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Poor Survival for Veterans with Pathologic Stage I Non-Small Cell Lung Cancer

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Abstract

Background—Pathologic stage (pStage) IA and IB non-small cell lung cancer (NSCLC) has a median survival time of 119 and 81 months, respectively. We describe the outcomes of veterans with pStage I NSCLC.

Methods—A retrospective review of 78 patients with pStage I NSCLC who underwent cancer resection was performed at the Tennessee Valley Veterans Affairs Hospital between 2005 and 2010. All-cause 30-day, 90-day, and overall mortality were determined. Survival was assessed with Kaplan-Meier and Cox proportional hazards methods.

Results—There were 55 (71%) pStage IA and 23 (29%) IB patients. Thirty- and 90-day mortality was 3.8% (3/78) and 6.4% (5/78), respectively. Median survival was 59 and 28 months for pStage IA & IB, respectively. Postoperative events were associated with impaired survival on multivariable analysis (HR = 1.26, $p = 0.03$).

Conclusion—Veterans with pStage I NSCLC at our institution have poorer survival than the general population. More research is needed to determine the etiology of this disparity.

Keywords

veteran; lung cancer; NSCLC; survival

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Introduction

Lung cancer is the leading cause of cancer death in the US, with an overall 5-year survival of approximately 16%.¹ Among US military veterans, the 5-year survival is only 12%.² Early detection and surgical resection provide a curative option for patients with non-small cell lung cancer (NSCLC). However, once having undergone resection for early stage disease, there is very little data on long term post-operative mortality. The International Association for the Study of Lung Cancer Staging Project demonstrated a median survival rate after surgical resection of 119 and 81 months for pathologic stage (pStage) IA and IB, respectively, in a study of over 6,700 patients with pStage I NSCLC.^{3,4} A single study in 1988 investigated the outcomes of 384 veterans who underwent lung resection for Stage I NSCLC, but it utilized older staging systems, did not include comorbidities or complications in the analyses, and median survival was not reported.⁵ To our knowledge, no studies within the past two decades have examined short and long term survival for veterans with pStage IA or IB disease after surgical intervention.

US veterans have a 76% higher incidence of lung cancer than the general population.^{2,6} Veterans treated at Veterans Affairs (VA) hospitals have a higher incidence of comorbidities, a greater frequency of multiple comorbid conditions, and an overall poorer level of health than non-veteran populations.^{7,8} Together these factors suggest the importance of examining lung cancer survival among veterans.

The purpose of this study is to describe the clinical characteristics, morbidity, all-cause mortality, survival, and to determine the impact of comorbidities and postoperative events on survival for veterans with pStage I NSCLC who underwent surgical resection within the Veterans Affairs Tennessee Valley Healthcare System (VA-TVHS) between 2005 and 2010.

Methods

This retrospective study was approved by the VA-TVHS Institutional Review Board. All patients who underwent a lung resection operation at the VA-TVHS between the years of 2005 and 2010 were identified. The medical records of these patients were reviewed to identify all patients who underwent resection for known or suspected lung cancer (n = 159), not including those with multiple primary lung cancers or a prior history of lung cancer. Patients were excluded if the final pathology was benign (n = 14), small cell lung cancer (n = 1), or a non-lung primary neoplasm (i.e. metastasis; n = 1). Of these 143 patients with primary NSCLC, 78 had pStage I disease and were included in the analysis.

Information on preoperative clinical staging, surgical procedure, operative approach, % predicted forced expiratory volume in 1 second (FEV₁), race, gender, body mass index (BMI), smoking status, comorbidities, and pathological data including histology, size, and stage were collected. Outcomes data on postoperative events, length of stay (LOS), all-cause mortality, and survival were also collected. Vital status was determined either by reports of death within the medical record, or from the Social Security Death Index if the medical record did not contain this information. All-cause mortality was chosen as the outcome measure due to inability to identify the cause of death for all patients. A smoking status of “current” was defined as actively smoking or quit 2 weeks or less pre-operatively, and “former” was defined as having quit greater than 2 weeks pre-operatively and having smoked over 100 cigarettes total in his lifetime. Chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes, peripheral vascular disease, cerebrovascular accident, congestive heart failure, and end stage renal disease (ESRD) on dialysis were included as comorbidities. Postoperative events (defined as occurring prior to hospital discharge) included urinary tract infection, pneumonia, reintubation, prolonged mechanical

ventilation (>48 hours), cardiac arrest, myocardial infarction, atrial fibrillation, bleeding requiring transfusion, sepsis, and prolonged chest tube duration (defined as being discharged with a chest tube in place). The need for re-operation within 30 days of lung resection was also included as an event. All postoperative events were captured using standard VA National Surgical Quality Improvement Program methodology.⁹ Pathologic stage was determined using the American Joint Committee on Cancer Staging Manual, 7th edition.¹⁰

