<40	445 (11.9%)	165 (13.3%)	369 (11.3%)	
Laterality of procedure				
Right	1804 (40.1%)	530 (42.9%)	1274 (39.1%)	**.02**
Left	2694 (59.9%)	706 (57.1%)	1988 (60.9%)	
Type of pneumonectomy				
Standard	3204 (71.2%)	812 (65.7%)	2392 (73.3%)	**<.001**
Extended	1294 (28.8%)	424 (34.3%)	870 (26.7%)	
Lymphadenectomy				
Systematic	4313 (95.9%)	1181 (95.6%)	3132 (96.0%)	.537
Sampling/none	185 (4.1%)	55 (4.4%)	130 (4.0%)	
Operative time, min (mean ± SD)	148.5 ± 1.2	155 ± 2.2	146 ± 0.4	**<.001**
Neoadjuvant therapy				
No	3262 (72.5%)	—	—	—
Chemotherapy	1116 (24.8%)			
Radiotherapy	18 (0.4%)			
Chemoradiotherapy	102 (2.3%)			

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TABLE 1. Continued

Variables	Overall population N = 4498	Induction therapy Yes (n = 1236)	No (n = 3262)	*P* value —
Histology				
Adenocarcinoma	1453 (32.3%)	438 (35.4%)	1015 (31.1%)	**.01**
Other	3045 (67.7%)	798 (64.6%)	2247 (68.9%)	
pStage				
Localized (I-II)	1928 (42.9%)	441 (35.7%)	1487 (45.6%)	**<.001**
Locally advanced (III)	2341 (52.0%)	710 (57.5%)	1630 (50.0%)	
Metastatic (IV)	229 (5.1%)	85 (6.8%)	145 (4.4%)	
Completeness of resection				
R0	4252 (94.5%)	1169 (94.6%)	3083 (94.5%)	.907
R1 and R2	246 (5.5%)	67 (5.4%)	179 (5.5%)	
Years from 2003 (mean ± SD)	4.8 ± 2.8	4.4 ± 2.7	4.9 ± 2.8	**<.001**

Bold values: $P < .05$. *ASA*, American Society of Anesthesiology; *BMI*, body mass index; *COPD*, chronic obstructive disease; *FEV1*, forced expiratory volume in 1 second; *MRC*, Medical Research Council; *SD*, standard deviation; *WHO*, World Health Organization.

extended procedures. Induction therapy was identified as a robust protective factor (OR, 0.62; $P = .001$), and overweight BMI category was close to being a significant protector (OR, 0.59; $P = .054$).

The comparison of the characteristics of patients who received induction therapy with those of naïve patients is shown in Table 1. The proportion of patients who received induction therapy decreased during the study period. Patients who received neoadjuvant therapy were younger and presented with lower dyspnea scores. They had significantly less comorbidities and chronic lung infections, but a more advanced disease, and a higher proportion of adenocarcinoma. Compared with naïve patients, they received more right-sided and extended procedures, and their operative time was longer. Independent predictors of mortality at multivariate analysis in those patients who received induction therapy were age more than 65 years (OR, 1.795; 95% CI, 1.1-3.0; $P = .03$), male gender (OR, 3.145; 95% CI, 1.3-7.7; $P = .013$), ASA score 3 or greater (OR, 2.498; 95% CI, 1.4-4.4; $P = .002$), and right laterality of the procedure (OR, 1.9; 95% CI, 1.2-3.3; $P = .011$). The performance of an extended pneumonectomy (OR, 1.618; 95% CI, 0.958-2.735; $P = .072$) approached statistical significance.

