Final Progress Report

Mortality Assessment in Lung Cancer Resection

University of Virginia

July 1, 2009 – June 30, 2014

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1. Structured Abstract:

Purpose: **Specific Aim 1** was to develop a clinically useful method to estimate patient specific survival following lung cancer resection. **Specific Aim 2** was to determine the specific threshold value of hospital volume at which mortality risk is substantially increased following lung cancer resection.

Scope: Lung cancer is the leading cause of cancer death in the United States. Surgical resection remains the optimal therapy for the management of patients with early-stage disease. Determining which patients have the greatest capacity to benefit from surgical therapy requires estimating the combined effects of the patient's severity of disease, age, and comorbid disease on mortality risk.

Methods: **Specific Aim 1** was addressed using data from the Society of Thoracic Surgeons Database. Logistic regression estimated the probability of survival as a function of patient preoperative characteristics. **Specific Aim 2** used the Nationwide Inpatient Sample. Piecewise polynomial functions (spline regression) were used to determine the specific threshold value for the volume of lung cancer resections that substantially increases mortality risk.

Results: (**Aim 1**) There were 18,800 lung cancer resections performed at 111 participating centers. Perioperative mortality was 413/18,800 (2.2%). Composite major morbidity or mortality occurred in 1,612 patients (8.6%). The largest predictors of mortality were procedure type, performance status, renal insufficiency, and induction therapy. (**Aim 2**) In total, 40,460 lung cancer resection patients from 436 hospitals were identified. Models demonstrated excellent performance characteristics (C index = 0.92, Nagelkerke R2 = 0.37). There was no significant relationship between volume and in-hospital mortality using spline regression (P=0.42).

Key Words: Lung cancer, predictive modeling, mortality risk, volume-outcome relationship, hospital performance variation.

Specific Aim 1:

2. Purpose

To develop and validate an efficient and clinically useful statistical model for use in estimating patient specific survival following lung cancer resection.

3. Scope

Lung cancer resection is the best treatment for patients with early-stage lung cancer. The society of Thoracic Surgeons (STS) General Thoracic Database is the most comprehensive and validated clinical database to compare surgical outcomes. Our goal was to create perioperative risk models for lung cancer resection and compare hospital performance.

4. Methods

The STS General Thoracic Database was queried for all patients treated with resection for primary lung cancer between January 1, 2002, and June 30, 2008. Three separate multivariable risk models were constructed (mortality, major morbidity, and composite mortality or major morbidity). Missing values were imputed, and patients missing the mortality outcome were excluded. Hospital performance was compared using Bayesian analyses and standardized incidence ratios.

5. Results

There were 18,800 lung cancer resections performed at 111 participating centers. Perioperative mortality was 413/18,800 (2.2%). Composite major morbidity or mortality occurred in 1,612 patients (8.6%). Predictors of mortality are shown in Table 1. The C index for the mortality model was 0.77.

Table 1: Predictors of Mortality

	Odds Ratio (95% CI)	P value
Pneumonectomy	3.9 (2.5 , 6.2)	< 0.001
Anesthesiology Rating (≥ 3 vs. 1)	3.6 (1.5 , 8.6)	0.004
Zubrod Performance Status	3.1 (1.9 , 4.8)	<0.001
Renal Insufficiency	2.5 (1.4 , 4.3)	0.001
Induction Chemoradiation	2.1 (1.2 , 3.8)	0.01
Steroids	1.9 (1.3 , 2.9)	0.002
Age (10-year increase)	1.8 (1.6 , 2.1)	<0.001
Urgent Procedure Status	1.7 (1.1 , 2.6)	0.01

