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### **Seasonal variation influences outcomes following lung cancer** resections, **\***,\*\*

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#### **Abstract**

**Objective—**The effect of seasonal variation on postoperative outcomes following lung cancer resections is unknown. We hypothesized that postoperative outcomes following surgical resection for lung cancer within the United States would not be impacted by operative season.

**Methods—**From 2002 to 2007, 182 507 isolated lung cancer resections (lobectomy (*n* = 147 937), sublobar resection ( $n = 21$  650), and pneumonectomy ( $n = 13$  916)) were evaluated using the Nationwide Inpatient Sample (NIS) database. Patients were stratified according to operative season: spring (*n* = 47 382), summer (*n* = 46 131), fall (*n* = 45 370) and winter (*n* = 43 624). Multivariate regression models were applied to assess the effect of operative season on adjusted postoperative outcomes.

**Results—**Patient co-morbidities and risk factors were similar despite the operative season. Lobectomy was the most common operation performed: spring (80.0%), summer (81.3%), fall (81.8%), and winter (81.1%). Lung cancer resections were more commonly performed at large, high-volume ( $>75$ th percentile operative volume) centers ( $P < 0.001$ ). Unadjusted mortality was lowest during the spring  $(2.6\%, P < 0.001)$  season compared with summer  $(3.1\%)$ , fall  $(3.0\%)$  and winter  $(3.2\%)$ , while complications were most common in the fall  $(31.7\%, P < 0.001)$ . Hospital length of stay was longest for operations performed in the winter season  $(8.92 \pm 0.11$  days,  $P \lt$ 0.001). Importantly, multivariable logistic regression revealed that operative season was an independent predictor of in-hospital mortality  $(P < 0.001)$  and of postoperative complications  $(P < 0.001)$ 0.001). Risk-adjusted odds of in-hospital mortality were increased for lung cancer resections occurring during all other seasons compared with those occurring in the spring.

**Conclusions—**Outcomes following surgical resection for lung cancer are independently influenced by time of year. Risk-adjusted in-hospital mortality and hospital length of stay were lowest during the spring season.

#### **Keywords**

Season; Lung Cancer; Surgery; Outcomes

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#### **1. Introduction**

The influence of season on patient outcomes has been a focus of many different medical and surgical subspecialties. Seasonal variation has been shown to exert epidemiologic effects on the presentation and treatment of various medical conditions, including coronary artery syndromes [1], pneumonia rates [2], asthma hospitalizations [3], and cancer [4,5]. In addition, the impact of academic season and new hospital trainees on surgical outcomes has been explored within teaching hospitals among a variety of surgical subspecialties [6–9].

Lung cancer remains the leading cause of cancer-related deaths among both men and women within the United States. According to the U.S. Cancer Statistics Working Group, more than 90 000 men and almost 70 000 women die annually from lung cancer, and newly detected lung cancer is discovered in over 107 000 men and 89 000 women [10]. Moreover, outcomes following lung cancer resections have improved over time. Recently, mortality rates for lung cancer resections have been reported to occur in <4.0% of cases within the United States [11], and important risk factors for lung cancer resection patients include: age, male sex, Zubrod score, American Society of Anesthesiologists (ASA) score, diabetes, renal failure, preoperative forced expiratory volume in 1 s  $(FEV_1)$ , and smoking status [12]. However, the independent effect of seasonal variation on postoperative outcomes following lung cancer resections is unknown.

The objective of this study was to examine the effect of operative season on outcomes and resource use among patients undergoing lung cancer resections. We used a large, national administrative database to more completely examine this important question and hypothesized that outcomes following surgical resection for lung cancer within the United States would not be impacted by operative season.