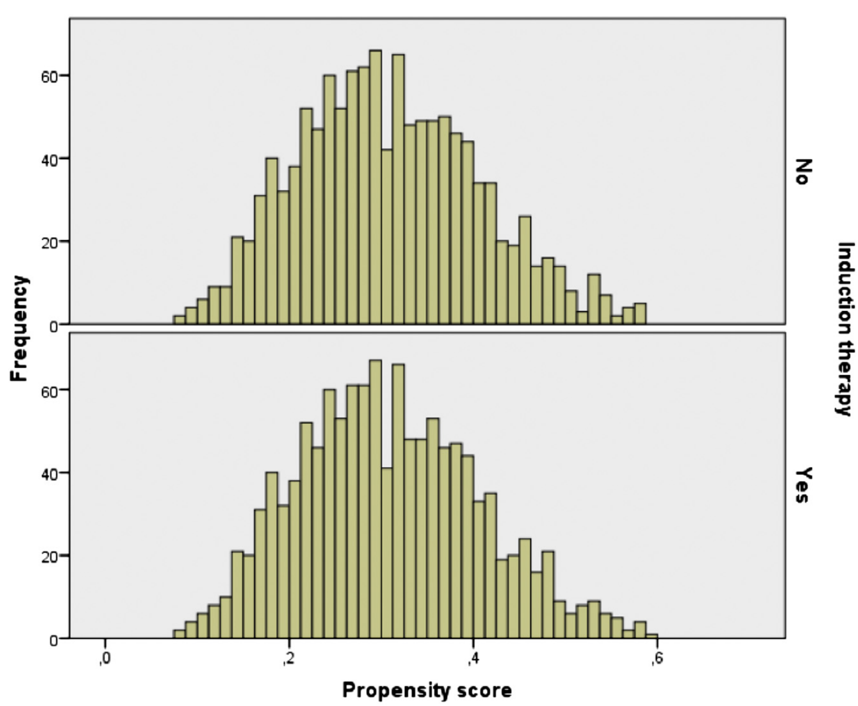

FIGURE 1. Graph of propensity scores in the 2 groups of patients as defined by the performance or not of induction therapy. Each *bar* represents the number of patients with the same propensity score in both groups.

TABLE 2. Operative mortality

Variables	Operative mortality Yes (n = 351)	No (n = 4147)	*P**	aOR	95% CI Lower	Upper	*P*†
Age							
>65 y	181 (11.3)	1423 (88.7)	<.001	1.937	1.531	2.451	**<.001**
≤65 y	170 (5.9)	2724 (94.1)		1			
Sex							
Male	309 (8.5)	3344 (91.5)	.001	1.815	1.282	2.571	**.001**
Female	42 (5.0)	803 (95.0)		1			
BMI categories							
Normal (BMI 18.5-24.9 kg/m^{-2})	176 (8.0)	2029 (92.0)	.002	1			
Underweight (BMI <18.5 kg/m^{-2})	28 (14.5)	165 (85.5)		2.072	1.303	3.294	**.002**
Overweight (BMI 25-29.9 kg/m^{-2})	104 (6.7)	1450 (93.3)		0.773	0.595	1.005	.054
Obesity (BMI ≥30 kg/m^{-2})	43 (7.9)	503 (92.1)		0.834	0.58	1.201	.329
No. of comorbidities							
<3	316 (7.4)	3960 (92.6)	<.001	1			
≥3	35 (15.8)	187 (84.2)		1.887	1.242	2.867	**.003**
ASA score							
<3	184 (5.6)	3091 (94.4)		1			
≥3	167 (13.7)	1056 (86.3)		2.192	1.693	2.836	**<.001**
Laterality of procedure							
Right	194 (10.8)	1610 (89.2)	<.001	2.194	1.743	2.762	**<.001**
Left	157 (5.8)	2537 (94.2)		1			
Type of pneumonectomy							
Standard	220 (6.9)	2984 (93.1)	<.001	1			
Extended	131 (10.1)	1163 (89.9)		1.292	1.008	1.657	**.043**
Lymphadenectomy							
Systematic	330 (7.7%)	3983 (92.3%)	.089				
None/sampling	21 (11.4%)	164 (88.6%)					
Neoadjuvant therapy							
Yes	71 (5.7)	1165 (94.3)	.002	0.625	0.471	0.83	**.001**
No	280 (8.6)	2982 (91.4)		1			

Bold values: $P < .05$. *aOR*, Adjusted odds ratio; *ASA*, American Society of Anesthesiology; *BMI*, body mass index; *CI*, confidence interval. *Unadjusted analysis. †Adjusted analysis.