Univariate comparisons between pStage IA and IB groups utilized Fisher's exact test for categorical variables, and the student's t-test for continuous variables. We determined the overall, 30-day, and 90-day mortality. Operative mortality was defined as any in-hospital death, or any death within thirty days of surgery. There were no patients in this study who died during their initial hospital stay, so thirty-day mortality is reported. Ninety-day mortality was defined as death between postoperative day 31 and 90, and does not include patients who died within the first 30 days after surgery. Overall mortality was compared between pStage IA and pStage IB groups using Fisher's exact test. Kaplan-Meier survival curves were estimated for pStage IA and IB, and compared using both the log rank test. Kaplan-Meier survival curves were also estimated for patients with and without postoperative events, and compared using the log rank test. Survival curves comparing postoperative event groups were estimated both from the day of surgery, and from 90 days postoperatively.

To determine the factors associated with death, two multivariable Cox Proportional Hazards models were created to generate adjusted hazard ratios for death based on the methodology described by Harrell.¹¹ There were 37 deaths, and so only four variables were included in each model (one variable for each degree of freedom, and one degree of freedom for every 10 events). Pathologic stage, age, number of comorbidities, and number of postoperative events were chosen as the variables. We used a simple tally of the number of comorbidities per patient in our model due to limitations imposed by our small sample size—a method previously described.^{12–14} Both models met the proportional hazards assumption. The first model used the day of surgery as time zero, and the second model used 90 days postoperatively as time zero. This was done to gauge the effect of postoperative events on survival. All analyses were done using Stata® Statistical Software: Release 11 (StataCorp. 2009. College Station, TX), and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 78 patients were included in the analysis. All patients were male, with a mean age of 64.5 years and a mean preoperative FEV₁ of 70.5% predicted. Twenty eight patients (39%) were current smokers, 41 (57%) former smokers, and 3 (4%) never smoked. There were 6 patients with missing data on smoking status. Mean tumor size was 2.3cm (range 8mm to 4.7cm). There were 55 (70.5%) pStage IA and 23 (29.5%) pStage IB patients. See Table 1 for full details of population characteristics.

Preoperatively, all patients had a computed tomography (CT) scan of the chest, approximately two thirds (64%) had a positron emission tomography (PET) scan, and a small minority (5%) had a magnetic resonance imaging (MRI) of the head. There were no endobronchial ultrasounds performed at our institution during this study period. Most patients (96%) had a complete (R0) resection. The median total # of lymph nodes resected was 9 (range 0 – 44) with 68 patients (93.2%) having > 3 stations sampled. The detailed information regarding clinical and operative staging is provided in Table 2.

There were 70 (89.7%) patients with at least one comorbidity, and the mean number of comorbidities per patient was 2 (standard deviation (SD) = 1.4). There were 58 (74%) patients with hypertension, 32 (41%) with COPD, 24 (31%) with coronary artery disease, 15 (19%) with diabetes, 12 (15%) with peripheral vascular disease, 11 (14%) with a history of stroke, 4 (5%) with congestive heart failure, and 2 (3%) with ESRD on dialysis. There were 25 (32%) patients with at least one postoperative event, and the mean number of events per patient was 0.7 (SD = 1.4). The distribution of postoperative events is shown in Table 3. There was no difference in the frequency or mean number of comorbidities per patient or postoperative events per patient between those with pStage IA and IB disease ($p>0.05$).

