The Side of Pneumonectomy Influences Long-Term Survival in Stage I and II Non-Small Cell Lung Cancer

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Background. **The impact of pneumonectomy as an independent factor on long-term survival after lung resection for centrally or locally advanced non-small cell lung cancer (NSCLC) remains controversial. The aim of this paper is to study the impact of pneumonectomy, and the influence of side of surgery, on long-term survival in patients with pathologic stage I and II NSCLC.**

Methods. **A retrospective review of a prospective multiinstitutional database of patients operated on for lung cancer was undertaken. In all, 1,475 patients with pathologic stage I or II NSCLC were studied (421 underwent pneumonectomy; 1,054 had a lobectomy/bilobectomy). Survival and impact of side of surgery for pneumonectomy and lesser resection groups were analyzed and compared using the Kaplan-Meier method and the Cox proportional hazards model.**

Results. **Median survival was worse after pneumonectomy than after less extensive resections for patients overall (33 versus 57 months) and for those with stage I NSCLC (38 versus 70 months); however, median survival was better after pneumonectomy for stage II left tumors (55 versus 19 months). Pneumonectomy was an independent adverse determinant of survival for both stage I right tumors ($p < 0.001$) and stage I left tumors ($p < 0.001$), but was associated with improved survival for stage II left tumors ($p = 0.009$).**

Conclusions. **Pneumonectomy was found to be an independent determinant of survival in patients with stage I and II NSCLC, but results differed for right- and left-sided tumors. Further studies of survival comparing pneumonectomy with lesser resections should differentiate between right and left procedures.**

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For decades, pneumonectomy was considered the only appropriate surgical therapy for localized non-small cell lung cancer (NSCLC). Although in most cases anatomic lobectomy is currently the surgical treatment of choice, controversy continues over appropriate management for centrally and locally advanced tumors. Pneumonectomy could achieve better tumoral tissue clearance for these kinds of tumors, but it is associated with significant morbidity and mortality [1, 2]. In addition, the long-term consequences of pneumonectomy on cardiorespiratory function and quality of life are well documented [3, 4]. Nevertheless, the impact of pneumonectomy as an independent factor on long-term survival after lung resection remains controversial [2, 5–7].

On the other hand, it is well known that right lung contribution to overall lung function is normally higher than that of the left lung. Moreover, several studies have found that patients who underwent a right-sided pneumonectomy, rather than a left-sided pneumonectomy, have been shown to have higher morbidity and mortality [8–10]. While it is reasonable to anticipate differences in long-term survival after right and left pneumonectomy, little has been reported in the medical literature [11].

The purpose of this study was to reassess the impact of pneumonectomy on long-term survival in patients with pathologic stage I and II NSCLC, and to study the side of pneumonectomy as a possible confounding variable when trying to identify independent prognostic factors for survival across resected stage I and II NSCLC.

Material and Methods

This is a retrospective review of a prospective database of patients who underwent surgery for lung cancer in hospitals pertaining to the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S) [12]. The study was approved by the

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*See Appendix for the full list of members of the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery.

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Table 1. Significant Differences Between Variables in the Pneumonectomy and Lesser Resection Group

	Pneumonectomy	Lesser Resections	*p* Value
All patients (n = 1,475)	n = 421	n = 1054	
Age (years)	63.8 (SD 9.1)	65.3 (SD 8,8)	0.004
Current smoker	61.8%	53.3%	0.003
Female	3.3%	8.2%	0.001
pTNM stage I	59.1%	80.8%	<0.001
Squamous cell carcinoma	78.6%	55.4%	<0.001
Tumor size (cm)	5.1 (SD 2.5)	4.3 (SD 2.3)	<0.001
Preoperative plasma hemoglobin (g/dL)	13.6 (SD 1.8)	14 (SD 1.6)	<0.001

Continuous data are presented as mean (SD) and categorical variables as percentages.

GCCB-S Coordinating Center Ethical Committee, and individual patient consent was not required.

