Published in final edited form as:

Ann Thorac Surg. 2014 May ; 97(5): 1678–1685. doi:10.1016/j.athoracsur.2013.12.028.

National Cooperative Group Trials of “High-risk” Patients with Lung Cancer: Are They Truly “High-risk”?

Varun Puri, MD, Traves D. Crabtree, MD, Jennifer M. Bell, BSN, Daniel Kreisel, MD, PhD, Alexander S. Krupnick, MD, Stephen Broderick, MD, G. Alexander Patterson, MD, and Bryan F. Meyers, MD

Department of Surgery, Washington University, St. Louis, St. Louis, MO, USA

Abstract

Background—The American College of Surgery Oncology Group (ACOSOG) trials z4032 and z4033 prospectively characterized lung cancer patients as “high-risk” for surgery and these results have appeared frequently in literature. We hypothesized that many patients meeting objective enrollment criteria for these trials (“high-risk”) have similar perioperative outcomes as “normal-risk” patients.

Methods—We reviewed a prospective institutional database, and classified patients undergoing resection for clinical stage I lung cancer as “high-risk” and “normal-risk” by ACOSOG major criteria.

Results—From 2000 – 2010, 1066 patients underwent surgery for clinical stage I lung cancer. Of these, 194 (18%) met ACOSOG major criteria for risk (preoperative FEV1 or DLCO < 50% predicted). “High-risk” patients were older (66.4 vs. 64.6 years, $p=0.02$) but similar to controls in gender, prevalence of hypertension, diabetes, and coronary artery disease (CAD). “High-risk” patients were less likely than normal patients to undergo a lobectomy (117/194, 60% vs. 665/872, 76%, $p<0.001$). “High-risk” and control patients experienced similar morbidity (any complication: 55/194, 28% vs. 230/872, 26%, $p=0.59$), and 30-day mortality (2/194, 1% vs. 14/872, 2%, $p=0.75$).

In a regression analysis, age (HR 1.04, 95% CI 1.02–1.06), and CAD (HR 1.58, 95% CI 1.05–2.40) were associated with an elevated risk of complications in those undergoing lobectomy, while female gender (HR 0.63, 95% CI 0.44–0.91) was protective. ACOSOG “high-risk” status was not associated with perioperative morbidity.

Conclusions—There are no important differences in early outcomes between lung cancer patients characterized as “high-risk” and “normal-risk” by ACOSOG trial enrollment criteria, despite a significant proportion of “high-risk” patients undergoing lobectomy.

©2014 The Society of Thoracic Surgeons. Published by Elsevier Inc. All rights reserved.

Corresponding author: Varun Puri, MD, 3108 Queeny Tower, Barnes Jewish Hospital, One Barnes Jewish Hospital Plaza, St. Louis, MO 63110, puriv@wudosis.wustl.edu, Phone – 314-362-6044.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Lung cancer; spirometry; diffusing capacity; risk

Introduction

Patients undergoing pulmonary resection for lung cancer are usually older than 60 years of age, smokers, and have multiple comorbidities. Hence, short-term outcomes after surgery for these patients are often worse than operations for other cancers. (1) Conventionally, surgeons have relied upon a combination of subjective and objective criteria to assess perioperative risk of major adverse events, including mortality, in these patients. (2–6) These efforts to assess risk have been accompanied by systemic and technical improvements, including better perioperative medical management and the utilization of minimally invasive techniques to diminish short-term morbidity and mortality.

A variety of patient-dependent variables have been associated with an elevated risk of perioperative complications after lung resection, with evidence derived from institutional studies as well as larger repositories, such as the Society of Thoracic Surgeons (STS) General Thoracic Database (GTDB). These variables include male gender, preoperative FEV1 (forced expiratory volume in 1 second), preoperative DLCO (diffusing capacity for carbon monoxide), poor performance status (high Zubrod score), obesity, renal disease, diabetes, malnutrition, steroid use, and congestive heart failure.(3–9) Some of these variables have been incorporated into statistical models to study and predict high-risk patients (4–6), and similar tools are well-integrated into cardiac surgical practice. (10–12) However, a lack of consensus among lung cancer surgeons on how to define the “high-risk” patient has prevented the use of sophisticated statistical models to assess risk in patients undergoing lung resection.

Surgical resection has traditionally been the gold-standard for treatment of early-stage lung cancer. The American College of Surgery Oncology Group (ACOSOG), a national cancer cooperative group, led several multicenter trials in thoracic surgery and is now a part of the Alliance for Clinical Trials in Oncology (Alliance). The ACOSOG z4032, z4033 and z4099 trials included enrollment criteria that defined lung cancer patients as “high risk” for surgery. The enrollment criteria (definition of “high-risk” status) for these trials were decided upon by expert consensus and the ability to obtain audit verification, not empiric evidence, and the dissemination of these definitions for “high risk” has the potential to codify them in the lung cancer community without firm evidence. These highly visible trials are likely to impact the care of lung cancer patients.