By using the propensity score, 98.9% (1223/1236) of the patients who had received a preoperative induction treatment were matched to 1223 single patients who did not, with no residual significant imbalances in baseline characteristics. Operative mortality analysis, adjusted for the propensity scores, identified induction therapy (OR, 0.63; 95% CI, 0.5-0.9; *P* = .005) and overweight BMI category (OR, 0.60; 95% CI, 0.4-0.9; *P* = .033) as protective factors, whereas age more than 65 years (OR, 2.1; 95% CI, 1.5-2.9; *P* < .001), underweight BMI category (OR, 2.2; 95% CI, 1.2-4.0; *P* = .009), ASA score 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) were risk predictors.

The overall postoperative complication rate was 33%; 1943 complications developed in 1485 patients. Surgical, cardiovascular, pulmonary, and infectious complication rates were 14.9%, 14.1%, 11.5%, and 2.7%, respectively. Induction therapy was identified as a detrimental risk factor for none of these major adverse outcomes.

Predictors of surgical complications were left-sided procedures (OR, 1.5; *P* < .001), MRC dyspnea score 2 or greater (OR, 1.5; *P* < .001), and increasing operative times in minutes (OR, 1.004; *P* < .001). After propensity score matching, the same factors were identified as predictors. The associated mortality was 9.6% (N = 70). The most frequent single surgical complication was recurrent nerve palsy (N = 282; 6.3%). A bronchial stump fistula occurred in 130 patients (2.9%), and its related mortality was 20.8% (N = 27). Its incidence in patients who received induction therapy was 3.1% (N = 38) versus 2.8% (N = 92) (*P* = .7) in patients who did not. Predictors of bronchial fistula at multivariate analysis were active smoking (OR, 1.6; *P* = .017), alcohol abuse/dependence (OR, 2.2; *P* = .005), MRC dyspnea score 2 or greater (OR, 1.8; *P* = .036), right-sided procedures (OR, 2.1; *P* < .001), increasing operative times (OR, 1.006; *P* < .001), and date of operation (OR, 0.8; *P* < .001). Male gender

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TABLE 3. Pulmonary complications

Variables	Pulmonary complications Yes (n = 518)	Pulmonary complications No (n = 3980)	P*	aOR	95% CI Lower	95% CI Upper	P†
Age							
>65 y	211 (13.2)	1393 (86.8)	.01	1.261	1.036	1.536	**.021**
≤65 y	307 (10.6)	2587 (89.4)		1			
Sex							
Male	449 (12.3)	3204 (87.7)	.001	1.53	1.161	2.015	**.003**
Female	69 (8.2)	776 (91.8)		1			
BMI categories							
Normal (18.5-24.9 kg/m^{-2})	257 (11.7)	1948 (88.3)	.003	1			
Underweight (<18.5 kg/m^{-2})	32 (16.6)	161 (83.4)		1.477	0.971	2.245	.068
Overweight (25-29.9 kg/m^{-2})	151 (9.7)	1403 (90.3)		0.796	0.640	0.989	**.04**
Obesity (≥30 kg/m^{-2})	78 (14.3)	468 (85.7)		1.129	0.852	1.496	.4
ASA score							
<3	316 (9.6)	2959 (90.4)	<.001	1			
≥3	202 (16.5)	1021 (83.5)		1.444	1.026	2.032	**.035**
WHO performance status							
<2	422 (10.6)	3577 (89.4)	<.001	2.194	1.743	2.762	**<.001**
≥2	96 (19.2)	403 (80.8)		1			
Laterality of procedure							
Right	276 (10.2)	2418 (89.8)	.001	1.388	1.148	1.678	**.001**
Left	242 (13.4)	1562 (86.8)		1			
Type of pneumonectomy							
Standard	187 (14.5)	1107 (85.5)	<.001	1			
Extended	331 (10.3)	2873 (89.7)		1.259	1.028	1.542	**.026**
COPD							
No	363 (10.2%)	3198 (89.8%)	<.001	1			
Yes	155 (16.5%)	782 (88.6%)		1.653	1.336	2.044	**<.001**
Operative time							
Mean ± SD	163.7 ± 3.6	146.5 ± 1.2	<.001	1.003	1.002	1.005	**<.001**