General Methodology

From October 1993 to September 1997, every patient with bronchogenic carcinoma who underwent a thoracotomy in a GCCB-S hospital was registered prospectively [12]. The annual cumulative number of cases was close to 50% of the patients operated on for lung cancer in Spain during the same time period. The GCCB-S centers were representative of hospitals throughout Spain providing a wide variety of services and activities [13]. The final registry included 2,994 patients.

All GCCB-S hospitals used similar criteria to assess the functional operability of patients and the oncological operability of the tumors [14]. Patients were staged according to the 1997 TNM staging classification system [15]. Pathologic N0 was classified by mediastinal nodal dissection or sampling of at least four lymph node areas (2 [only in right lung tumors]; 4, 7, and 10 on the same side as the tumor), especially in pT3 [16]. Operative mortality included death within or outside the hospital within 30 days of operation, or death at anytime after operation if the patient did not leave the hospital. All long-term survivors were followed up for more than 5 years. Internal and external audits were conducted [17].

Specific Methodology

After pulmonary resection with curative intent, 1,642 patients were pathologically diagnosed as stage I or II NSCLC. A total of 421 patients (25.6%) underwent pneumonectomy, 1,054 (64.2%) had either a lobectomy or bilobectomy, and 167 (10.2%) had a less extensive resection. Patients with resections less extensive than lobectomy were excluded from the study. Consequently, the study included a total of 1,475 patients (1,375 men), with a median age of 66 years (range, 36 to 87). A total of 1,101 cases was classified stage I (IA 221, IB 880) and 374, stage II (IIA 31, IIB 343). Histologic types included 922 (62.5%) squamous cell carcinomas, 357 (24.2%) adenocarcinomas, 90 (6.1%) large cell carcinomas, 58 (3.9%) unspecified non-small cell carcinomas, and 48 (3.3%) bronchoalveolar carcinomas. According to the standard of care during the time period of the study, no patient received induction treatment, and 216 patients (14,6%) received some kind of adjuvant therapy.

Definitions and Statistics

Eleven variables were tested with univariate and multivariate analysis with the endpoint being survival: age, sex, pathologic TNM stage (pTNM), squamous cell carcinoma, comorbidity, smoking, preoperative plasma hemoglobin, preoperative forced expiratory volume in one second (FEV_1), side of surgery, tumor size, and type of resection (pneumonectomy versus lesser resection). Variables were selected for analysis based on an extensive literature review, clinical experience, and availability and completeness of data in the registry (missing data for each variable <5%).

The presence of comorbidity was considered when chronic obstructive pulmonary disease, arterial hypertension, previous tumor, cardiac disease, peripheral vascular disease, or diabetes appeared alone or as an associated disease. Chronic obstructive pulmonary disease was defined when a compatible clinical picture existed, when there was a chronic obstruction to the air flow, and when other conditions with similar symptoms were ruled out. Obstruction to the air flow was confirmed when the postbronchodilator FEV_1/FVC was less than 0.7 [18]. Any type of neoplasia occurring in any previous period of time was registered as a previous tumor, excluding nonmelanoma skin tumors. The presence of cardiac disease was considered when there was valve disease, heart failure, ischemic heart disease, or a combination of these.

Table 2. Risk Factors: Univariate Analysis[a] for Long-Term Survival in Stage I and Stage II Nonsmall-Cell Lung Cancer

Variable	Hazard Ratio	(95% CI)	*p* Value
Tumor size (cm)	1.10	1.07–1.13	<0.001
Age (years)	1.02	1.01–1.03	<0.001
Preoperative plasma hemoglobin (g/dL)	0.90	0.86–0.93	<0.001
FEV_1 (L)	0.79	0.70–0.89	<0.001
Pathologic stage II (versus stage I)	1.67	1.45–1.93	<0.001
Pneumonectomy (versus lesser resection)	1.41	1.22–1.62	<0.001
Comorbidity (versus no comorbidity)	1.40	1.22–1.61	<0.001
Right side (versus left side)	1.10	0.96–1.26	0.160
Female (versus male)	0.82	0.62–1.09	0.168
Squamous cell carcinoma versus others)	0.98	0.85–1.13	0.757
Current smoker (versus no smoker)	0.98	0.86–1.12	0.778

[a] Univariate analysis was performed using the Cox proportional hazard model.

CI = confidence interval.