We sought to challenge this risk assessment with the suspicion that this simple declaration of “high-risk” for clinical trial audit is not meaningful in guiding clinical care in lung cancer. Hence, we hypothesized that patients meeting enrollment criteria for these trials, the so-called “high-risk”, have similar perioperative outcomes compared to “normal-risk” patients.

Patients and Methods

The ACOSOG z4032 trial randomized 224 patients with clinical stage I lung cancer to sublobar resection with or without brachytherapy. The major and minor enrollment criteria for ACOSOG z4032 are detailed in Table 1. In the ACOSOG z4032 trial, 187 of 222 (84%) patients eligible for analysis were admitted based upon meeting major criteria. This study completed accrual in January, 2010. Perioperative outcomes have recently been reported, and the analysis of cancer-related outcomes is awaited.⁽¹³⁾ The ACOSOG z4099 trial was subsequently launched with the aim to compare sublobar resection versus stereotactic body radiation therapy (SBRT) in clinical stage I lung cancer patients considered “high-risk” for a lobectomy. The objective enrollment criteria are identical to those for the ACOSOG z 4032 trial (Table 1).

With approval from the institutional review board at Washington University School of Medicine, a single-center, retrospective review of our database was performed to identify patients who had undergone resection for clinical stage I lung cancer between January, 2000 and December, 2010. We chose a start date of 2000 for the study since electronic patient records first became available for review at that time. Patients meeting either or both of the ACOSOG major enrollment criteria (preoperative FEV1 or preoperative DLCO less than or equal to 50% of predicted) were categorized as “high-risk”. The remaining patients were considered “normal-risk”. We utilized a prospectively maintained database to abstract information about patient demographics, diagnosis, workup, operation, perioperative course, and outcomes. Missing data were obtained by a review of patient charts. Perioperative events were defined per STS data collection guidelines. Follow-up data were obtained from clinic notes and supplemented by querying the social security death index to determine survival.

Data were managed using Microsoft Excel and analyzed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics are expressed as mean $\pm$ standard deviation unless otherwise specified. Categorical data are expressed as counts and proportions. Comparisons were done with paired, two-tailed *t* tests for means of normally distributed continuous variables. Matched ordinal data were analyzed using Wilcoxon’s rank test, and differences among the categorical data were analyzed with either Fisher’s exact test or chi-square comparison. We generated Kaplan Meier (product limit) survival plots, and survival comparisons between groups of patients were completed using the Mantel-Haenszel log rank test. All *p* values less than 0.05 are considered to be statistically significant. After an initial exploratory comparison between the “high-risk” and “normal-risk” groups, logistic regression models were created to assess the influence of preoperative variables on postoperative major morbidity and mortality. Separate models were fitted for those patients undergoing lobectomy or sublobar resection. Importantly, we utilized ACOSOG definition of “high-risk” as an independent variable for this analysis. For the purpose of this study, in keeping with STS definitions, conditions signifying major perioperative morbidity are summarized in Appendix 1.

Results

Between January, 2000 and December, 2010, 1066 patients underwent surgery for clinical stage I lung cancer. Of these, 194 (18%) met ACOSOG z4032/z4033/z4099 major entry criteria for risk (preoperative FEV1 or DLCO $\leq$ 50% predicted). “High-risk” patients were older than “normal-risk” patients (66.3 ± 8.9 vs. 64.6 ± 11.8 years, $p = 0.03$) but similar in gender distribution and prevalence of pre-operative hypertension, coronary artery disease, diabetes, peripheral vascular disease, and clinical stage IA disease (Table 2).

“High-risk” patients were less likely than “normal-risk” patients to undergo a lobectomy (117/194, 60% vs. 665/872, 76%, $p < 0.001$); there were no differences in the utilization of VATS, or the final pathologic staging (Table 3). “High-risk” and “normal-risk” patients experienced similar overall morbidity (any complication: 55/194, 28% vs. 230/872, 26%, $p = 0.59$), and 30-day mortality (2/194, 1% vs. 14/872, 2%, $p = 0.75$). There were no differences in the incidence of postoperative respiratory failure, re-operations for bleeding, myocardial infarction, and stroke. Hospital stays were similar between the high-risk and low-risk groups (6.8 ± 7 days vs. 6.5 ± 8 days, $p = 0.69$) (Table 4).

Although the ACOSOG trials had considered only sublobar resection for surgery in the “high-risk” group, since 60% of our so-called “high-risk” patients had undergone a lobectomy, we stratified patients according to type of resection. In those undergoing lobectomy, perioperative outcomes including major morbidity, and hospital mortality were identical between the “high-risk” and “normal-risk” groups. Patients in the “high-risk” group had a longer hospital stay. (Table 5) Similarly, when considering sublobar resections, the 2 risk groups had statistically similar outcomes. (Table 6)

For the logistic regression analysis, we considered age, gender, hypertension, coronary artery disease (CAD), diabetes, and ACOSOG risk stratification as independent variables. For the outcome of major perioperative morbidity in the lobectomy group, age (HR 1.04, 95% CI 1.02–1.06), and history of CAD (HR 1.58, 95% CI 1.05–2.40) were associated with an elevated risk while female gender (HR 0.63, 95% CI 0.44–0.91) was protective. For the outcome of major perioperative morbidity in those undergoing sublobar resection, only age was associated with a higher risk of events (HR 1.04, 95% CI 1.00–1.08). ACOSOG “high-risk” status was not associated with a risk of perioperative complications in the lobectomy or sublobar resection groups.