#### **2. Methods**

#### **2.1. Data source**

Due to the absence of patient identifiers and because the data are collected for purposes other than research, this study did not meet the regulatory definition of human subjects research. Thus, the University of Virginia Institutional Review Board (IRB) did not perform a formal review of this study. Data were obtained from the Nationwide Inpatient Sample (NIS) databases for the years 2002–2007. NIS is maintained by the Agency for Healthcare Research and Quality (AHRQ) and is the largest, publicly available all-payer, inpatient care database in the United States. Each year, it records data from 5 to 8 million hospital admissions from approximately 1000 hospitals. The data represent an approximate 20% stratified random sample of all hospital discharges in the United States. NIS includes hospitals designated as 'community hospitals' ('all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions') in the American Hospital Association (AHA) Annual Survey, which includes both public and privately owned centers. Sampling strata used by the NIS are based upon five hospital characteristics (geographic region, urban or rural location, ownership/control, teaching status, and hospital bed size) contained in AHA hospital files. Data include inpatient hospital discharge records collected for patients of all ages and sources of insurance. A discharge weight is provided for each discharge record to represent the relative proportion of the total US inpatient hospital population for each record.

#### **2.2. Patients**

Using International Classification of Diseases-Ninth Revision, Clinical Modifications (ICD-9-CM) procedure and diagnostic codes, we identified all patients in the NIS data set undergoing lung resections (ICD-9-CM codes 323, 3230, 3239, 324, 3241, 3249, 325, 3250,

and 3259) with a primary diagnosis of lung cancer (ICD-9-CM codes 162, 1622, 1623, 1624, 1625, 1628, and 1629). Patients were stratified by operative season into four comparison groups: spring (March–May), summer (June–August), fall (September– November), and winter (December–February). Patient co-morbid disease was assessed using 30 different AHRQ co-morbidity measures and categories developed by Elixhauser et al. [13].

#### **2.3. Hospitals**

Hospital-related details were obtained through data available in the NIS database as well as through the Association of American Medical College's Graduate Medical Education Tracking System. Thoracic surgery teaching hospitals (TSTHs) were identified by linking the AHA identification numbers of all hospitals within the study data set with hospital reports from the Association of American Medical College's Graduate Medical Education Tracking System. Hospital operative volume was calculated from frequency of thoracic resections performed at each hospital and then categorized into quartiles: low [<25th percentile], medium [26–49th percentile], high [50–74th percentile], and very high [>75th percentile]. The rest of the hospital variables reflect those as defined in the NIS database.

#### **2.4. Outcomes measured**

The primary outcomes of interest in this study were adjusted in-hospital mortality, inhospital complications, hospital length of stay, and total costs. In-hospital complications were categorized according to the ICD-9-CM-based coding scheme developed by Guller et al. (Table 1): wound, infections, urinary, pulmonary, gastrointestinal, cardiovascular, and systemic and procedural complications [14]. Death occurring during the inpatient stay, mean hospital length of stay, and total costs were identified from individual discharge records.

#### **2.5. Statistical analysis**

The frequencies of categorical variables are expressed as a percentage of the group of origin. Continuous variables are reported as either means  $\pm$  standard deviation for patient age and total costs or means  $\pm$  standard error for all time-related variables (hospital length of stay). The incidences of preoperative characteristics, hospital variables, and unadjusted outcomes were compared using analysis of variance (ANOVA) for continuous variables and Pearson's χ 2 test for all categorical variables. All group comparisons were unpaired. All reported *P*values are two-tailed with statistical significance set to  $P < 0.05$ . Data analysis was performed using Statistical Package for Social Sciences (SPSS) software, version 17 (SPSS, Chicago, IL, USA).

Multivariable logistic regression analysis was used to estimate the adjusted odds of inhospital death and in-hospital complications among patients undergoing surgical resection for lung cancer. In our statistical methodology, all covariates (patient age, gender, elective operative status, hospital geographic region, thoracic surgery teaching hospital status, type of operation, operative year, operative volume, and categories for co-morbid disease) entered into each model were selected *a priori* based upon established clinical risk or were considered potential confounders for the effect of operative season among lung cancer resection patients. All covariates contributing cases to each estimated outcome, including non-significant variables, were retained in the final models. The estimated odds of inhospital death and in-hospital complications were adjusted for all covariates. All logistic regression models included appropriate adjustments for variance components estimated from the weighted study population. The statistical significance of the association between operative season and in-hospital death or complications was assessed using the Wald  $\chi^2$  test. Confidence intervals (CIs) for all adjusted odds ratios (ORs) were calculated using an alpha of 0.05. The discrimination achieved by these models was assessed using the area under the

receiver operating characteristics curve (AUC). AUC values of 1.0 indicate perfect discrimination between outcome groups, while values of 0.5 indicate results equal to chance. The Hosmer–Lemeshow test was used to assess the statistical significance of differences in each model's calibration across deciles of observed and predicted risk. The results of all logistic regression models are reported as adjusted ORs with a 95% CI.

