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Preoperative Pulmonary Function Tests (PFTs) and Outcomes from Resected Early Stage Non-small Cell Lung Cancer (NSCLC)

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Abstract. *Background: Preoperative pulmonary function tests (PFTs) predict operative morbidity and mortality after resection in lung cancer. However, the impact of preoperative PFTs on overall outcomes in surgically-resected stage I and II non-small cell lung cancer (NSCLC) has not been well studied. Patients and Methods: This is a retrospective study of 149 patients who underwent surgical resection as first-line treatment for stage I and II NSCLC at a single center between 2003 and 2014. PFTs [forced expiratory volume in 1 sec (FEV1), Diffusing Capacity (DLCO)], both absolute values and percent predicted values were categorized into quartiles. The Kaplan–Meier method and Cox regression analysis were used to determine whether PFTs predicted for overall survival (OS). Logistic regression was used to estimate the risk of postoperative complications and length of stay (LOS) greater than 10 days based on the results of PFTs. Results: The median age of the cohort was 68 years. The cohort was predominantly males (98.6%), current or ex-smokers (98%), with stage I NSCLC (82.76%). The majority of patients underwent a lobectomy (n=121, 81.21%). The predominant tumor histology was adenocarcinoma (n=70, 47%) followed by squamous cell carcinoma (n=61, 41%). The median follow-up of surviving patients was 53.2 months. DLCO was found to be a significant predictor of OS (HR=0.93, 95% CI=0.87-0.99; p=0.03) on univariate analysis. Although PFTs did not predict for postoperative complications, worse PFTs were significant predictors of length of stay >10 days. Conclusion: Preoperative PFTs did not predict for survival from resected early-stage NSCLC, but did predict for prolonged hospital stay following surgery.*

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Lung cancer is a leading cause of mortality in United States (1). About 20% of lung cancers are diagnosed in a localized stage and approximately 85% of diagnosed lung cancers are non-small cell lung cancer (NSCLC) (2). Overall survival (OS) in lung cancer depends heavily on the stage at diagnosis, demonstrating a 5-year survival of 54% for cases diagnosed at a localized stage, while 4% for those at a distant stage (3).

Currently, the preferred treatment for stages I and II NSCLC is surgical resection (4). Lobectomy or greater resection with mediastinal lymphadenectomy usually remains the preferred approach. For stage II NSCLC, surgical resection and the use of adjuvant chemotherapy have also been shown beneficial (5).

In stage I and II NSCLC, several factors have been identified to play a role in immediate and long-term outcomes following surgery. Brunelli *et al*. found that prior history of cardiac disease; stroke or kidney disease had a significant impact on outcomes after pneumonectomy (6). Functional status has also been shown to affect the outcomes (7). Berry *et al*. showed that forced expiratory volume in 1 sec (FEV1) was an independent predictor of respiratory complications postoperatively (8), but FEV1 is often less reliable in patients with airflow obstruction (9). Diffusion capacity (DLCO) is considered an independent predictor of postoperative morbidity as well, which is even more reliable

Table I. *Patient demographics*.

	N (%)
Gender	
Male	147 (98.66)
Female	2(1.34)
Smoking	
Never smoker	3(2.01)
Ex-smoker	91 (61.07)
Current smoker	55 (36.91)
Comorbidities	
Respiratory	83 (55.70)
Cardiac	69 (46.31)
Stroke	19 (12.75)
CKD	9 (6.04)
DM	34 (22.82)
Other	77 (51.68)
Type of surgery	
Pneumonectomy	6 (4.03)
Lobectomy	121 (81.21)
Lobectomy and anatomic segmentectomy	1 (0.67)
Anatomic segmentectomy	1 (0.67)
Wedge resection	20 (13.42)
Pathological stage	
I	120 (80.53)
II	25 (16.78)
III	4 (2.68)
Histology	
Adenocarcinoma	
70 (46.98)	
Squamous cell carcinoma	61 (40.94)
NSCLC NOS	13 (8.72)
Large cell carcinoma	4 (2.68)
Adenosquamous carcinoma	1 (0.67)
Postoperative complications	
Total	94 (63.09)
Respiratory	48(32.21)
Cardiac	27(18.12)
Surgical mortality	7 (4.70)
Infection	22 (14.77)

CKD, Chronic kidney disease; DM, NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

Table II. *Patient characteristics*.

Variable	N	Median	Range
Age (years)	149	68	38-88
Tumor size (cm)	143	2.3	0.2-12
FEV1 (l)	149	2.16	0.25-3.77
FEV % of predicted	149	68.3	7.4-123
DLCO (ml/min/mmHg)	138	16.1	6.6-29.2
DLCO % of predicted	142	71.7	16.4-158.5

FEV1, Forced expiratory volume in 1 sec; DLCO, diffusing capacity.

than FEV1 (10). Cerfolio *et al*. in their study found that age, history of smoking, FEV1, predicted postoperative FEV1, DLCO and predicted postoperative DLCO can have an impact on postoperative morbidity (11).