Additionally, an exploratory analysis revealed that hospital length of stay was longer in those patients who had both FEV1 and DLCO less than 50% predicted ($n = 29$, 10.7 ± 10.9 days vs. 6.1 ± 5.2 days, $p = 0.03$). This subgroup also had a higher incidence of postoperative atrial fibrillation (11/29, 38% vs. 14/165, 9%, $p < 0.0001$).

Overall median survival for the entire group was 8.8 years. The “normal-risk” cohort was associated with improved long-term survival (median survival 9.5 years vs. 6.5 years, $p = 0.004$) (Figure 1).

Comment

Defining operative risk is critically important to health-care providers for optimizing patient selection, informed consent, and comparing procedure-related outcomes. Of late, risk stratification has formed the primary basis for comparing conventional treatment strategies with newer, less invasive forms of therapy in large scale clinical trials for disease processes like aortic stenosis, abdominal aortic aneurysms, and prostate cancer. Based upon risk stratification, national organizations like the STS and the Veterans Affairs hospital system currently provide a summary of observed to expected treatment-related adverse events to participating providers. Risk assessment also allows patients to make truly informed decisions about treatment options.

Lung cancer has been a key area of investigation for the American College of Surgery Oncology Group (ACOSOG). ACOSOG recently merged with the Cancer and Leukemia Group B (CALGB) and the North Central Cancer Treatment Group (NCCTG) to form the Alliance for Clinical Trials in Oncology. Recent ACOSOG trials have focused on the evaluation of therapies for lung cancer patients considered to be “high-risk” surgical candidates.(13, 14) The ACOSOG z4032 trial randomized “high-risk” surgical patients with early-stage lung cancer to sublobar resection with or without brachytherapy. The overall combined 30-day morbidity and mortality were 27.9% and 1.4% respectively in this “high-risk” cohort. These outcomes are similar to the pooled results from our study (morbidity 27%, mortality 1.5%) and those from other large cohorts combining “normal-risk” and “high-risk” patients.(5, 15)

The ACOSOG z4099 was subsequently designed as a multicenter trial studying “high-risk” patients with clinical stage I lung cancer, with patients randomly allocated to either sublobar resection or stereotactic body radiation therapy (SBRT). The criteria determining “high-risk” are identical for these 2 trials (Table 1). The vast majority of patients enrolled in the z4032 trial were deemed eligible by meeting one of the two major criteria. In comparison, some of the minor entry criteria for these trials were subjective (MMRC dyspnea scale), and others were not routinely available for all patients (paO₂, paCO₂). Hence, we elected to stratify our study population based upon the major entry criteria for these trials and not upon the minor criteria. This could potentially result in misclassification error, in which patients characterized as “high-risk” based on minor criteria in the ACOSOG scheme might be labeled as “normal-risk” in this paper, representing a limitation to our investigation. The observed risk in either group was so low that this potential shortcoming seems not to have influenced the outcome of this study.

The 2 major entry criteria utilized by our study and the ACOSOG trials are preoperative FEV1% predicted and preoperative DLCO% predicted. Preoperative FEV1 has been traditionally considered an important predictor of postoperative morbidity.(8, 16) While some recent studies have confirmed the predictive role of FEV1 (5), several reports, including the current one, have not found specific cut-off values of FEV1 to be an independent risk factor.(17–19) This has been especially true in patients with lower levels of preoperative FEV1 (3) and may be partly explained by benefits derived from the so-called “lung volume reduction effect” of surgery in patients with emphysema. These findings have

led a joint task force of the European Respiratory Society and the European Society of Thoracic Surgeons to recommend that predicted postoperative FEV1 should not be used alone for patient selection for lung cancer surgery.(20)

On the other hand, since an initial report by Ferguson et al (21), low preoperative DLCO values have been consistently found to be associated with adverse perioperative outcomes after lung resection.(22, 23) DLCO has also been useful as a marker of need for admission to an intensive care unit after surgery (24) and a predictor of postoperative quality of life. (3) Our study found that patients with both FEV1 and DLCO less than or equal to 50% of predicted values experienced longer hospital stays than other patients. This can be partly explained by a higher incidence of atrial fibrillation in this subgroup. We did not find the arbitrary value of DLCO less than or equal to 50% of predicted to be associated with elevated perioperative risk. This finding may be related to chance, a limited sample size, or a suboptimal cutoff for DLCO set at 50%. Analysis of ACOSOG z4032 found that the DLCO less than the study median of 46% was associated with adverse outcomes at 30 and 90 days after surgery. Despite the recent focus on DLCO, it has not featured prominently in multivariable risk assessment models as it has been infrequently and inconsistently recorded in preoperative pulmonary function testing.(4, 6)