To validate the estimated effects of each logistic regression model, we performed sensitivity analyses. Specifically, for each model, we assessed the likelihood that the estimated effect of operative season on outcomes could be a spurious result, reflecting the influence of an unmeasured confounder. Using an established sensitivity analysis technique described by Lin et al., each model was re-estimated after removing the most statistically significant covariate as measured by the Wald statistic [15]. With this approach, the likelihood for an originally observed spurious result is reduced, if the observed effect remains statistically significant and is not substantially attenuated after re-estimation.

#### **3. Results**

#### **3.1. Patient and hospital characteristics**

During the 6-year study period, we identified a total of 37 110 discharge records for isolated lung cancer resections, representing a weighted estimate of 182 507 patients nationwide. Frequencies of all patient characteristics stratified by operative season are listed in Table 2. The winter season showed the least percentage of lung cancer resections (23.9%) compared with spring (26.0%), summer (25.3%), and fall (24.9%); however, the relative distribution of operations remained clinically similar, despite season. Mean patient age was comparable between operative season groups, and female gender was the most common among patients undergoing operations in the fall (50.5%). Elective operations occurred in approximately 90% of all resections, despite operative season. Lobectomy was the most common resection performed within all operative seasons: spring (80.0%), summer (81.3%), fall (81.8%), and winter (81.1%). The total number of resections increased by calendar year throughout the study period, while the distribution of resections within a given calendar year was similar between operative seasons. Patient co-morbidities and risk factors were similar despite operative season. The overall frequency of major cardiovascular and pulmonary disease states included: congestive heart failure (4.7%), chronic pulmonary disease (49.3%), hypertension 47.8%), peripheral vascular disorders (5.9%), pulmonary circulatory disease (0.9%), and valve disease (4.2%).

The frequencies of hospital characteristics among all operative season groups are listed in Table 3. The large majority of surgical resections occurred in an urban setting for all patient groups and within large hospital bed size hospitals. Overall, 14.8% of all lung cancer resections were performed at TSTHs, and a higher percentage of these cases were performed in the spring  $(15.6\%)$  and fall  $(15.2\%)$  compared with summer  $(14.1\%)$  and winter  $(14.2\%)$ . *P* < 0.001). The Southern geographic region performed the highest proportion of resections  $(31.8\%, P = 0.001)$  for all seasons. Lung cancer resections were more commonly performed at large, high-volume ( $>75$ th percentile operative volume) centers ( $P < 0.001$ ).

#### **3.2. Unadjusted outcomes**

Unadjusted outcomes by operative season appear in Table 4. Overall, complications were most common in the fall  $(31.7\%, P < 0.001)$  while patients undergoing lung cancer resections in the spring incurred the lowest incidence of wound- (0.7%), infectious (0.4%), genitourinary (1.1%), gastrointestinal (1.2%), and procedure-related (2.5%) complications. Performance of lung cancer resection in the spring and summer seasons conferred the lowest mean hospital length of stay  $(8.79 \pm 0.04$  days and  $8.60 \pm 0.03$  days, respectively) and total

costs (\$54 659  $\pm$  261 and \$54 648  $\pm$  259) among all operative groups. Unadjusted mortality was lowest during spring (2.6%, *P* < 0.001) compared with summer (3.1%), fall (3.0%), and winter (3.2%) seasons.

#### **3.3. Adjusted outcomes for the effect of operative season**

Results of multivariable logistic regression models used to estimate the effect of operative season on postoperative outcomes are shown in Table 5. After adjustment for the concurrent effects of over 40 patient, hospital, and operative factors, operative season was found to be a highly significant, independent predictor of in-hospital mortality ( $P < 0.001$ ). Performance of lung cancer resections in winter (OR = 1.33 (1.22–1.44)), summer (OR = 1.25 (1.15– 1.36)), and fall ( $OR = 1.17 (1.08 - 1.28)$ ) were associated with increased risk-adjusted mortality compared with those occurring in the spring.