Bold values: $P < .05$. *aOR*, Adjusted odds ratio; *ASA*, American Society of Anesthesiology; *BMI*, body mass index; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *SD*, standard deviation; *WHO*, World Health Organization. *Unadjusted analysis. †Adjusted analysis.

approached statistical significance (OR, 1.8; $P = .05$). After propensity score matching, predictors of overall surgical complications were active smoking (OR, 1.7; $P = .03$), MRC dyspnea score 2 or greater (OR, 2; $P = .034$), right-sided procedures (OR, 1.9; $P = .011$), increasing operative times (OR, 1.009; $P < .001$), and date of operation (OR, 0.8; $P < .001$). Male gender (OR, 1.9; $P = .095$) and alcohol abuse/dependence (OR, 1.9; $P = .096$) were close to being statistically significant.

The mortality related to cardiovascular complications was 14.8% (N = 94). The most frequent single cardiovascular complication was arrhythmia (10.6%; N = 477). Predictors of cardiovascular complications were age greater than 65 years (OR, 1.9; $P < .001$), WHO performance status 2 or greater (OR, 1.6; $P = .006$), active smoking (OR, 1.3; $P = .011$), extended procedures (OR, 1.3; $P = .004$), increasing operative times (OR, 1.001; $P = .043$), FEV1 in milliliters/kilograms/second (OR, 0.74; $P = .023$), and year of operation (OR, 1.04; $P = .023$). After propensity score matching, predictors of cardiovascular complications were age greater than 65 years (OR, 1.9; $P < .001$), male gender (OR, 1.8; $P = .003$), WHO performance status 2 or greater (OR, 1.7; $P = .014$), active smoking (OR, 1.4; $P = .015$), extended procedures (OR, 1.5; $P = .001$), increasing operative times (OR, 1.002; $P = .04$), and R1/R2 resections (OR, 1.07; $P = .03$).

The mortality related to pulmonary complications was 34% (N = 176). Pneumonia occurred in 229 patients (5.1%), in whom ARDS developed in 40. Overall, ARDS occurred in 189 patients (4.2%), after right pneumonectomy in 105 and left pneumonectomy in 84 (5.8% vs 3.1%; $P = .028$). Its related mortality was 59.8% (N = 113). Predictors of pulmonary complications at multivariate analysis (Table 3) were age greater than 65 years, male gender, ASA score 3 or greater, WHO performance status 2 or greater, presence of chronic obstructive pulmonary disorder (COPD), left-sided procedures, performance of an extended pneumonectomy, and increasing operative times. Number of comorbidities, underweight BMI category, and alcohol abuse approached statistical significance. Overweight BMI category was protective against the risk of pulmonary complication. After propensity score matching, predictors of pulmonary complications were age greater than 65 years (OR, 1.3; $P = .043$), male gender (OR, 1.7; $P = .005$), WHO performance status 2 or greater (OR, 2; $P = .002$), presence of COPD (OR, 1.8; $P < .001$), and increasing operative times (OR, 1.004; $P = .001$). The overweight BMI category remained as a protective factor (OR, 0.6; $P = .002$).

The mortality related to infectious complications was 26.4% (N = 32). Predictors of infectious complications were presence of a chronic lung infection (OR, 2.5; $P = .018$), increasing operative times (OR, 1.005; $P < .001$), and most recent years of operation (OR, 1.1; $P = .003$). Presence of COPD ($P = .077$), alcohol abuse or dependence ($P = .099$), MRC scores 2 or greater ($P = .08$), and underweight BMI category ($P = .059$) were close to being statistically significant. After propensity score matching, predictors of infectious complications were FEV1 in milliliters/kilograms/second (OR, 0.433; $P = .039$) and increasing operative times (OR, 1.006; $P < .001$).