Over the last 2 decades, a number of risk stratification models have been developed for patients undergoing lung resection. Several of these studies have used large national and international databases for model development and validation.(4–6, 9, 15, 17) Amongst these, the European Society Objective Score (ESOS) (4) and Thoracscore (6) have received much attention in Europe while a model derived from the Society of Thoracic Surgeons database is based upon the North American experience. The ESOS is a parsimonious model incorporating only age and predicted postoperative FEV1%, however it was developed as a secondary goal in a study by Berrisford et al, and “could not be tested robustly”.(4) The Thoracscore was developed from a large French database and is composed of 9 variables predicting hospital mortality.(6) Kozower et al have described a regression model that linked more than 15 variables with a composite outcome of major morbidity or mortality.(5) Unlike the cardiac surgical literature, these models have found limited application in daily clinical practice and have subsequently been overlooked during the development of clinical trials.

Our current practice pattern of preoperative evaluation broadly mirrors the recommendations of the American College of Chest Physicians.(16) Patients routinely undergo pulmonary function tests including DLCO. Those with predicted postoperative FEV1 or DLCO less than 40% are further evaluated with quantitative ventilation/perfusion scans, 6-minute walk test, and cardiopulmonary exercise testing. In addition, a subjective assessment of frailty and performance status often plays a role in patient selection. Patients deemed to be at a high-risk by the surgeons are discussed and presented at a multidisciplinary meeting for consideration of non-operative therapies.

Our study found a long-term survival advantage for those in the “normal-risk” group. The majority of patients (134/194, 69%) in the “high-risk” group had DLCO less than or equal to 50% of predicted values. Recent reports have identified low preoperative DLCO as a strong, negative predictor of long-term survival (25, 26), and this effect is independent of the impact

of DLCO on perioperative outcomes. (26) An analysis by Liptay et al showed a low preoperative DLCO to be associated with non-cancer related deaths in long-term follow-up. (25) Thus, low DLCO may be a proxy for poor cardiopulmonary reserve, independent of pulmonary mechanics.

Limitations to our study include the inherent biases of a retrospective study, the most important of which is selection bias in treatment allocation. Additionally, sample size limitations from a single-center study introduce the possibility of type II error in the analysis, where true differences between groups may not become apparent due to sample size constraints. Lastly, the subjectivity of intraoperative decision-making, and the management of perioperative complications that lung resection patients experience can lead to misclassification bias. We have sought to avoid underestimating the morbidity of the operations by adopting a stringent approach toward enumerating complications based upon STS definitions, preferring to classify an event as a complication if there was some doubt on chart review.

In conclusion, our study shows that a significant proportion of patients deemed “high-risk” by national cooperative group trials safely undergo lobectomy. The ACOSOG trial enrollment criteria of “high-risk” status are not an independent predictor of perioperative morbidity. The question of who can and should have a lobectomy or a sublobar resection requires far more information than a routine pulmonary function test can provide. A true definition of “high-risk” remains a critical unmet need in patient care in early-stage lung cancer.

References

1. Khuri SF, Daley J, Henderson W, et al. Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. *J Am Coll Surg*. 1997; 185:315–327. [PubMed: 9328380]
2. Ferguson MK, Siddique J, Karrison T. Modeling major lung resection outcomes using classification trees and multiple imputation techniques. *Eur J Cardiothorac Surg*. 2008; 34:1085–1089. [PubMed: 18760930]
3. Brunelli A. Risk assessment for pulmonary resection. *Semin Thorac Cardiovasc Surg*. 2010; 22:2–13. [PubMed: 20813311]
4. Berrisford R, Brunelli A, Rocco G, Treasure T, Utey M. The European Thoracic Surgery Database project: modelling the risk of in-hospital death following lung resection. *Eur J Cardiothorac Surg*. 2005; 28:306–311. [PubMed: 16144067]
5. Kozower BD, Sheng S, O'Brien SM, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. *Ann Thorac Surg*. 2010; 90:875–881. discussion 881–873. [PubMed: 20732512]
6. Falcoz PE, Conti M, Brouchet L, et al. The Thoracic Surgery Scoring System (Thoracoscore): risk model for in-hospital death in 15,183 patients requiring thoracic surgery. *J Thorac Cardiovasc Surg*. 2007; 133:325–332. [PubMed: 17258556]
7. Ferguson MK, Gaissert HA, Grab JD, Sheng S. Pulmonary complications after lung resection in the absence of chronic obstructive pulmonary disease: the predictive role of diffusing capacity. *J Thorac Cardiovasc Surg*. 2009; 138:1297–1302. [PubMed: 19783010]
8. Licker MJ, Widikker I, Robert J, et al. Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg*. 2006; 81:1830–1837. [PubMed: 16631680]