Multivariable logistic regression models constructed for in-hospital complications further implicated operative season as an independent predictor of morbidity. Among operative seasons, resections performed in fall were associated with increased odds of postoperative complications (OR =  $1.04$  (1.01–1.07)) compared with spring. In addition, the fall (OR = 1.84 (1.21–2.79)) and winter (OR = 1.71 (1.11–2.62)) seasons incurred increased risk of infections compared with spring.

The statistical performance of each model was further validated. The regression models for in-hospital mortality and complications achieved adequate discrimination with  $AUC = 0.83$ and 0.79, respectively. In addition, each model demonstrated appropriate calibration with Hosmer–Lemeshow *P*-values of <0.05. Upon sensitivity analysis, the effect of operative season on the estimated odds of each outcome were not significantly attenuated  $\left($ <10%) after removing the most significant covariate from each logistic regression model; and all originally observed statistically significant effects remained.

#### **4. Discussion**

To our knowledge, this study represents the largest and most comprehensive review of contemporary outcomes for lung cancer resection as a function of operative season. In this study, we have demonstrated disparate differences in short-term outcomes among operative season groups. The inclusion of a broad, generalizable surgical population allows us to more confidently comment upon trends that have been previously reported among smaller, more specific, surgical patient groups. Our results indicate that outcomes following surgical resection for lung cancer are independently influenced by time of year. Specifically, we have demonstrated that risk adjusted in-hospital mortality was lowest during the spring season. Moreover, our results demonstrate significant differences in resource use across seasons, as patients undergoing lung cancer operations in spring and summer accrued the shortest hospital length of stay and lowest total costs. These findings bolster those of other smaller series that have been performed in select surgical populations, and it extends the examination of timing of operations for lung cancer resections to include a large, nationwide, diverse, surgical population.

The influence of operative season on patient outcomes has garnered attention within surgical literature. Several studies have demonstrated that patients undergoing operations during the winter months have increased morbidity and mortality. Kocer et al. examined prognostic factors for morbidity and mortality among 269 patients undergoing operations for peptic ulcer perforations [16]. After adjustment, operative season was determined to be an independent predictor of morbidity within this cohort, and performance of an operation during the winter conferred significantly increased odds of morbidity ( $OR = 2.239$  (1.056– 4.751), *P* = 0.036). A similar association between season and cardiac surgical outcomes

were observed for a cohort of 16 290 patients undergoing coronary artery bypass grafting (CABG) [17]. For this patient group, performance of CABG during the winter increased the odds of hospital mortality ( $OR = 1.29 (1.01-1.63)$ ,  $P = 0.04$ ) and was associated with the longest mean intensive care unit (ICU) length of stay compared with other operative seasons. Further, in a recently presented abstract at the 17th European Conference on General Thoracic Surgery in 2009, Turna et al. from Turkey suggested a significant effect of operative season on survival following surgical resections for non-small-cell lung carcinoma [18]. Using univariate and multivariate survival analyses, they reported that surgical resections performed in winter conferred reduced survival compared with those performed in the summer in a retrospective, single-institution study of 698 patients (621 men, 57 women). In addition, they suggested a correlate between the presence of a vitamin D receptor polymorphism within surgical patients and improved prognosis. These results are in agreement with the primary outcomes of this study. After adjusting for the potential confounding influence of patient- and hospital-related factors, we found that performance of lung cancer resections in the spring was associated with the lowest odds of in-hospital mortality, while operations performed in winter, summer and fall were associated with a 33%, 25% and 17% increase in the odds of death, respectively. We further demonstrated a seasonal effect on the estimated odds of postoperative complications as well as on overall resource use.