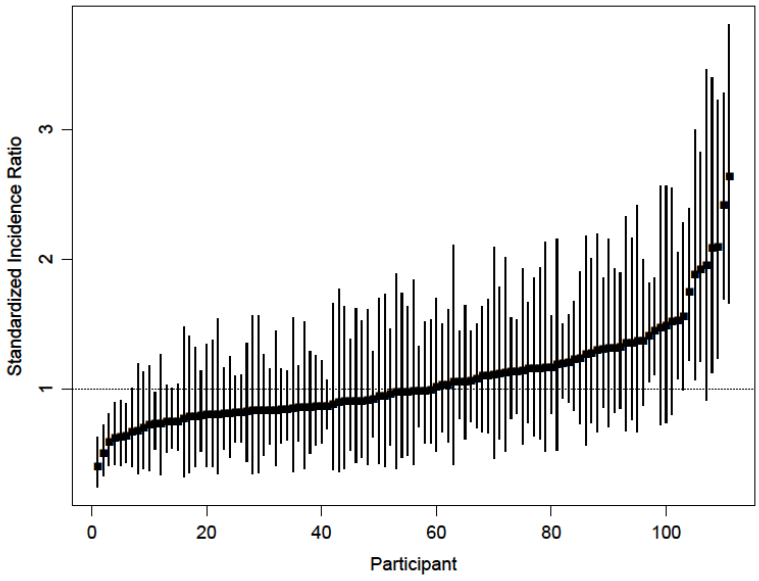
Male Gender	1.4 (1.1 , 1.7)	0.01
Forced Expiratory Volume in 1 second	1.1 (1.0 , 1.2)	<0.001
Body Mass Index	0.7 (0.6 , 0.9)	0.01

Variation in Hospital Performance

To explore variation in hospital performance, the model developed for major morbidity or mortality was subsequently refit as a two-level hierarchical model with nesting of patients within participants. The hierarchical model included the same set of patient factors described above, plus a set of random hospital-specific effects. The hospital-specific effects are interpreted as reflecting underlying differences in performance that systematically increase or decrease risk of all patients at the same hospital. Performance variation was summarized by calculating the hospital-specific standardized incidence ratio (SIR) of mortality or major morbidity. The SIR is defined as the ratio of the participant's risk-adjusted rate divided by the risk-adjusted rate of a hypothetical "average" participant.

A SIR value greater than 1.0 implies that a participant's rate of mortality or major morbidity is higher than the rate that would be projected for an average participant who operated on the same case mix of patients. Uncertainty surrounding the estimated SIR was quantified by calculating Bayesian 95% probability intervals. Figure 1 shows the SIR for the 111 participating centers.

Figure 1: Hospital Performance Variation – Mortality or Major Morbidity



The first study is the largest study to date and uses the Society of Thoracic Surgeons General Thoracic Surgery Database to identify and quantify predictors of mortality and major morbidity following lung resection. These models will help surgeons and patients estimate perioperative risk and provide risk-adjusted outcomes for quality improvement.

The second study demonstrates that the model of composite mortality or major morbidity facilitates a meaningful comparison of quality between hospitals. The majority of the 111 hospitals performed in a similar fashion, but there were significant differences between some of the best and worst performers. This work was presented at the recent Society of Thoracic Surgeons meeting as the J. Maxwell Chamberlain Award Presentation, and the manuscript has been submitted to the Annals of Thoracic Surgery.

Specific Aim 2

2. Purpose

To determine the specific threshold value of hospital volume at which mortality risk is substantially increased following surgical resection.

3. Scope

The volume-outcome relationship has been proposed as a quality measure and was being considered as a metric to guide thoracic surgical procedures to high-volume centers. The methodology behind much of the supporting research for this policy is quite flawed, so we took a very careful look at the data and analyzed the continuous variable and volume using restricted cubic spline regression to account for the linear and non-linear relationships.

4. Methods

Surgical patients for four high-risk procedures were identified from the 2008 Nationwide Inpatient Sample. Hospital volume was measured using three different methods: as a continuous linear function, as a non-linear function using restricted cubic splines, and as the frequently used method of quintile categories. The statistical significance of the relationship between hospital volume and mortality risk was assessed, adjusted for patient age, procedure status, and comorbid disease, and correlated events within hospitals.