9. Wright CD, Gaissert HA, Grab JD, et al. Predictors of prolonged length of stay after lobectomy for lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk-adjustment model. *Ann Thorac Surg.* 2008; 85:1857–1865. discussion 1865. [PubMed: 18498784]
10. Shahian DM, Edwards FH. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: introduction. *Ann Thorac Surg.* 2009; 88:S1. [PubMed: 19559821]
11. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. *Ann Thorac Surg.* 2009; 88:S2–S22. [PubMed: 19559822]
12. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 3--valve plus coronary artery bypass grafting surgery. *Ann Thorac Surg.* 2009; 88:S43–S62. [PubMed: 19559824]
13. Fernando HC, Landreneau RJ, Mandrekar SJ, et al. Thirty- and ninety-day outcomes after sublobar resection with and without brachytherapy for non-small cell lung cancer: results from a multicenter phase III study. *J Thorac Cardiovasc Surg.* 2011; 142:1143–1151. [PubMed: 21872277]
14. Fernando HC, Timmerman R. American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2012; 144:S35–S38. [PubMed: 22795435]
15. Harpole DH Jr, DeCamp MM Jr, Daley J, et al. Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. *J Thorac Cardiovasc Surg.* 1999; 117:969–979. [PubMed: 10220692]
16. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest.* 2007; 132:161S–177S. [PubMed: 17873167]
17. Ceppa DP, Kosinski AS, Berry MF, et al. Thoracoscopic lobectomy has increasing benefit in patients with poor pulmonary function: a Society of Thoracic Surgeons Database analysis. *Ann Surg.* 2012; 256:487–493. [PubMed: 22868367]
18. Brunelli A, Al Refai M, Monteverde M, et al. Predictors of early morbidity after major lung resection in patients with and without airflow limitation. *Ann Thorac Surg.* 2002; 74:999–1003. [PubMed: 12400735]
19. Linden PA, Bueno R, Colson YL, et al. Lung resection in patients with preoperative FEV1 < 35% predicted. *Chest.* 2005; 127:1984–1990. [PubMed: 15951309]
20. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J.* 2009; 34:17–41. [PubMed: 19567600]
21. Ferguson MK, Little L, Rizzo L, et al. Diffusing capacity predicts morbidity and mortality after pulmonary resection. *J Thorac Cardiovasc Surg.* 1988; 96:894–900. [PubMed: 3193801]
22. Ferguson MK, Vigneswaran WT. Diffusing capacity predicts morbidity after lung resection in patients without obstructive lung disease. *Ann Thorac Surg.* 2008; 85:1158–1164. discussion 1164–1155. [PubMed: 18355489]
23. Santini M, Fiorello A, Vicidomini G, Di Crescenzo VG, Laperuta P. Role of diffusing capacity in predicting complications after lung resection for cancer. *Thorac Cardiovasc Surg.* 2007; 55:391–394. [PubMed: 17721850]
24. Pieretti P, Alifano M, Roche N, et al. Predictors of an appropriate admission to an ICU after a major pulmonary resection. *Respiration.* 2006; 73:157–165. [PubMed: 16155356]
25. Liptay MJ, Basu S, Hoaglin MC, et al. Diffusion lung capacity for carbon monoxide (DLCO) is an independent prognostic factor for long-term survival after curative lung resection for cancer. *J Surg Oncol.* 2009; 100:703–707. [PubMed: 19798693]
26. Ferguson MK, Dignam JJ, Siddique J, Vigneswaran WT, Celauro AD. Diffusing capacity predicts long-term survival after lung resection for cancer. *Eur J Cardiothorac Surg.* 2012; 41:e81–e86. [PubMed: 22368187]

Appendix 1

Appendix 1

Major perioperative morbidities as defined by the Society of Thoracic Surgeons General Thoracic Database.

Pulmonary
Atelectasis requiring bronchoscopy
Pneumonia
ARDS/Respiratory Failure
Bronchopleural Fistula/Empyema
Pulmonary Embolus
Initial Ventilator support >48 hours
Reintubation
Tracheostomy
Cardiovascular
Atrial Arrhythmia requiring treatment
Ventricular Arrhythmia requiring treatment
Myocardial Infarction
Deep Vein Thrombosis requiring treatment
Infection
Surgical Site infection, specify:
Sepsis
Neurology
New Central Neurological Event
Miscellaneous
New Renal Failure per RIFLE criteria
Other events requiring OR with General Anesthesia, specify

Appendix 2

Discussion

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of “High-Risk” Patients with Lung Cancer: Are
They Truly High-Risk? Paper presented by Varun Puri, MD, St. Louis, MO.
puriv@wudosis.wustl.edu

Discussion by Mark K. Ferguson, MD, Illinois mferguso@surgery.bsd.uchicago.edu

Dr. M. Ferguson (Chicago, IL):

I would like to congratulate Dr. Puri and his colleagues on their work, and Dr. Puri in particular on his excellent presentation.

Dr. Puri and his colleagues pose several important questions in the design of their study of lung resection patients: Do we agree on how to define high risk? Do we know what high risk means in terms of outcomes? And is the promulgation of clinical trials investigating so-called "high risk" patients unfairly stigmatizing patients and skewing outcomes expectations?

Use of the label "high risk" is clearly inappropriate based on the current study. The reasons for choosing the cutoff values used by cooperative studies are manifold: not forcing surgeons into considering operations for truly highest risk patients, generating adequate numbers for a clinical trial, finding common ground among participants who may honestly disagree about definitions, and so on. These are all constraints created by cooperative group dynamics.