The potential for a 'July Effect' has been postulated as one potential explanation for seasonal variations in patient outcomes during the summer following both medical and surgical hospitalizations. The July Effect describes the effect of new trainees on medical and surgical outcomes at the beginning of an academic calendar year at teaching institutions. Several observational studies have examined the influence of a July effect among various patient populations with mixed results [6–9,19]. In a large, multi-institutional cohort study of 60 000 patients undergoing major surgical operations, Englesbe et al. demonstrated a 41% increase in the risk of mortality for operations performed during July and August [19], and Rich et al. demonstrated the presence of a July effect among patients with internal medicine diagnoses [8]. However, several studies have failed to demonstrate the effect of a July phenomenon on surgical outcomes [7–9], including cardiac surgery operations at teaching hospitals [6]. In our analyses, we attempted to control for the confounding influence of a July effect through the inclusion of thoracic surgery teaching hospital status as an important covariate in each of our predictive models. Even after these adjustments, the effect of operative season was highly associated with patient mortality and morbidity. Furthermore, within our patient cohort, approximately 85% of all patients underwent lung cancer resections at non-thoracic surgery teaching hospitals. As a result, these data suggest that the seasonal effects we observed on risk-adjusted outcomes occur independently despite the influence of thoracic surgical trainees; and any influence of a July effect within this population during the summer is minimal.

The demonstrated effect of operative season on lung cancer resection outcomes in this study is likely multi-factorial in origin and may reflect the influence of certain chronobiologic influences. Several physiologic (blood pressure, serum cholesterol, glucose tolerance, and infection rates), lifestyle (obesity, exercise, and smoking), and environmental (temperature and ultraviolet radiation) risk factors have been associated with seasonal variations in coronary heart disease, which may indirectly influence overall patient condition and perioperative events related to pulmonary resections [20,21]. Neurobiologic phenomena such as activation of the neuroaxial system in response to cold climate has been linked to accelerated inflammatory pathways and enhanced arrhythmia rates in canine models, suggesting a higher propensity for adverse surgical outcomes during the winter months [22]. A higher incidence of depression, seasonal affective disorder, and physical and emotional stress may also contribute to differences in outcomes for patients operated on at different

times of the year. Moreover, seasonal variations in pulmonary-related processes may account for observed trends in lung-cancer-resection patients. Several series have demonstrated the impact of season on asthma exacerbations [3], pneumonia hospitalizations [2], respiratory viral infection clustering [23,24], and the seasonal onset of bronchiolitis obliterans following lung transplant [25]. In the current study, several patient, social, and lifestyle-related factors were accounted for during data analyses: patient obesity, depression, alcohol and drug abuse, and cardiac disease. The relative even distribution of these and other co-morbid disease states across operative seasons implies that the seasonal effect we observed is likely unrelated to underlying patient disease, and suggests the concomitant influence of several environmental stressors, pulmonary specific infections or pathology, or other biophysiologic influences related to seasonal change.

This study has important clinical relevance as it provides an extension of an increasingly reported epidemiologic phenomenon to thoracic oncology and surgical outcomes literature. As our data analyses indicate and as others have shown, the independent influence of season on outcomes following lung cancer resections represents a valid, contemporary trend. To our knowledge, this study represents the largest, and first nationwide description of such an influence within a thoracic oncology patient population. While we recognize the moderate effect size represented in our analyses, we have been careful not to conclude or recommend a delay in patient care for those requiring timely oncologic resections but rather to highlight an often-overlooked risk factor for patient morbidity and mortality following lung cancer resections. Furthermore, to completely address the precise clinical impact of seasonal variation on lung cancer resection outcomes as a rationale for delay in surgery would require a more stringent, prospective evaluation. Thus, our results remain hypothesis generating and provide a legitimate clinical context from which future prospective studies should be derived. Nevertheless, the presented data support the adoption of operative season as an important patient risk factor that should be considered during individual patient risk stratification in the preoperative setting.

