Marginal pulmonary function should not preclude lobectomy in selected patients with non–small cell lung cancer

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Objective: Current clinical trials are investigating the role of stereotactic body radiation therapy (SBRT) versus sublobar resection for patients with non–small cell lung carcinoma (NSCLC) and marginal pulmonary function tests (M-PFTs). We compared the outcomes of patients undergoing lobectomy with M-PFTs characterized by 2 accepted M-PFT criteria.

Methods: A total of 1,259 consecutive patients underwent lobectomy for NSCLC between 1999 and 2011. Patients were stratified into 2 classifications of M-PFT: American College of Surgeons Oncology Group (ACOSOG) Z4099/Radiation Therapy Oncology Group (RTOG) 1021 trial or American College of Chest Physicians (ACCP) criteria. There were 206 patients classified as having M-PFT according to ACOSOG Z4099/RTOG 1021 criteria and 131 patients classified as having M-PFT by ACCP criteria. The primary endpoints of the study were post-operative complications and survival.

Results: Median follow-up was 3.8 years. Cox-proportional survival analysis found that pathologic stage ($P < .001$), age ($P < .001$), and higher Zubrod functional status ($P < .001$) were independent predictors of mortality. Using multivariable analysis for major morbidity, M-PFT status was not associated with the development of a major complication following lobectomy ($P = .68$). M-PFT classification was not an independent predictor of mortality when controlling for other variables (ACOSOG Z4099/RTOG 1021 [$P = .34$]; ACCP criteria [$P = .83$]). A composite major morbidity analysis for major morbidity following lobectomy showed no association between clinicopathologic variables or M-PFTs and the occurrence of a major postoperative morbidity.

Conclusions: In carefully selected patients with M-PFTs, lobectomy for NSCLC can be performed with acceptable morbidity and mortality. These results need to be considered when deciding if a patient should undergo lobectomy or other therapies for resectable NSCLC. (J Thorac Cardiovasc Surg 2014;147:738-46)

Recent prospective clinical trials have investigated the use of stereotactic body radiotherapy (SBRT) (Radiation Therapy Oncology Group [RTOG] 0236), sublobar resection (American College of Surgeons Oncology Group [ACOSOG] Z4032), and radiofrequency ablation (RFA) (ACOSOG Z4033) for early stage non–small cell lung carcinoma (NSCLC) for patients who have been considered medically inoperable or at high-risk for surgical intervention.[1] Although results for ACOSOG Z4032 and ACOSOG Z4033 have not been published to date, the phase II trial of SBRT (ie, RTOG 0236) demonstrated a 3-year overall survival of 56% and disease-free survival of 48% for patients with stage I NSCLC.[2] The results of this study resulted in the randomized clinical trial (ie, ACOSOG Z4099/RTOG 1021) comparing SBRT to sublobar resection in high-risk patients with stage I disease based on marginal pulmonary function tests (M-PFTs) and comorbidities.

Although interest in SBRT and sublobar resection for early stage NSCLC in high-risk patients has grown over the past 10 years, the current gold standard therapy for NSCLC is lobectomy. Ginsberg and colleagues[3] previously demonstrated a 3-fold increase in locoregional recurrences in patients with T1N0 disease undergoing wedge resection or segmentectomy. In a retrospective analysis,[4] we showed that sublobar resection is associated with a 4-fold increase in locoregional recurrence after R0 resection. Additionally, some patients with M-PFTs have centrally located tumors or larger tumors and lobectomy is often required to obtain an R0 resection.

We investigated the outcomes of patients undergoing lobectomy for NSCLC classified as high risk for surgery using both the inclusion criteria for the ACOSOG Z4099/RTOG 1021 trial and American College of Chest Physicians (ACCP) criteria.

METHODS

Patient Selection

A retrospective analysis of a prospectively maintained General Thoracic Surgery Database at the University of Virginia from July 1999 through

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Abbreviations and Acronyms

ACCP = American College of Chest Physicians
ACSOG = American College of Surgeons Oncology Group
CT = computed tomography
DLCO = diffusing capacity for carbon monoxide
FEV1 = forced expiratory volume in 1 second
M-PFT = marginal pulmonary function test
NSCLC = non–small cell lung carcinoma
RFA = radiofrequency ablation
RTOG = Radiation Therapy Oncology Group
SBRT = stereotactic body radiotherapy
STS = The Society of Thoracic Surgeons

August 2011 was performed. The General Thoracic Surgery Database is maintained by the Division of Thoracic and Cardiovascular Surgery and includes all data fields contained within the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database in addition to other important clinicopathologic variables. All standardized variables analyzed represent STS definitions. Clinicopathologic variables were selected a priori and included age, sex, pathologic stage, Zubrod function status, hypertension, coronary artery disease, peripheral vascular disease, diabetes (requiring hypoglycemic medications), M-PFT status, and need for home oxygen therapy (continuous or nocturnal). The Human Investigations Committee at the University of Virginia approved this study.