One of the shortcomings of these clinical trial definitions is the lack of further investigation of patients deemed to be at increased risk, such as measurement of peak oxygen consumption during exercise. This is generally recognized as a useful final evaluation before recommendations are made for surgery.

Another shortcoming of the clinical trial definitions is the lack of quantification of the surgeon's estimates of risk based on clinical judgment. Judgment obviously influenced surgeon selection of the extent of surgery in the current study, but I imagine there is no objective way to assess that judgment retrospectively.

The authors provide us with important information about some of the fallacies surrounding clinical trials and the definitions used within them. Further work on more accurately defining risk will be of use in future trials but will be most important in making decisions about our patients and informing them about the potential risks of surgery.

I have two questions.

First, from what I understood, you conclude that there were no important differences in outcomes between high risk and normal risk groups. However, your subgroup analyses demonstrate differences in respiratory failure and length of stay comparing the high risk and normal risk lobectomy patients. Isn't this a meaningful finding that is potentially obscured by the admixture of lobar and sublobar resections?

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of "High-Risk" Patients with Lung Cancer: Are
They Truly High-Risk? Response by Varun Puri, MD, St. Louis, MO.

DR. PURI: Dr. Ferguson, thank you very much for your pioneering work in this field and your extremely insightful comments.

Very true, the lobectomy patients did have a somewhat higher incidence of postoperative respiratory failure, which did translate into a prolonged stay in the high risk lobectomy patients, although the mortality and incidence of all other major perioperative complications was similar between the groups. This is similar to what several other authors have published. And also we did notice in our analysis that the incidence of postoperative respiratory failure

was quite low to nonexistent in the sublobar resection group. So another way of looking at the data may be that maybe we are not offering lobectomy to some patients who may actually be good candidates for a lobectomy. The incidence of postoperative respiratory failure ranged from 5 to 6% in the lobectomy patient population, which is similar to what others have published and maybe at the lower end of the spectrum of what has been published in literature.

DR. FERGUSON: And second, with improvements in surgical techniques and anesthetic management, the definition of high risk seems to be a moving target, particularly with regards to acute outcomes, although I think long-term outcomes are probably fixed with regards to physiologic variables. How do you currently define the "high risk" patients? You didn't present data on additional testing used for assessing risk. What has been your routine, and do you plan to change that going forward to help assess risk more accurately?

DR. PURI: Our current definition of high risk is an amalgamation of age, the Zubrod score, performance in general, the patient's motivation status. As Bryan Meyers often puts it, it does matter whether the patient comes into the office wearing pajamas or a tie. And these are all subjective criteria that we utilize in assessing risk, in addition to the objective criteria of predicted postoperative DLCO, which is what we are using more and more frequently after published literature over the last five years, and predicted postoperative FEV1. Additional testing is ordered in generally the following fashion: Individuals who we think are at somewhat higher risk for a lobectomy undergo a six-minute walk test, which is low-hanging fruit in terms of functional testing, and subsequently we utilize cardiopulmonary exercise stress testing to measure VO2 max, which has been shown in several studies over the last decade to be one of the best predictors of perioperative outcomes in these individuals.

Going forward, we have more liberally utilized lobectomy in individuals who in an earlier era we might not have considered for lobectomy because of minimally invasive techniques and better perioperative management, just like you allude to, and also going forward we are in the course of designing an institutional trial where we will utilize one of the commonly utilized scores, either the Thoracscore or the ESOS score, to stratify patients. We have not chosen the arbitrary cutoff yet, but patients meeting that cutoff will be discussed at a multi-surgeon conference prior to them being considered for resection. This is an approach that the cardiac surgical literature has published in the past.

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of "High-Risk" Patients with Lung Cancer: Are
They Truly High-Risk? Paper presented by Varun Puri, MD, St. Louis, MO.
puriv@wudosis.wustl.edu

Discussion by David Tom Cooke, MD, California davidt.cooke@ucdmc.ucdavis.edu

Dr. D. Cooke (Sacramento, CA):

It was an excellent presentation and very important findings. The question I have is in your lobectomy group, the lobectomy group had higher pulmonary complications. Did you do a subset analysis to see if tumor location was predictive of complications? For instance, in this

population with low DLCO, low FEV1, perhaps the distribution of their emphysema was relevant to their outcome. So upper lobectomy, better outcomes than, say, lower lobectomy.

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of "High-Risk" Patients with Lung Cancer: Are
They Truly High-Risk? Response by Varun Puri, MD, St. Louis, MO.

DR. PURI: Unfortunately, for this particular analysis we did not do a subgroup analysis to look at the complications in the lobectomy patients. However, in an earlier paper that we published a couple of years ago, we had looked at both perioperative complications as well as long-term survival in early stage lung cancer based upon the lobar location of those tumors. And in our analysis for that particular study, which was two years ago and did not include the last three years or so of data, we had not found any difference in the upper or lower lobar location as a predictor of perioperative or long-term outcomes in these patients.