DISCUSSION

This study is the most contemporary assessment of early outcomes after pneumonectomy for primary lung cancer based on a comprehensive, nationwide, population-based cohort. It shows that from 2003 to 2013, pneumonectomies represented 12.3% of all lung cancer operations performed in France and had a related mortality of 7.8%. This crude mortality rate is close to the 6.5% national mean in-hospital mortality reported for 2008 to 2010 by the United Kingdom's second National Thoracic Surgery Activity and Outcomes Report in which the incidence of pneumonectomy was 8.8% of all lung resections for primary lung cancer.[8] It is higher than the 5.6% rate observed for the period 2002 to 2007 in the Society of Thoracic Surgeons General Thoracic Surgery Database, in which pneumonectomy represented only 6.3% of all lung cancer resections.[9,10] Thus, it appears that in population-based registries, the higher the incidence of pneumonectomy, the higher the related mortality. These indicators reflect on diverse and evolving policies regarding the stringency of the selection of candidates for pneumonectomy along with a heightened awareness of the risks of this procedure.

Unsurprisingly, our multivariate analysis disclosed male gender, advanced age, highest ASA scores, right-sided pneumonectomies, extended procedures, comorbidities, surgery duration, and smoking status as predictors of several adverse events. These features are supported by a host of literature and do not deserve further comment.

The role of nutrition in predicting the outcome of operations for lung cancer is of growing interest. We identified the underweight BMI category as a potential risk factor of pulmonary and infectious complications, because it approached statistical significance in both cases. Finally, it was clearly identified as a risk predictor of mortality after propensity score matching. Conversely, overweight appeared to be a robust protective factor against the risks of pulmonary complications and operative mortality. A previous analysis of the EPITHOR database disclosed similar findings in patients with non–small cell lung cancer who underwent a lobectomy between 2005 and 2011.[11] The detrimental impact of malnutrition, as assessed with biological markers, has been recently emphasized for pneumonectomy.[12] Theoretic reasons for the development of pulmonary and infectious complications include the combination of immunodeficiency and impaired ventilatory mechanics due to respiratory muscle fatigue in undernourished patients.[13] The protective effect of overweight on early mortality is known as the "obesity paradox." A higher BMI has been shown to be associated with a better outcome in several chronic diseases, such as COPD, and a lower mortality for several surgical procedures. The obesity paradox mostly has been reported in the elderly. Its exact explanatory physiologic mechanisms have not been elucidated. Hypotheses for explaining the obesity paradox include protective peripheral body fat, reduced inflammatory response, and greater metabolic reserve to face the increasing post-aggressive catabolic burden.[14]

The most striking finding in the present study was the protective effect of induction therapy, chemotherapy in the majority of the cases, against operative mortality. Indeed, pneumonectomy has been regularly related to augmented operative risk in the situation of induction therapy.[15] In the Society of Thoracic Surgeons General Thoracic Surgery Database, induction chemoradiation was shown as an independent risk factor for major adverse events after pneumonectomy, whereas chemotherapy was associated with only a nonstatistically significant trend toward increased risk of major morbidity and mortality.[9] The most recently reported prospective randomized trials driven in the United States are in line with this trend. A 25.9% 30-day mortality rate was noted in patients with stage IIIA-N2 undergoing pneumonectomy after platinum-based induction chemotherapy plus radiotherapy in the INT 0139 trial.[16] The Southwest Oncology Group S9900 study pointed to early-stage non-N2 non–small cell lung cancer, and a 17% 30-day mortality rate after pneumonectomy was noticed in patients who received 3 cycles of paclitaxel and carboplatin versus 0% in the control group.[17] Conversely, the operative mortality of pneumonectomy was nil in the 42 patients who received the operation in the frame of the American College of Surgeons Oncology Group Z0030 trial, which intended to compare the outcomes of patients receiving first-line surgery and lymph node sampling versus lymph node dissection in early-stage disease.[18]

GTS

The evidence is different in European trials, in which the reported operative risk seems to be substantially lower. Two randomized studies[19,20] found 30-day mortality rates of 5% and 7%, respectively, after 3 cycles of platinum-based chemotherapy in both early-stage[19] and advanced-stage diseases.[20] The German Lung Cancer Cooperative Group reported that in patients receiving a pneumonectomy, treatment-related mortality increased in patients treated with preoperative chemoradiation (14%) compared with those who received 3 cycles of cisplatin and etoposide preoperatively (6%).[21] From these data, it seems that the operative risk is more likely to be related to the modalities of the neoadjuvant therapy than to the treatment strategy itself. Of note, chemoradiation as induction treatment is seldom used in France (8.2% of all induction regimens in the present cohort) compared with the United States (58.7% according to the last available date of the Society of Thoracic Surgeons General Thoracic Surgery Database).[9] In addition to these concerns about toxicity, published evidence does not support the inclusion of radiation therapy in induction approaches for stage IIIA-N2 non–small cell lung cancer in terms of long-term survival.[22]