A study population of 1259 patients who underwent a lobectomy for NSCLC was selected for analysis. Patients with carcinoid histology, second lung primary lesions, and sublobar resection were excluded from the study. The majority of patients had clinical stage I NSCLC. Pathology reports were staged using the seventh edition of the American Joint Cancer Committee/Union Internationale Contre le Cancer criteria. Postoperatively, patients were initially seen at 2 to 3 weeks by the thoracic surgeon, and then again every 6 months following resection with contrast-enhanced chest computed tomography (CT) for 5 years. Subsequent to this visit, either a chest roentgenogram or CT of the chest was reviewed annually. Positron emission tomography with CT or magnetic resonance imaging was used as clinically warranted. All visits were completed in concert with the referring oncologist when indicated. The primary outcome of interest was to examine postoperative complications and survival in patients with M-PFTs compared with patients with non–M-PFTs following lobectomy for NSCLC.

Classification and Calculation of M-PFT

All patients had pulmonary spirometry performed with measurement of forced vital capacity, forced expiratory volume in 1 second (FEV1), and diffusing capacity for carbon monoxide (DLCO). Patients were stratified into two M-PFT categories: ACOSOG Z4099/RTOG 1021 randomized trial for SBRT versus sublobar resection (FEV1 $\leq$50% or DLCO $\leq$50% or age >75 years and FEV1 50%-60% or age >75 years and DLCO 50%-60%) and ACCP criteria (postoperative FEV1 <40% or postoperative DLCO <40%). Although the majority of patients had pre-resection quantitative perfusion scans, not all patients did. Therefore, for the purposes of this study the post-resectional corrected postoperative FEV1 and postoperative DLCO were calculated based on the remaining bronchopulmonary segments following lobectomy.

Composite Major Morbidity Model

To compare the likelihood of a major postoperative morbidity in patients undergoing lobectomy for NSCLC, we created a composite major morbidity model that would define associations between clinicopathologic variables and the postoperative occurrence of at least 1 major morbidity. We performed 2 separate statistical analyses investigating the composite major morbidity model using the entire cohort based upon separate M-PFT definitions. The first analysis investigated the composite major morbidity model of patients using the ACOSOG Z4099/RTOG 1021 trial definition included 206 patients with M-PFT and 1053 patients with non–M-PFTs. The second analysis of composite major morbidity used the ACCP M-PFT definition and included 131 patients with M-PFT and 1128 patient with non–M-PFTs. The complications included in the model were postoperative pneumonia, myocardial infarction, reintubation, renal failure, and atrial arrhythmia. The risk-adjusted composite major morbidity and the association with clinicopathologic variables were assessed using Cox-proportional hazards regression analysis.

Statistical Analysis

The effect of PFT status on patient short-term and long-term outcomes was assessed using standard hypothesis testing statistical analyses. Categorical variables are presented as a percentage of the group of origin, whereas continuous variables are presented as mean $\pm$ standard deviation (for normally distributed data) or median (interquartile range) (for non-normally distributed data). Descriptive and unadjusted differences between marginal and non-marginal study cohorts were determined using the χ^2 or Fisher exact test for categorical variable comparisons, whereas single-factor analysis of variance or the Mann Whitney U test were used to compare continuous data where appropriate.

The effect of PFT status on overall survival was assessed using unadjusted and risk-adjusted survival analyses. Two separate statistical analyses investigating overall survival were performed for all patients included in the study based upon separate M-PFT definitions. The first analysis investigated the overall survival of patients using the ACOSOG Z4099/RTOG 1021 trial definition, which included 206 patients with M-PFTs and 1053 patients with non–M-PFTs. The second analysis of overall survival used the ACCP M-PFT definition and included 131 patients with M-PFTs and 1128 patient with non–M-PFTs. The unadjusted relationship between PFT status and survival was assessed using Kaplan-Meier analysis with the log-rank test, whereas risk-adjusted survival differences as a function of PFT status were assed using Cox-proportional hazards regression analysis.

Calculated test statistics were used to determine all probability estimates, and standard statistical significance was set to $\alpha < 0.05$. All statistical analyses were performed using PASW version 19.0.0 (IBM Corp, Armonk, NY).

RESULTS

The demographic characteristics of the populations investigated are shown in Table 1. Using ACOSOG Z4099/RTOG 1021 M-PFT criteria, 206 patients were classified as having M-PFTs. With ACCP M-PFT criteria, 131 patients were classified as having M-PFTs. The mean age of patients and sex distribution with M-PFTs were not significantly different compared with the non-marginal group in both categories. Of all patients within the study, 6.1% had induction therapy before resection. Both M-PFT categories had equal proportions of both upper and lower lobectomies. Middle lobectomies were more common in both categories of M-PFTs compared with patients with non–M-PFTs. There was no significant difference in the proportion of pathologic stages between both categories of M-PFT compared with patients with non–M-PFTs. The proportion of M-PFT patients with a