5. Results

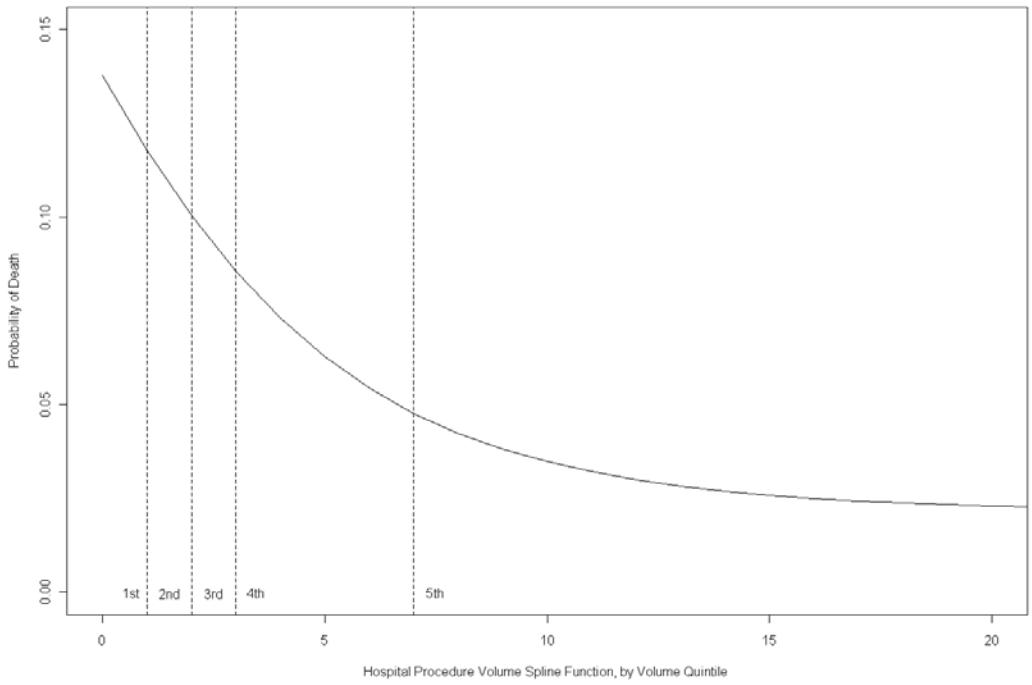
In total, 261,412 surgical patients were identified between esophageal cancer resection, pancreatic cancer resection, abdominal aortic aneurysm repair, and coronary artery bypass grafting. Hospital procedure volume was not a statistically significant predictor of in-hospital mortality for any of the four procedures. Each of the models demonstrated excellent performance characteristics (C index > 0.8, Nagelkerke R2 = 0.16-0.58).

Hospital esophagectomy volume was not associated with mortality for any of the three models (Table 2). Figure 2 displays the functional form of the spline regression for esophageal volume.

Table 2: Tests of Volume Statistical Significance

	Model 1: volume as linear effect		**Model 2: volume as non-linear effect, restricted cubic spline**		**Model 3: volume as non-linear effect, quintiles**	
	Likelihood Ratio test statistic	P value	Likelihood Ratio test statistic	P value	Likelihood Ratio test statistic	P value
Volume (total effect)	0.44	0.51	2.11	0.54	2.44	0.66
	F test statistic	P value	F test statistic	P value	F test statistic	P value
Volume (linear effect)	0.23	0.63	0.91	0.34	n.a.	n.a.
Volume (spline term 1)	n.a.	n.a.	0.15	0.69	n.a.	n.a.
Volume (spline term 2)	n.a.	n.a.	0.12	0.73	n.a.	n.a.
Volume (quintiles)	n.a.	n.a.	n.a.	n.a.	0.66	0.62

Figure 2: The Relationship of Volume to In-hospital Mortality



This work is extrememly important because it does not demonstrate a significant association between hospital esophagectomy volume and mortality. Our work demonstrates that patient factors are much more important in predicting postoperative mortality. This contradicts the majority of previously published work and demonstrates the flaws with previous methodologies. It is an important topic because AHRQ currently uses hospital esophagectomy volume as a quality indicator.