Despite our significant results, there are several noteworthy limitations to this study. First, as a retrospective study, inherent selection bias must be considered; however, the likelihood of this bias is reduced due to the strict methodology and randomization of the NIS database. Second, the potential for unrecognized miscoding of diagnostic and procedure codes as well as variations in the nature of coded complications must be considered. However, as the NIS data set is validated both internally and externally for each year, we believe it is reasonable to assume that such data are accurately represented in our analyses. In addition, we are only able to comment on in-hospital, short-term outcomes, which may underestimate true perioperative mortality and morbidity rates that may have occurred following the patient's discharge. With respect to co-morbid disease, we are unable to comment on lung cancer disease stages or severity. In statistical analyses, the possibility of heterogeneity between hospitals was not considered, which could have been taken into account using randomeffects logistic regression modeling. We believe, however, that the effect of such an unmeasured influence would result in a small overall impact on the observed results as suggested by the performed sensitivity analysis. Furthermore, due to the constraints of NIS data points, we are unable to include adjustments for other well-established surgical risk factors such as low preoperative albumin levels, poor nutrition, or preoperative performance status measures such as the Zubrod score. However, our statistical models proved resilient to the presence of a potentially unmeasured confounder.

#### **5. Conclusion**

In this study, we conclude that risk-adjusted patient morbidity and mortality following surgical resection for lung cancer is independently influenced by operative season.

Performance of lung cancer resections in the spring confers the lowest risk of mortality. Spring and summer operations accrue the shortest hospital lengths of stay and lowest total costs. These differences should be considered during patient risk stratification and may serve as a proxy for important chronobiologic events that may be targeted to improve thoracic surgical outcomes.

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#### **References**

- 1. Ornato JP, Peberdy MA, Chandra NC, Bush DE. Seasonal pattern of acute myocardial infarction in the National Registry of Myocardial Infarction. J Am Coll Cardiol. 1996; 28(7):1684–8. [PubMed: 8962552]
- 2. Lin HC, Lin CC, Chen CS, Lin HC. Seasonality of pneumonia admissions and its association with climate: an eight-year nationwide population-based study. Chronobiol Int. 2009; 26(8):1647–59. [PubMed: 20030547]
- 3. Chen CH, Xirasagar S, Lin HC. Seasonality in adult asthma admissions, air pollutant levels, and climate: a population-based study. J Asthma. 2006; 43(4):287–92. [PubMed: 16809242]
- 4. Oh EY, Wood PA, Du-Quiton J, Hrushesky WJ. Seasonal modulation of post-resection breast cancer metastasis. Breast Cancer Res Treat. 2008; 111(2):219–28. [PubMed: 17934872]
- 5. Tang D, Santella RM, Blackwood AM, Young TL, Mayer J, Jaretzki A, Grantham S, Tsai WY, Perera FP. A molecular epidemiological case-control study of lung cancer. Cancer Epidemiol Biomarkers Prev. 1995; 4(4):341–6. [PubMed: 7655328]
- 6. Bakaeen FG, Huh J, Lemaire SA, Coselli JS, Sansgiry S, Atluri PV, Chu D. The July effect: impact of the beginning of the academic cycle on cardiac surgical outcomes in a cohort of 70,616 patients. Ann Thorac Surg. 2009; 88(1):70–5. [PubMed: 19559195]
- 7. Englesbe MJ, Fan Z, Baser O, Birkmeyer JD. Mortality in medicare patients undergoing surgery in July in teaching hospitals. Ann Surg. 2009; 249(6):871–6. [PubMed: 19474693]
- 8. Rich EC, Hillson SD, Dowd B, Morris N. Specialty differences in the 'July Phenomenon' for Twin Cities teaching hospitals. Med Care. 1993; 31(1):73–83. [PubMed: 8417272]
- 9. Schroeppel TJ, Fischer PE, Magnotti LJ, Croce MA, Fabian TC. The July phenomenon: is trauma the exception? J Am Coll Surg. 2009; 209(3):378–84. [PubMed: 19717044]
- 10. U.S. Cancer Statistics Working Group. United States cancer statistics: 1999–2005 incidence and mortaltiy web-based report. Department of Health and Human Services, Center for Disease Control; 2005.
- 11. Meguid RA, Brooke BS, Chang DC, Sherwood JT, Brock MV, Yang SC. Are surgical outcomes for lung cancer resections improved at teaching hospitals? Ann Thorac Surg. 2008; 85(3):1015–24. [discussion 24–5]. [PubMed: 18291190]
- 12. Wright CD, Gaissert HA, Grab JD, O'Brien SM, Peterson ED, Allen MS. 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(6):1857–65. [discussion 65]. [PubMed: 18498784]
- 13. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998; 36(1):8–27. [PubMed: 9431328]
- 14. Guller U, Hervey S, Purves H, Muhlbaier LH, Peterson ED, Eubanks S, Pietrobon R. Laparoscopic versus open appendectomy: outcomes comparison based on a large administrative database. Ann Surg. 2004; 239(1):43–52. [PubMed: 14685099]
- 15. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics. 1998; 54(3):948–63. [PubMed: 9750244]