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of "High-Risk" Patients with Lung Cancer: Are
They Truly High-Risk? Paper presented by Varun Puri, MD, St. Louis, MO.
puriv@wudosis.wustl.edu

Discussion by Frank C. Detterbeck, MD, Connecticut frank.detterbeck@yale.edu

Dr. F. Detterbeck (New Haven, CT):

Varun, did you look at VATS lobectomy versus open lobectomy and what effect that had?

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of "High-Risk" Patients with Lung Cancer: Are
They Truly High-Risk? Response by Varun Puri, MD, St. Louis, MO.

DR. PURI: In this analysis we did not specifically look at VATS lobectomy or open lobectomy, but we have our six monthly institutional M & Ms or divisional M & Ms where we routinely study this. And we have noticed a significant diminishing trend of both perioperative outcomes as well as perioperative mortality over the last several years as we have liberally applied the use of minimally invasive techniques.

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of "High-Risk" Patients with Lung Cancer: Are
They Truly High-Risk? Paper presented by Varun Puri, MD, St. Louis, MO.
puriv@wudosis.wustl.edu

Discussion by Fred H. Edwards, MD, Florida fhe@comcast.net

Dr. F. Edwards (Jacksonville, FL):

Congratulations on a nice presentation. Frailty is a hot topic in cardiac surgery and there are a variety of different objective ways to calculate this. Frankly, I couldn't tell whether you really were examining frailty and perhaps calling it something else or whether you did not. Could you comment on your use of frailty as part of your assessment?

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of “High-Risk” Patients with Lung Cancer: Are
They Truly High-Risk? Response by Varun Puri, MD, St. Louis, MO.

DR. PURI: We have not specifically used either a frailty or a modified frailty index in these individuals. However, the subjective approach that we have utilized is, I would say, a good real world indicator of an objective evaluation of these patients for a frailty index. But we have not specifically utilized a frailty index.

Unfortunately, the thoracic surgical literature has lagged behind cardiac literature in this particular arena. In cardiac surgical literature, for both clinical trial evaluation as well as day-to-day patient evaluation there is routine use of, say, the STS score or other risk scores, which are not being utilized in the thoracic surgical literature.

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of “High-Risk” Patients with Lung Cancer: Are
They Truly High-Risk? Paper presented by Varun Puri, MD, St. Louis, MO.
puriv@wudosis.wustl.edu

Discussion by Leslie Kohman, MD, New York kohmanl@upstate.edu

Dr. L. Kohman (Syracuse, NY):

We have heard that there are many other factors going into the decision about surgery in these high risk patients. The survival was lower in the high risk patients overall. What about the rest of the patients who met the high risk criteria who never were chosen for surgery either by the surgeons or prior to arrival at the surgeon's office? That group would be extremely important to compare the long-term survival with to see whether the surgery really added anything to their survival.

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of “High-Risk” Patients with Lung Cancer: Are
They Truly High-Risk? Response by Varun Puri, MD, St. Louis, MO.

DR. PURI: Very true, and this is a common problem both with our own work as well as the work of most other published surgical series or databases. One really does not know what the true denominator is in this patient population. Unfortunately, our work cannot really answer your question, but I fully agree with you.

When one does compare raw outcomes in long-term survival of lung cancer patients who are maybe considered at a high risk versus those who do not undergo any treatment, the radiation oncology literature is the one that comes closest to answering that question. And several retrospective studies have shown that offering these individuals some treatment, which may be stereotactic radiation or external beam radiation, versus no treatment does significantly improve survival, specifically in that order: highest for stereotactic radiation, next for external beam radiation, and poorer survival for those who were not treated with anything at all.

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of “High-Risk” Patients with Lung Cancer: Are

They Truly High-Risk? Paper presented by Varun Puri, MD, St. Louis, MO.
puriv@wudosis.wustl.edu

Discussion by Hiran Fernando, MD, Massachusetts hiran.fernando@bmc.org

Dr. H. Fernando (Boston, MA):

Varun, were you able to tease out in the high risk patients why surgeons in your institution selected lobectomy over sublobar resection? And the second question was, in the Z4032 group we did look at data and tried to look at cut points that predicted higher complications and also looked at median values for DLCO in our patients and found that patients with a low DLCO, less than the median value, less than 46%, predicted poorer outcome. Did you perform any of those analyses?

59. J. Maxwell Chamberlain Memorial Paper for General Thoracic Surgery:
National Cooperative Group Trials of "High-Risk" Patients with Lung Cancer: Are
They Truly High-Risk? Response by Varun Puri, MD, St. Louis, MO.

DR. PURI: In answering your questions, when we look at our own retrospective data sets to analyze why surgeons performed a lobectomy, there is no objective way to answer that question. But when I reviewed the literature from other institutions and looked at the risk profiles of patients undergoing resections, our lobectomy rate may be somewhat higher than published literature, but there is no true way to compare that objectively.

Again, I appreciate the comment about the DLCO median of 46% from 4032. Our own DLCO median was 45%, too, but we did not feel that was a fair analysis in a retrospective fashion for us to come up with cutoff values when the study had been performed in a retrospective fashion simply to try and validate or disprove previously published enrollment criteria.

