Outcomes After Surgery in High-Risk Patients With Early Stage Lung Cancer

Manu S. Sancheti, MD, John N. Melvan, MD, PhD, Rachel L. Medbery, MD, Felix G. Fernandez, MD, Theresa W. Gillespie, PhD, Qunna Li, MBBS, Jose N. Binongo, PhD, Allan Pickens, MD, and Seth D. Force, MD

Departments of Surgery and Hematology and Medical Oncology, Winship Cancer Institute, and Rollins School of Public Health, Emory University School of Medicine, Atlanta, Georgia

Background. Patients with early stage lung cancer considered high risk for surgery are increasingly being treated with nonsurgical therapies. However, consensus on the classification of high risk does not exist. We compared clinical outcomes of patients considered to be high risk with those of standard-risk patients, after lung cancer surgery.

Methods. A total of 490 patients from our institutional Society of Thoracic Surgeons data from 2009 to 2013 underwent resection for clinical stage I lung cancer. High-risk patients were identified by ACOSOG z4032/z4099 criteria: major: forced expiratory volume in 1 second (FEV_1) 50% or less or diffusing capacity of lung for carbon monoxide (D_{LCO}) 50% or less; and minor: (two of the following), age 75 years or more, FEV_1 51% to 60%, or D_{LCO} 51% to 60%. Demographics, perioperative outcomes, and survival between high-risk and standard-risk patients undergoing lobectomy and sublobar resection were compared. Univariate analysis was performed using the χ^2 test/Fisher's exact test and the t test/Mann-Whitney U test. Survival was studied using a Cox regression model to calculate hazard ratios, and Kaplan-Meier survival curves were drawn.

Results. In all, 180 patients (37%) were classified as high risk. These patients were older than standard-risk patients (70 years versus 65 years, respectively; $p < 0.0001$) and had worse FEV_1 (57% versus 85%, $p < 0.0001$), and D_{LCO} (47% versus 77%, $p < 0.0001$). High-risk patients also had more smoking pack-years than standard-risk patients (46 versus 30, $p < 0.0001$) and a greater incidence of chronic obstructive pulmonary disease (72% versus 32%, $p < 0.0001$), and were more likely to undergo sublobar resection (32% versus 20%, $p = 0.001$). Length of stay was longer in the high-risk group (5 versus 4 days, $p < 0.0001$), but there was no difference in postoperative mortality (2% versus 1%, $p = 0.53$). Nodal upstaging occurred in 20% of high-risk patients and 21% of standard-risk patients ($p = 0.79$). Three-year survival was 59% for high-risk patients and 76% for standard-risk patients ($p < 0.0001$).

Conclusions. Good clinical outcomes after surgery for early stage lung cancer can be achieved in patients classified as high risk. In our study, surgery led to upstaging in 20% of patients and acceptable 1-, 2-, and 3-year survival as compared with historical rates for nonsurgical therapies. This study suggests that empiric selection criteria may deny patients optimal oncologic therapy.

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Anatomic surgical resection with systematic lymph node evaluation is considered the gold standard for patients with stage I non-small cell lung cancer (NSCLC) [1]. Most patients with lung cancer who undergo pulmonary resection are older than 60 years and have a significant smoking history and numerous comorbidities [2]. These factors can lead to higher postoperative morbidity and mortality after lung cancer resection [3]. Consequently, 1 of 5 patients with stage I NSCLC is deemed to be inoperable or at high risk for complications after lung resection [4]. The survival with untreated stage

I NSCLC is dismal. Thus, the importance in elucidating an effective treatment plan for these patients cannot be overstated.

Determination of operative risk is vital in forming a patient's specific treatment plan. Traditionally, a combination of subjective and objective data is utilized by the surgeon to determine perioperative risk [3]. More recently, a number of risk stratification models have been developed and scrutinized as potential tools for the thoracic surgeon [3, 5, 6]. In an attempt to address the question about risk, the American College of Surgery Oncology Group (ACOSOG) developed enrollment criteria to determine high-risk patients for participation

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in prominent randomized trails (ACOSOG z4032, z4033, z4099) [7, 8]. To date, however, a consensus definition of "high risk" has not been reached, thus hindering patient's risk stratification and subsequent treatment plan.

Although lobectomy is the preferred method for treatment of stage I lung cancer, high-risk patients have often been treated with various other modalities. Sublobar resections, specifically segmentectomy, have been shown to have acceptable locoregional recurrence and survival rates [9–12]. In contrast, stereotactic body radiotherapy has been advocated by some as a preferable therapy for high-risk patients with stage I lung cancer [13]. Radiofrequency ablation has also been employed in this population [4]. The goal of this study to examine our institutional outcomes regarding pulmonary resections for stage I NSCLC of patients categorized as high risk.