- 16. Kocer B, Surmeli S, Solak C, Unal B, Bozkurt B, Yildirim O, Dolapci M, Cengiz O. Factors affecting mortality and morbidity in patients with peptic ulcer perforation. J Gastroenterol Hepatol. 2007; 22(4):565–70. [PubMed: 17376052]
- 17. Shuhaiber JH, Goldsmith K, Nashef SA. The influence of seasonal variation on cardiac surgery: a time-related clinical outcome predictor. J Thorac Cardiovasc Surg. 2008; 136(4):894–9. [PubMed: 18954627]
- 18. Turna A, Pekcolaklar A, Metin M, Yaylim I, Gurses A. The effect of season of operation on the survival of resected patients with non-small cell lung cancer. Interact CardioVasc Thorac Surg. 2009; 9(Suppl):S5–6.
- 19. Englesbe MJ, Pelletier SJ, Magee JC, Gauger P, Schifftner T, Henderson WG, Khuri SF, Campbell DA. Seasonal variation in surgical outcomes as measured by the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP). Ann Surg. 2007; 246(3):456–62. [discussion 63–5]. [PubMed: 17717449]
- 20. Fischer T, Lundbye-Christensen S, Johnsen SP, Schonheyder HC, Sorensen HT. Secular trends and seasonality in first-time hospitalization for acute myocardial infarction–a Danish population-based study. Int J Cardiol. 2004; 97(3):425–31. [PubMed: 15561329]
- 21. Pell JP, Cobbe SM. Seasonal variations in coronary heart disease. Q J Med. 1999; 92(12):689–96.
- 22. Scherlag BJ, Patterson E, Lazzara R. Seasonal variation in sudden cardiac death after experimental myocardial infarction. J Electrocardiol. 1990; 23(3):223–30. [PubMed: 2384728]
- 23. Gottlieb J, Schulz TF, Welte T, Fuehner T, Dierich M, Simon AR, Engelmann I. Communityacquired respiratory viral infections in lung transplant recipients: a single season cohort study. Transplantation. 2009; 87(10):1530–7. [PubMed: 19461490]
- 24. Nicolas RT, Hills C, Moller JH, Huddleston CB, Johnson MC. Early outcome after Glenn shunt and Fontan palliation and the impact of operation during viral respiratory season: analysis of a 19 year multi-institutional experience. Ann Thorac Surg. 2005; 79(2):613–7. [discussion 17]. [PubMed: 15680845]
- 25. Hohlfeld J, Niedermeyer J, Hamm H, Schafers HJ, Wagner TO, Fabel H. Seasonal onset of bronchiolitis obliterans syndrome in lung transplant recipients. J Heart Lung Transplant. 1996; 15(9):888–94. [PubMed: 8889984]

#### **Appendix A. Conference discussion**

*Dr T. Grodzki* (*Szczecin, Poland*): I don't remember a bigger analysis than this, and it is extremely important, but I think we should keep it a secret, because otherwise you will have a flood of patients who want to be operated on in April and May because they know that the best outcome is expected in spring.

I would like to ask a question, because there was a discussion in the Journal of Thoracic and Cardiovascular Surgery, for example, about the length of postoperative chest drainage due to the season, I mean, the location of the center, the average pressure in the area, et cetera. I presume you didn't go so deeply. You just analyzed the raw data. Altogether you presented very good facts, but despite a possible explanation, in my opinion it is kind of a mystery. Can you comment on that?

*Dr LaPar*: I am sorry, I missed the last part of your question.