For patients with stage I and II NSCLC, surgery is offered based on preoperative physiologic assessments like predicted postoperative (PPO) FEV1 and DLCO, because they are known to independently predict outcomes (9). PPO lung functions are considered the best predictors of postoperative morbidity and mortality in such patients, rather than percentage predicted FEV1 or DLCO mostly based on retrospective studies (12, 13).

In this retrospective study, we focused on the effect of preoperative FEV1 and DLCO on immediate, as well as long-term post-surgical outcomes in patients with stage I and II NSCLC undergoing surgical resection.

Patients and Methods

Patients. After appropriate institutional approvals, medical records of patients with stage I and II NSCLC, who underwent surgical resection from 2001 through 2014 at a single institution, were reviewed for this analysis. Their charts were retrospectively reviewed for type and stage of cancer, demographic variables (age, race, and gender), smoking status, preoperative PFTs, type of surgical resection, postoperative complications and OS. FEV1 and DLCO values, both absolute and percent predicted values, were abstracted from the medical record. The stage of NSCLC was per the appropriate TNM classification at the time of diagnosis (American Joint Committee on Cancer 6th and 7th editions).

Patients over the age of 89 (consistent with institutional regulations), patients with SCLC, those with metachronous malignancy, a primary tumor outside of the lung, and those with benign histology on the pathologic report were excluded. Patients who received any chemotherapy or radiation prior to their surgery were also excluded. The study was approved by the Veterans Affairs Nebraska-Western Iowa Health Care System Institutional Review Board (IRB). The IRB also approved a waiver of informed consent.

Statistical analysis. OS was defined as time from surgery to death or last contact. Patients alive at the date of last contact were censored. Kaplan–Meier method was used to determine whether lung function variables (categorized into quartiles or at the median) were predictors of OS. Multivariate and univariate Cox regression analyses were used to determine whether lung function variables (continuous) predicted for OS. Multivariate logistic regression models were used to determine if lung function variables predict length of stay (LOS) greater than 10 days while adjusting for age and other variables that were significantly associated with LOS in univariate analysis including stage and postoperative complications. All *p*-values less than 0.05 were considered statistically significant. SAS Software, version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

One hundred and sixty patients were identified from the registry. Out of these patients, 7 did not have data on PFTs, 3 had stage III disease, and 1 received neoadjuvant therapy

Table III. *Overall survival predicting factors: Multivariate Cox regression model.*

Parameter		HR; 95% CI	*p*-Value
Age	One-year increase	1.01; 0.98-1.04	0.56
Gender	Female *vs*. male	1.5; 0.18-12.34	0.71
Surgery type	Pneumonectomy *vs*. lobectomy	1.87; 0.57-6.13	0.52
	Other *vs*. lobectomy	0.84; 0.35-1.97	
Pathological stage	2 *vs*. 1	1.33; 0.66-2.7	0.43
Creatinine >ULN	Yes *vs*. no	2.03; 0.82-5.05	0.13
DLCO*	One-unit increase	0.95; 0.88-1.02	0.12

HR, Hazard ratio; CI, confidence interval; ULN, upper limit of normal; DLCO, diffusing capacity. *Continuous variable.

Table IV. *Preoperative forced expiratory volume in 1 sec (FEV1) and diffusing capacity (DLCO) on the length of stay (LOS).*

Multivariate model for LOS >10 days^	Odds ratio	95% CI	*p*-Value
FEV1*	0.34	(0.16-0.76)	0.0087
FEV1* (percentage predicted)	0.96	(0.94-0.99)	0.0033
DLCO*	0.78	(0.68-0.90)	0.0004
DLCO* (percentage predicted)	0.96	(0.94-0.99)	0.0060

CI, Confidence interval. ^Multivariate models adjusted for age, pathological stage, respiratory complication, cardiac complication, and infection complication. *Continuous variables.

and hence, they were excluded. The final analysis included 149 patients (Table I). The median age of this cohort was 68 years (range=38-88 years). The cohort was predominantly males (n=147, 98.6%), current or ex-smokers (98%), with stage I NSCLC (82.76%). The predominant tumor histology was adenocarcinoma (n=70, 47%) followed by squamous cell carcinoma (n=61, 41%). The most common surgical procedure was a lobectomy (n=121, 81.21%).

The median length of stay was 7 days (range=0-62). Approximately 63% (n=94) of the patients had complications, including 7 deaths (n=4.7%). Respiratory complications were the most common (32%. n=48), followed by cardiac (18%, n=27) and infection complications (15%, n=22). At the last follow-up, 42% (n=63) of patients died and 58% (n=86) were alive. The median follow-up of the patients alive at the last follow-up was 53.2 months (range=2.7-136.7) (Table II).

On univariate Cox regression analysis, DLCO was found to be a significant predictor of OS (HR=0.93; 95% CI=0.87-0.99; p=0.027). However, it was no longer a significant predictor of survival on multivariate analysis (HR=0.95; 95% CI=0.88-1.02; p=0.12). The effects of various patient, disease, and treatment factors on OS are shown in Table III.