Figure 1.
Long-term survival in the “high-risk” and “normal-risk” groups by Kaplan-Meier method.

Table 1

Enrollment criteria for ACOSOG z4032 and ACOSOGz4099 studies. Patients have to meet 1 major, or 2 minor criteria to be considered high-risk, and thus be potential participants in the study.

Major Criteria	
☐	FEV1 50% predicted
☐	DLCO 50% predicted
Minor Criteria	
☐	Age 75
☐	FEV1 51-60% predicted
☐	DLCO 51-60% predicted
☐	Pulmonary hypertension (defined as apulmonary artery systolic pressure greater than 40mm Hg) as estimated by echocardiography or right heart catheterization
☐	Poor left ventricular function (defined as an ejection fraction of 40% or less)
☐	Resting or Exercise Arterial pO2 55 mm Hg or SpO2 88%
☐	pCO2 > 45 mm Hg
☐	Modified Medical Research Council (MMRC) Dyspnea Scale 3.

Table 2

Preoperative variables in the “high-risk” and “normal-risk” study groups.

Variable	High-risk (n=194)	Normal-risk (n=872)	P-value
Female Gender	108 (56%)	462 (53%)	0.53
Mean age (years)	66.4 ± 8.9	64.6 ± 11.8	0.02
Hypertension	103 (53%)	459 (53%)	0.94
Coronary artery disease	40 (21%)	164 (19%)	0.55
Clinical Stage IA	128 (66%)	591 (68%)	0.67

Table 3

Details of procedure performed and final pathologic staging in the study groups. VATS—Video-assisted Thoracic Surgery

Variable	High-risk (n=194)	Normal-risk (n=872)	P-value
VATS approach	60 (31%)	268 (31%)	1.00
Open approach	134 (69%)	604 (69%)	
Lobectomy	117 (60%)	665 (76%)	<0.0001
Sublobar/other resection	77 (40%)	205 (24%)	
Final pathology			0.61
Stage 0	1 (0.5%)	6 (0.7%)	
Stage I	179 (92%)	795 (91%)	
Stage II	8 (4%)	50 (6%)	
Stage III	6 (3%)	17 (2%)	
Stage IV	0	4 (0.5%)	

Table 4

Comparison of perioperative outcomes in the two study groups.

Variable	High-risk (n=194)	Normal-risk (n=872)	P-value
Mean Hospital stay (days)	6.77 ± 6.6	6.54 ± 7.6	0.69
Respiratory failure	7 (4%)	41 (5%)	0.70
Pneumonia	9 (5%)	51 (6%)	0.61
Air leak > 5 days	16 (8%)	54 (6%)	0.36
Empyema	1 (0.5%)	3 (0.3%)	0.55
Atrial Fibrillation	25 (13%)	116 (13%)	1.00
Hemorrhage requiring reoperation	2 (1%)	8 (1%)	1.00
Pulmonary Embolism	2 (1%)	3 (0.3%)	0.23
Myocardial Infarction	0	5 (1%)	0.59
Stroke	0	3 (0.3%)	1.00
30 day/hospital mortality	2 (1%)	14 (2%)	0.75

Table 5

Comparison of perioperative outcomes in “high-risk” and “normal-risk” patients undergoing lobectomy. LOS –length of stay.

Variable	“High-risk” lobectomy (n=117)	“Normal-risk” lobectomy (n=665)	P-value
Mean hospital LOS (days)	7.9 ± 7.8	6.6 ± 6.7	0.05
Respiratory failure	7 (6%)	3 (5%)	0.65
Pneumonia	5 (4%)	40 (6%)	0.66
Air leak > 5 days	11 (9%)	45 (7%)	0.33
Empyema	0	2 (0.3%)	1.00
Atrial fibrillation	17 (14%)	95 (14%)	1.00
Hemorrhage requiring reoperation	1 (1%)	6 (1%)	1.00
Pulmonary Embolism	2 (2%)	2 (0.3%)	0.11
Myocardial Infarction	0	4 (0.6%)	1.00
Stroke	0	2 (0.3%)	1.00
30 day/hospital mortality	2 (2%)	12 (2%)	1.00

Table 6

Comparison of perioperative outcomes in “high-risk” and “normal-risk” patients undergoing sublobar resection. LOS –length of stay.

Variable	“High-risk” sublobar (n=72)	“Normal-risk” sublobar (n=112)	P-value
Mean hospital LOS (days)	4.8 ± 3.3	5.7 ± 11.9	0.53
Respiratory failure	0	1 (1%)	1.00
Pneumonia	4 (6%)	5 (5%)	0.74
Air leak > 5 days	5 (7%)	5 (5%)	0.52
Empyema	1 (1%)	1 (1%)	1.00
Atrial fibrillation	8 (11%)	7 (6%)	0.28
Hemorrhage requiring reoperation	1 (1%)	1 (1%)	1.00
Pulmonary Embolism	0	1 (1%)	1.00
Myocardial Infarction	0	0	--
Stroke	0	1 (1%)	1.00
30 day/hospital mortality	0	1 (1%)	1.00