*Dr Grodzki*: Nevertheless, despite your explanation, it is still a little bit mysterious, these spring favorable results.

*Dr LaPar*: What we did in our study was to identify the operative season as an independent risk factor for compromised patient outcomes following lung cancer resection. I agree with you that although we were able through our modeling to control for several independent known risk factors, there still may be something else explaining the observed influence of operative season.

Although the sensitivity analyses of our models reassured us that the effect of season was a valid, independent predictor of patient outcomes, I believe that it is probable that the concomitant influence of many different variables may explain our results. Unfortunately in our modeling efforts we weren't able to include interactions between every single different covariate entered, because that would probably get us into some problems with multiple hypothesis testing.

Overall, we believe that prospective studies may help to better explain this complex phenomenon, but, more importantly, we believe our results demonstrate verifiably that the effect of operative season on outcomes is real and that it should be considered during individual patient risk stratification.

*Dr F. Detterbeck* (*New Haven, CT*): I have a question along those lines. How sure are you that this is a real finding? If you look at enough different factors, you will find factors that by chance will play out, and as I was listening to the presentation it seemed the length of stay was decreased in the summer, the operative mortality was decreased in the spring, the complication rate was increased in the fall, and so there are different factors, and it makes me wonder if some of these fell out by chance. And so one of the thoughts I had was did you look within a region, for example? Is this consistent within each region of the country? If you postulate, for example, that weather has something to do with it and ambient temperature, well, that is something that might come out differently in different regions.

And then the other question I have is, there have been a few other studies that have looked at outcomes in relation to seasonal variation, and is this consistent or inconsistent with other studies?

*Dr LaPar*: Certainly. We are confident that the effect of seasonal variation has tremendous influence on patient outcomes. We did not perform any additional subset analyses in terms of region and so forth, simply because, as you mentioned, the more tests that you do the more likely you are to run into something being significant by chance. When we set out to design this study, we identified our primary outcomes at the beginning. We predefined these outcomes and the predictive models for each outcome to avoid the possibility of the multiple hypothesis testing that you are referring to. We did attempt to control as best we could for region by including it as an important covariate, and I know that within the literature there are some studies that have shown similar seasonal influences, for example, in California, in cardiac surgery outcomes.

*Dr Detterbeck*: Do they affect them in the same way? Is it the same time of year that you see changes?

*Dr LaPar*: Interestingly, there have been some studies that have shown that seasonal variations occur even within temperate climates, or regions that have consistent climates.

International classification of diseases-ninth revision, clinical modifications (ICD-9-CM) diagnostic codes for in-hospital complications.



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- Postoperative shock (septic, hypovolemic): 998.0
- Postoperative fever: 998.89
- *Complications during procedure*
- Accidental puncture or laceration, complicating surgery: 998.2
- Foreign body accidentally left during procedure: 998.4
- Bleeding complicating procedure: 998.11

Patient characteristics for all patients undergoing lung cancer resection operations by season.



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 $a<sup>a</sup>$ Means  $\pm$  standard deviation, rheumatoid arthritis (RA).

Hospital characteristics for all patients undergoing lung cancer resection operations.



Primary unadjusted outcomes for all patients undergoing lung cancer resection operations. Primary unadjusted outcomes for all patients undergoing lung cancer resection operations.



Adjusted odds ratios for the effect of season on postoperative outcomes among patients undergoing lung cancer resection. Adjusted odds ratios for the effect of season on postoperative outcomes among patients undergoing lung cancer resection.



AUC: area under receiver operator curve. Results reflect adjusted odds ratio [95% confidence interval]. Reference group: Hospital category (non-thoracic hospital), season (spring), operative volume (very<br>high, >75th percen AUC: area under receiver operator curve. Results reflect adjusted odds ratio [95% confidence interval]. Reference group: Hospital category (non-thoracic hospital), season (spring), operative volume (very high, >75th percentile), hospital region (South), year (2002), operation (lobectomy). Covariates: age, gender, elective operative status, year, hospital category, hospital region, operative volume, operation, patient co-morbidities. patient co-morbidities.

*\* P* < 0.05.