The finding that induction therapy emerged as a protective factor regarding operative mortality, whereas none of the single major complications after pneumonectomy differed in incidence and severity, strongly suggests a bias. Because this protective effect remained in the propensity score–matched analysis, possibly implicated covariates are among those that were not observed. Because we previously demonstrated that in the context of the French health care system, hospital volume, public/private, and academic/nonacademic practice settings did not influence early outcomes,[23] we did not consider these variables in our analysis. Likewise, in keeping with the first National Cancer Plan launched in 2003 and its legal requirements for the practice of oncology, lung cancer surgery in France is provided only in accredited institutions by board-certified thoracic surgeons.[24] We speculate on the acute knowledge of the threatening association of induction therapy and pneumonectomy along with implementation of selection stringency together with surgical strategies to minimize postoperative complications, that is, conservative fluid management, protective one-lung ventilation with low tidal volume, bronchial stump coverage, or chest tube handling to avoid mediastinal shifting. This assertion is supported by several important findings of this study. First, the decrease by half of the proportion of patients who received pneumonectomy during the study period, combined with the concomitant stepwise decrease in the proportion of pneumonectomies preceded by induction therapy, suggests a continuous restraining selection process. Second, the significant decrease in the incidence of bronchial stump fistula with time indicates a probable adherence of French thoracic surgeons to their national guidelines recommending routine bronchial stump coverage in this situation. Accordingly, the team at Memorial Sloan-Kettering Cancer Center showed a sharp decline of contemporary postoperative mortality after postinduction pneumonectomy (4.3%) from its previous experience (11.3%), and in a particularly spectacular way after ride-sided procedures (3.3% vs 23.9%).[25,26] Some European teams have reported similar figures, with a 3% 90-month mortality after pneumonectomy in this setting.[27]

Study Limitations

There are important limitations to our study. EPITHOR was not intended to document treatment other than surgical items and therefore did not provide information about the regimens of chemotherapy or radiation, completeness of therapy, toxicities before surgery, or delay between completion of the treatment and surgery. All these points may uncover differences in the performance of induction therapy among contributing centers. EPITHOR did not provide intention-to-treat evaluation of patients treated with neoadjuvant therapy. Adverse events were not recorded uniformly. In addition, extensive preoperative pulmonary function data were not available, in particular routine diffusion capacity values (diffusing capacity for carbon monoxide), quantitative ventilation perfusion scanning, and maximal oxygen consumption when appropriate, which are important preoperative indicators of operative risk. Our study also focused on in-hospital and 30-day mortality, which is an inadequate proxy for determining the safety of lung cancer surgery. Ninety-day mortality, which has been suggested as a finer risk indicator,[28] could not be evaluated thoroughly in EPITHOR because of the lack of midterm follow-up information. Observational studies notoriously are full of no responses and missing values. Our propensity score matching attempted to estimate the effect of chemotherapy by accounting for the covariates that predicted receiving this treatment before the operation. It inherently carries the limitation that it has been constructed a posteriori and therefore accounted only for observed covariates. Hidden bias may increase because matching on observed variables may unleash bias due to dormant unobserved confounders.[29]

CONCLUSIONS

This study provides a precise look at the early outcomes of pneumonectomy in daily practice. It demonstrates that it is possible to minimize the risks of this procedure. Moreover, a paradoxical protective effect of induction therapy was demonstrated, for which selection and perioperative management biases are suspected. At least, this suggests that induction chemotherapy by itself does not increase the operative risk of pneumonectomy in the hands of forewarned thoracic surgeons. This information is all the more important because current convincing data indicate that neoadjuvant chemotherapy may have greater potential to decrease distant recurrence at 5 years than adjuvant chemotherapy.[30]