The all-cause 30-day, 90-day, and overall mortality were 3.8% (3/78), 6.4% (5/78), and 47.4% (37/78), respectively. All-cause mortality was 42% (23/55) for pStage IA, and 61% (14/23) for pStage IB ($p=0.143$). The median survival time was 54 months for all patients, and was 59 and 28 months for pStage 1A & 1B, respectively (Figure 1). Among survivors, the mean follow up time was 45 months (SD = 18). Cox regression analysis showed that the mean number of postoperative events per patient was the only factor significantly associated with survival. This association was no longer statistically significant when the first 90 days after surgery were not included in the survival analysis (Table 4). The Kaplan Meier survival curves for patients with and without postoperative events are shown in Figure 2.

Discussion

We have presented our institution's experience with patients undergoing lung resection for pStage I NSCLC. This study reveals a 30-day mortality of 3.8%. The nationally reported operative mortality for non-veteran patients ranges from 1.4 to 3.0%.^{15–17} Ninety-day mortality was 6.4%, compared to 2.5% reported in a single institution study.¹⁶ The median survival time for our patients with pStage IA (59 months) and IB (28 months) is substantially lower than that reported by the International Association for the Study of Lung Cancer (119 and 81 months, respectively).^{3,4}

We identified the number of postoperative events as the only factor in multivariate analysis that impaired survival. However, when analyzing survival beyond an “extended postoperative period” (i.e. 90 days), postoperative events were no longer associated with survival. This supports the recommendation of Bryant and colleagues that 90-day mortality, as opposed to just 30-day, should be collected by both surgical and nonsurgical databases and included in investigations attempting to address the efficacy of specific treatment modalities.¹⁶

The detailed collection of comorbidity and postoperative event data adds an important component to understanding the contributors to mortality and survival. All patients had a complete (R0) resection (except 3 patients with missing data) which is comparable to previously published data.¹⁸ In addition, patients were aggressively staged pre- and intra-operatively with lymph node dissections performed.¹⁹ This study is limited by its retrospective study design, as well as the limited follow up time of patients treated in more recent years, which may result in an underestimated median survival for the study sample as a whole. These are a single institution's results with a relatively small sample size, which limits generalizability. The small sample size and low number of death “events” also limited the number of variables we could include in the multivariate cox proportional hazards model. Other factors likely to impact postoperative morbidity and mortality, such as pulmonary function (e.g. diffusing capacity (DLCO)²⁰ or FEV₁¹⁵), functional status (such as the American Society of Anesthesiologists or Zubrod scores), operative procedure, and active smoking status were not included. To address this limitation, the number of comorbidities was included as a continuous variable.^{12–14} Finally, we were unable to

identify a cause of death in 11 (30%) of the 37 total deaths, so all-cause mortality was used as the outcome measure. This decreases the ability to distinguish between outcomes related to poor overall condition versus cancer recurrence.

In this single institution study the survival of veterans with pStage I NSCLC is poorer than that of the general population. This finding may be related to the overall poor level of health of veterans receiving care at VA hospitals. More research with multi-institutional data (that includes 90-day mortality), and larger sample sizes is needed to understand the cause of this survival disparity and confirm our associations.

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Summary

Lung cancer is the leading cause of cancer death in the US, and US veterans have a substantially higher incidence of lung cancer than non-veterans. We describe the clinical characteristics, mortality, and survival data for veterans with pStage I NSCLC who underwent surgical resection at our institution between 2005 and 2010, and compare our population's survival to national norms. The long term survival of veterans with pathologic Stage I NSCLC is poorer than that of the general population, and more research is needed to determine the etiology of this health disparity.

Figure 1.

Kaplan-Meier survival curves comparing pStage IA and IB using the log rank test. This survival analysis begins at the day of surgery. Median survival for pStage IA and IB is 59 and 28 months, respectively. This is in contrast to the median survival of 119 and 81 months seen in the IASLC study.^{3,4}

Figure 2.

Kaplan-Meier survival curves comparing patients with (solid line) and without (dashed line) postoperative events. The log rank test was used to compare survival functions. A) Survival curves starting from the day of surgery. Patients with one or more postoperative event have statistically significantly lower survival than those with no events. B) This survival analysis begins at post-operative day 90. There is no longer a significant difference between groups ($p > 0.05$).

Table 1**Patient Characteristics**

Pre-operative and operative characteristics of study patients.