Patients and Methods

This study is a retrospective review of our institutional Society of Thoracic Surgeons general thoracic surgery database and was approved by our Institutional Review Board. Owing to the retrospective nature of this study and lack of patient specific identifiers, individual patient consent was waived.

A total of 490 patients underwent surgical resection from 2009 to 2013 for clinical stage I lung cancer. All lung cancers were staged using the American Joint Committee on Cancer (AJCC) seventh edition of lung cancer staging guidelines [14]. High-risk patients were identified by ACOSOG z4032/z4099 criteria [7, 8]. Major criteria included forced expiratory volume in 1 second (FEV_1) of 50% or less, or diffusing capacity of lung for carbon dioxide ($DLCO$) of 50% or less. Minor criteria (two of the following) included age 75 years or more, FEV_1 51% to 60%, or $DLCO$ 51% to 60%. Preoperative characteristics, intraoperative outcomes, and major and minor morbidity were then compared between the high-risk and standard-risk groups. Group proportions and means were compared using the χ^2 test/Fisher's exact test and t test/Mann-Whitney U test, respectively. That was then further analyzed with the subsets of lobar resection and sublobar resection in each group, high risk and standard risk. A Cox regression model with three predictors—high/standard risk, lobectomy/sublobar, and their interaction—was fit to evaluate survival, comparing overall high risk to standard risk for lobar and sublobar resections. Kaplan-Meier survival curves were constructed; the proportional hazards assumption was verified using Schoenfeld residuals plots. Follow-up was censored for all patients on January 1, 2014.

Results

Of the 490 patients undergoing surgical resection for clinical stage I NSCLC at our institution, 180 patients (36.7%) met criteria for high risk. Preoperative characteristics of the cohorts are depicted in Table 1. Compared with standard-risk patients, we found that high-risk patients were older, had worse lung function, and a greater number of smoking pack-years. Consequently, high-risk patients were more often diagnosed with chronic obstructive pulmonary disease and coronary artery disease. T1 tumors (less than 3 cm) represented 76.1% of the high-risk group and 73% of the standard-risk group. Regarding operative outcomes, high-risk patients had similar rates of intraoperative blood transfusion, nodal upstaging, and operative length of time. However, these patients had a longer hospital length of stay and were more likely to have major morbidities as compared with the standard-risk group. No difference was noted in inhospital deaths between the two groups. Total number of patients having minor morbidities was also greater for high-risk patients. Importantly, no difference was identified in nodal upstaging between the high-risk group and standard-risk group (20% versus 21%, $p = 0.79$).

We also studied high-risk patients within subgroups based on resection technique defined as lobectomy or sublobar. As seen in Table 2, high-risk patients undergoing lobectomy were older with worse lung function, and greater tobacco use. Compared with standard-risk patients, high-risk patients had longer hospital lengths of stay and more often required intraoperative blood transfusion. Patients having major morbidities were more prevalent in the high-risk group. No difference was identified for inhospital mortality.

Many preoperative characteristic differences between high-risk and standard-risk patients persisted for patients undergoing sublobar resection (Table 3). Within this subgroup, high-risk patients were older with worse lung function and longer hospital stays. High-risk patients, however, did have shorter operative times. The number of high-risk patients undergoing sublobar resection who had a major morbidity was similar to the standard-risk cohort. No inhospital deaths were noted in the sublobar group.

Kaplan-Meier survival curves were constructed for the overall, lobectomy, and sublobar cohorts. As shown in Figure 1, we found a reduced 3-year survival after surgical resection for high-risk patients as compared with standard-risk patients (59% versus 76%, respectively; $p < 0.01$; hazard ratio 2.27, 95% confidence interval: 1.49 to 3.45, $p = 0.0001$). Figure 2A and B depict survival in the high-risk and standard-risk groups based on lobectomy and sublobar resection, respectively. Our analysis showed a reduced 3-year survival after lobectomy for the high-risk patients as compared with the standard-risk patients (59% versus 77%; hazard ratio 2.42, 95% confidence interval: 1.50 to 3.89, $p < 0.01$). Reduced survival was also found in the sublobar high-risk patients but was not statistically significant (57% versus 71%; hazard ratio 1.91, 95% confidence interval: 0.79 to 4.61, $p = 0.15$).

Comment

Lobectomy with lymph node dissection is the standard of care for treatment of early stage lung cancer. This recommendation, however, is best reserved for patients with acceptable risk [1]. The categorization of high-risk patients continues to evolve. The objective of this study is to determine the role and outcome of surgical resection in this difficult patient population.