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Discussion

Dr Frank Detterbeck *(New Haven, Conn)*. This is a great article, and it helps to refocus our discussion a bit. The 0139 study has influenced us a lot, although I think Tony Kim showed that it was a statistical outlier. I think it's not about pneumonectomy, but about perioperative mortality, and you have shown us that perioperative mortality for pneumonectomy, even after neoadjuvant therapy, isn't necessarily so high that we need to always avoid it. One of the things, though, is that this is in the context of a very organized system. Can you tell us more about that? When was that started? Was that stable throughout the time period? Did that evolve throughout the time period? What is the average number of lung resections per institution in the database so we can compare that with our own system?

Dr Thomas. The first cancer plan was launched in 2003, as I showed in my pictures, and it has been effective since 2007. The main fact is that now it is completely forbidden for a general surgeon to deal with lung cancer surgery. This is one of the most striking results of this cancer plan. The second point is about the minimal level of activity. With these data, we are not able to show any impact of this measure since EPITHOR was launched by the French Society of Thoracic and Cardiovascular Surgeons. That means that those centers participating in EPITHOR were not affected by the establishment of this threshold. As a matter of fact, two thirds of the centers practicing thoracic surgery were closed, but it represented only 12% of all lung cancer surgery in France. In EPITHOR, only 6 centers had to be regrouped. They were not closed. They were regrouped to comply with this minimal threshold of activity. So we were unable to see any impact of this measure with the data collected in EPITHOR. Regarding the volume of activity, tomorrow, Pierre Falcoz will present a study we have performed showing that, provided these preliminary requisites, the volume of the institution by itself had no impact on the outcome in our health system organization.

Dr Detterbeck. What is the average number of resections in France so that I can compare it with the United States?

Dr Thomas. It's difficult to say. When I presented the data for lobectomy, it was approximately 30,000 lobectomies in a 10-year period, and now, approximately 5000 pneumonectomies in a 10-year period.

Dr Detterbeck. Okay. So your incidence of pneumonectomy decreased a lot, from approximately 20% to less than 10%. Why is that? Is that because there is less squamous cell now and more adenocarcinoma? Is it because there are more sleeve resections? Is it because there is more selection of patients and there are just less operations overall? Does that have anything to do with the operative mortality decreasing over time?

Dr Thomas. Well, it's impossible to answer with the data inside EPITHOR. Last year, we investigated the incidence of sleeve lobectomy to see if there was a change during the last 10 years. There was no change. The overall proportion was approximately 5%, and it didn't change during the last decade. I think it is predominantly a selection process, and this selection began with the oncologists who do not refer these patients to a surgeon anymore, especially when they have a right-sided tumor and if the operation would be pneumonectomy. Therefore, there is a diminishment of this operation. Our results clearly show that in expert centers at least, with certified thoracic surgeons, induction chemotherapy is not an issue.

Dr Detterbeck. In your propensity matching, I wonder if you shouldn't include the time period, early versus late cases. I don't think you did that. I wonder if you shouldn't, because things have changed a fair amount during the time period.

Dr Thomas. That is an excellent point, but we didn't.

Dr Mark Krasna *(Neptune, NJ)*. It was an excellent presentation, and I commend the Committee. This is the second excellent presentation today that shows the ability to perform pneumonectomy with a decreasing mortality over the last 10 years.

The last comment you made is worth reiterating. There is still a place for pneumonectomy in patients with non–small cell lung cancer who are well selected but who otherwise may have no other option, and it is crucial for us not to demonize the procedure because of the results of 0139 or any other single series. Again, I commend you and others and my former colleagues. There are now many series, and we had a pro/con debate here 2 years ago where we showed that in centers committed to performing this procedure, it can be done safely, with 0% to 10% mortality.

One specific question I would like to ask you about is the induction cases. It is, of course, counterintuitive but nice to think that induction therapy helped patients and caused a decrease in mortality. The only thing I can think of that would happen in my hands that might cause that is because I'm so careful in patients with induction therapy. I routinely use muscle flaps and other fluid-conserving therapy. You mentioned to us that you didn't have information on fluid management. Did the majority of these patients who did have induction therapy have a flap, whether it was a muscle flap or any other kind of flap, that helped protect the bronchus?