E. Publications

1. Hu Y, McMurry T, Isbell JM, Wells KM, Stukenborg GJ, ***Kozower BD**. Mortality Measures Following Lung Cancer Resection. Ann Thorac Surg. 2014; In Press.
2. McDonnell KK, Bullock FC, Hollen PJ, Heath J, **Kozower BD**. Evidence and emerging issues on the impact of smoking on HRQL in individuals with lung cancer and their families. Clin J Onc Nursing. 2014; 18(2):171-81.
3. Walters DM, McMurry TL, Isbell JM, Stukenborg GJ, **Kozower BD**. Understanding Mortality as a quality indicator after esophagectomy. Ann Thorac Surg. 2014;98(2):506-11.
4. Andritsos MJ, **Kozower BD**, Kennedy JL, Bergin JD, Blank RS. Anesthetic Management of Thoracoscopic Lobectomy in a Patient with Severe Biventricular Dysfunction. J Cardiothorac Vasc Anesth. 2014; In Press.
5. Taylor MD, LaPar DJ, Isbell JM, **Kozower BD**, Lau CL, Jones DR. Marginal pulmonary function should not preclude lobectomy in selected patients with non-small cell lung cancer. J Thorac Cardiovasc Surg. 2014;147(2):738-46.
6. Taylor MD, LaPar DJ, Thomas CJ, Persinger M, Stelow EB, **Kozower BD**, Lau CL, Jones DR. Lymph node ratio predicts recurrence and survival after R0 resection for non-small cell lung cancer. Ann Thorac Surg. 2013;96(4):1163-70.
7. Hu Y, Ezekian B, Wells KM, Burks SG, Jones DR, Lau CL, Schirmer BD, ***Kozower BD**. Long term satisfaction and medication dependence after antireflux surgery. Ann Thorac Surg. 2013;96(4):1246-51.
8. Magee MJ, Wright CD, Fernandez FG, McDonald D, ***Kozower BD**. External validation of the Society of Thoracic Surgeons Database. Ann Thorac Surg. 2013;96(5):1734-9.
9. Hennessy SA, Gillen JR, Hranjec T, **Kozower BD**, Jones DR, Kron IL, Lau CL. Influence of hemodialysis on clinical outcomes after lung transplantation. J Surg Res. 2013;183(2):916-21.
10. Taylor MD, LaPar DJ, Davis JP, Isbell JM, **Kozower BD**, Lau CL, Jones DR. Induction chemoradiotherapy and surgery for esophageal cancer: survival benefit with down staging. Ann Thorac Surg. 2013;96(1):225-30.
11. ***Kozower BD**, Larner JM, Detterbeck FC, Jones DR. Special Treatment Issues in Non-small Cell Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**.** Chest. 2013;143(5 suppl):e369S-e399S.

F. Project-Generated Resources

There are no project-generated resources to be shared.

G. Research Development

Dr. Kozower has dedicated the majority of his final year to working with SEER-Medicare data. This is an extraordinarily complicated dataset, and he has successfully completed three projects, one of which is published and two of which are in press. The majority of his research development has occurred during weekly meetings with his primary mentor, George Stukenborg, PhD, and his biostatistician, Tim McMurry, PhD.

During the past year of his award, Dr. Kozower has improved his biostatistical analysis and data management. He has improved these skills by working on his specific aims and on projects with the STS Database Taskforce.

Dr. Kozower has also been active in University research conferences, including the Research in Progress Seminar, Surgery Journal Club, the Lung Cancer Research Group, and the Department of Public Health Sciences Seminar. He made two formal presentations of his research at annual surgical meetings (STSA – November 2013 and STS – January 2014). Dr. Kozower also completed training in the responsible conduct of research and updated his Human Research Curriculum (CITI) in February 2013. Dr. Kozower has also been nominated and currently serves as the director of the Society of Thoracic Surgeons General Thoracic Surgery Database Taskforce. These efforts have been invaluable for his health services research and for obtaining access to the STS database. Two projects with the Database taskforce were presented at the STS annual meetings (January 2012 and 2013), and he is currently developing a method for public reporting of lung and esophageal cancer resections.

H. Other Activities

Dr. Kozower also has been active in career development activities during the fifth year of his award. He has participated in another course offered through the Leadership in Academic Matters program at the University of Virginia. He also attended the Surgical Outcomes Research Club at the American College of Surgeons Meeting and will attend the American Association for Thoracic Surgery Grant Writing Workshop Program. Dr. Kozower has a clinical practice as a thoracic surgeon (20% effort), which includes both clinical and teaching components. The clinical work of caring for patients and performing thoracic surgery provides the foundation for Dr. Kozower's understanding of lung cancer and helps shape his research interests. His administrative efforts require 5% effort and include Quality Officer for the Division of Cardiothoracic Surgery.

I. Research Development and Other Activities Planned for the Next Year

Dr. Kozower has completed the final year of his K08 award, and his PCORI contract began on July 1, 2014, after his K award ended. The PCORI award is a direct extension of the predictive modeling work performed by Dr. Kozower during his K award and will improve the effectiveness of routine surveillance following lung cancer resection.