Variable	All Patients
Total	78
Race/ethnicity, No (%)	
White	67 (90.5)
Black	6 (8.1)
Asian	1 (1.4)
Missing	4
Age in years, mean (SD)	64.5 (9)
BMI (kg/m ²), mean (SD)	25.6 (4.7)
Comorbidities per patient, mean (SD)	2 (1.4)
% Predicted FEV1, mean (SD)	70.5 (16.3)
Smoking status, No (%)	
Never	3 (4.2)
Former	41 (56.9)
Current	28 (38.9)
Surgical Procedure, No (%)	
Wedge resection	8 (10.3)
Lobectomy	69 (88.5)
Pneumonectomy	1 (1.3)
Operative Approach, No (%)	
Thoracotomy	58 (74.4)
Thorascopic	5 (6.4)
Converted	15 (19.2)
Tumor size, cm; mean (SD)	2.3 (0.9)
Histology, No (%)	
Adenocarcinoma	36 (46.1)
Squamous cell carcinoma	25 (32)
NSCLC NOS	7 (9)
Neuroendocrine	5 (6.5)
Bronchoalveolar carcinoma	3 (3.8)
Adenosquamous	1 (1.3)
Spindle cell carcinoma	1 (1.3)
Pathologic Stage, No (%)	
IA	55 (70.5)
IB	23 (29.5)
Length of Stay, days; median (IQR)	7 (4 – 10)

BMI – body mass index, SD – standard deviation, NSCLC – non-small cell lung cancer, NOS – not otherwise specified, IQR –interquartile range

Table 2**Preoperative and Operative Staging**

Frequencies of pre-operative clinical staging methods utilized. The extent of lymphadenectomy and the completeness of resection are also shown.

Clinical Staging	
CT Chest, N (%)	78 (100)
PET Scan, N (%)	50 (64.1)
MRI Brain, N (%)	4 (5.1)
EBUS, N (%)	0 (0)
Mediastinoscopy, N (%)	21 (26.9)
Operative Staging	
Total nodes per patient, median (IQR)	9 (6 – 13)
Number of Nodal stations, N (%)	
3 nodal stations	5 (6.4)
> 3 nodal stations	68 (87.2)
Missing	5 (6.4)
Resection (R) Status, N (%)	
R0	75 (96.2)
R1	0
R2	0
Missing	3 (3.8)

CT – Computed tomography; PET – positron emission tomography; MRI – magnetic resonance imaging; EBUS – endobronchial ultrasound; IQR – interquartile range

Table 3**Postoperative Events**

Distribution of post-operative events (collected using standard NSQIP methods).

Variable	All Patients (N=78)
One or more postop events, No (%)	25 (32)
Postop events per patient, mean (SD)	0.7 (1.4)
Postop events, No (%)	
Pneumonia	13 (16.7)
Reintubation	10 (12.8)
Urinary tract infection	7 (9)
Re-operation within 30 days	7 (9)
Atrial fibrillation	5 (6.4)
Sepsis	5 (6.4)
Prolonged ventilation	4 (5.1)
Bleeding requiring transfusion	3 (3.8)
Cardiac arrest	2 (2.6)
Myocardial infarction	1 (1.3)
Prolonged chest tube duration *	3 (3.9)

* Prolonged chest tube duration was defined as discharge with chest tube.

SD – standard deviation

Table 4**Multivariable Cox Proportional Hazard Model Results**

The adjusted hazards ratios for death are presented. When starting at the day of surgery, only postoperative events are significantly associated with increased risk of death (HR=1.26, $p<0.05$) after adjusting for pathologic stage, age, and number of comorbidities per patient. Using the same model, but starting at postoperative day 90, postoperative events are no longer associated with death ($p > 0.05$).

Variable	Hazard Ratio	95% CI	P value
Day of Surgery Model			
pStage			
IA	1.0	--	--
IB	1.51	0.75 – 3.04	0.253
Age	1.02	0.98 – 1.06	0.321
# Comorbidities per patient	1.26	0.96 – 1.64	0.099
# Postop events per patient	1.25	1.02 – 1.53	0.028
Postoperative Day 90 Model			
pStage			
IA	1.0	--	--
IB	1.41	0.64 – 3.12	0.399
Age	1.02	0.98 – 1.07	0.338
# Comorbidities per patient	1.15	0.83 – 1.58	0.410
# Postop events per patient	1.08	0.82 – 1.42	0.583