When the effect of various parameters on the LOS was evaluated, a higher pathologic stage, the development of postoperative complications, and worse PFT results were independently associated with a longer length of stay. After adjusting for age and other variables that were significantly associated with LOS, patients with lower DLCO [odds ratio (OR)=0.78, 95% CI=0.68-0.90; p=0.0004], and FEV1 (OR=0.34, 95% CI=0.16-0.76; p=0.0087) were found more likely to have a length of hospital stay of more than 10 days (Table IV). However, neither FEV1 (p=0.46) nor DLCO (p=0.42) could reliably predict postoperative complications.

Discussion

In our study, preoperative FEV1 and DLCO were significantly correlated with increased length of hospital stay but not with postoperative complications or OS. Our results are mostly consistent with prior studies and support current guidelines. Berry MF *et al*. (8) have previously studied the impact of preoperative PFTs on pulmonary morbidity in a cohort of 340 patients who underwent lobectomy for primary lung cancer. They demonstrated that DLCO, FEV1, and thoracotomy, as surgical approach, are significant predictors of pulmonary complications. However, Ferguson *et al*. (13), in a larger study on of 376 patients, have shown postoperative lung function to be a better predictor of both postoperative morbidity and mortality. Nevertheless, in that study, preoperative DLCO (but not FEV1) did have a statistically significant association with postoperative morbidity as well as mortality.

In another recent large single-center retrospective study, Berry MF *et al*. (14) explored the relationship between PFTs

and long-term survival after lobectomy in 972 patients with stage I NSCLC. Long-term OS was positively correlated with better PFTs, but interestingly, decreased values of FEV1 and DLCO were differentially associated with survival, thus revealing the unreliability of percent predicted values in the prediction of long-term outcomes. In contrast, in a Japanese study of 222 patients with cT1aN0M0 peripheral lung squamous cell carcinoma, a decreased vital capacity (<80%), but not a decreased FEV1, was associated with decreased OS following resection (15). In a similar study conducted in China, the presence of moderate to severe chronic obstructive pulmonary disease, as determined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria predicted for worse outcomes for lung cancer after adjusting for confounding factors (16). The disparities between the aforementioned studies and our present study might have been due to the smaller sample size in our study, the analysis of different modalities of surgery rather than just different approaches of lobectomy, the exclusion of patients who received preoperative chemotherapy or radiotherapy, and the stage of NSCLC that was studied which might skew the mortality data.

A significant association was demonstrated between PFTs and the LOS. The most common explanation for this is the development of postoperative complications that play a major role in prolonging LOS. In a prior study by Wang *et al*. (17), postoperative pulmonary complications increased the LOS by at least 2 days and nearly doubled the cost of hospitalization. In another analysis, Zhang *et al*. (18) demonstrated that the incidence of pulmonary complications was related to predicted postoperative lung function, regardless of the type of the procedure performed (open *vs*. thoracoscopic). On multivariate analysis, they found that predicted post-operative FEV1% and DLCO% were predictive of pulmonary complications. Surprisingly, in the present study, no significant association was found between the development of postoperative complications and PFTs. However, the predicted postoperative lung function was not assessed. We suggest that the association between LOS and PFTs may be an independent association that could be partly explained by the poor functional status in patients with worse PFTs, thus leading to a longer rehabilitation time.

The limitations of our study include its retrospective nature, which inherently brings in the possibility of selection bias in that our study population was predominantly patients who were deemed good surgical candidates. In addition, the cohort was predominantly male, as expected from a VA population, thereby raising the question of generalizability of the results to the entire patient population. The longer duration of follow-up in any study makes it vulnerable to possible changes in staging systems as well as treatment approaches to the disease studied, although the latter is beyond the scope of our study. Our emphasis was on the function and volume of lungs, hence, the type of surgery included was based on lung volume resected, rather than the type of surgery performed [video assisted thoracoscopy (VATS) versus open thoracotomy]. The type of surgery may have contributed to our increased LOS. The VATS versus open thoracotomy data in our review were also complicated by a number of VATS procedures being converted to an open thoracotomy, due to intra-procedural concerns. Another limitation of the study was that 6-minute walk test data were not correlated with PFTs, due to incomplete data. However, despite these drawbacks, a relatively homogeneous population treated uniformly at a single institution was analysed, hence, we believe our our data are valid.

In summary, no association was found between preoperative lung function and mortality from lung cancer. Increasing the focus towards optimization of preoperative pulmonary function tests in patients undergoing surgery for stage I and II NSCLC might minimize their LOS and potentially decrease the cost of cancer treatment and prevent complications as well.

Conflict of Interest

None of the Authors has any conflict of interest with the subject matters presented in the manuscript.

Ethical Approval

The local Institutional Review Board approved the study. All procedures performed were in accordance with the ethical standards of the institutional research committee.

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