Dr Thomas. I cannot answer your specific question with the data inside EPITHOR, but I can answer as one of the contributing centers. I can also answer as the main author of the recommendations for the French national guidelines in the surgical practices. Yes, these patients definitely are not managed as usual. As you mentioned, fluid management is strict and rigorous in those patients, and all these patients now receive a flap to reinforce the bronchial sutures. Also, at least in my institution, we remove the chest tube early to avoid all these bad things that could occur with the mediastinal shift and so on. Definitely, I think there is a management bias.

Dr Sudish Murthy *(Cleveland, Ohio)*. The audience has to recognize that induction chemotherapy is a different breed of cat than induction chemoradiation therapy, and that is where most of our data are generated from. The other thing about propensity analysis is that it takes a fair bit of bias of thinking what is going to affect the outcome in this patient group to come up with the variables that you need to impute into these algorithms. The fewer the variables, the less strenuous your matching algorithms are. When you have these large databases, they are only matching on 5 variables?

Dr Thomas. Nine variables.

Dr Murthy. With only 9 variables, you will no doubt lose some granularity in terms of pseudo-randomization.

EDITORIAL COMMENTARY

A French connection

Sudish C. Murthy, MD, PhD

See related article on pages 73-83.

Perhaps it's time for the STS (Society of Thoracic Surgeons) and SEER (Surveillance, Epidemiology, and End Results) databases to move over: There's a new sheriff in town. This issue contains a large study of pneumonectomy patients from France, the substrate of which is the EPITHOR database (French Society of Thoracic and Cardiovascular Surgery database). Data on nearly 4500 patients were able to be accessed, and we are all witnesses to the fruits of mining this database. The French report a nationwide mortality of just below 8% for pneumonectomy and identify the risks of early mortality and a few curious protective factors. The sheer size of the study immediately makes it interesting, regardless of the actual findings.

Some bias seems to exist against large database studies generated outside the United States, especially when the findings reflect a better outcome for patients than we report from our own US national registries or databases. Lung cancer survival in Japan trumps that in the United States on a stage-for-stage basis. The same could be said for management of gastric cancer. Perhaps we in the United States find this insulting and worry that it somehow brings our own capabilities into question. Our usual response to these types of reports is to write editorials that point out some ambiguity in the database, or mistake in the statistical analysis, as a principal reason for the survival advantage. Unfortunately, we often ignore the expert care and management of these patients and fail to consider that the presentation of the disease and response to therapy might simply be different elsewhere in the world.

To evaluate this possibility, the French database EPITHOR has served as the basis for a study of pneumonectomy for lung cancer. This data repository, as well as those created elsewhere in Europe, is part of a greater quality initiative and represents an attempt to standardize care across the country. EPITHOR is more than a registry, and surprisingly, contains fairly detailed information on postoperative complications that is used in this study. Because of the relative granularity of the database, the authors were able to perform modern comparative analytic techniques, including propensity matching, to fortify their conclusions. Most of their findings are in keeping with common sense and are not grossly dissimilar from results reported in this country, which I'm sure will be a relief to our US readership. A nationwide mortality of slightly less than 8% (over the past decade) is commendable. Risks for poor early outcome include age, low body mass index (BMI, a suspected surrogate for malnutrition), and poor performance status.

Curiously, these French authors also identify induction therapy and "overweight" BMI as "protective factors" after pneumonectomy. I suspect this should not be taken literally by the reader as an injunction to fatten up one's patients and inject them with systemic poisons just before taking them out to the proverbial woodshed for an old-fashioned beating to optimize outcome. Rather, these variables are likely surrogates for a more robust and hardy stock, and as with all large databases, this is where the facts end, and the speculation, conjecture, and innuendo begin.

It is easy to lose one's clinical perspective during a large number-crunching exercise such as this. "Statistics this" and "*P* value that" are great up to a certain point, at which clinical gestalt must reign supreme. French "overweight" is probably the equivalent of American "healthy." Most in the

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