Predicting Lung Cancer Prior to Surgical Resection in Patients with Lung Nodules

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Background: Existing predictive models for lung cancer focus on improving screening or referral for biopsy in general medical populations. A predictive model calibrated for use during preoperative evaluation of suspicious lung lesions is needed to reduce unnecessary operations for a benign disease. A clinical prediction model (Thoracic Research Evaluation And Treatment [TREAT]) is proposed for this purpose.

Methods: We developed and internally validated a clinical prediction model for lung cancer in a prospective cohort evaluated at our institution. Best statistical practices were used to construct, evaluate, and validate the logistic regression model in the presence of missing covariate data using bootstrap and optimism corrected techniques. The TREAT model was externally validated in a retrospectively collected Veteran Affairs population. The discrimination and calibration of the model was estimated and compared with the Mayo Clinic model in both the populations.

Results: The TREAT model was developed in 492 patients from Vanderbilt whose lung cancer prevalence was 72% and validated among 226 Veteran Affairs patients with a lung cancer prevalence of 93%. In the development cohort, the area under the receiver operating curve (AUC) and Brier score were 0.87 (95% confidence interval [CI], 0.83–0.92) and 0.12, respectively compared with the AUC 0.89 (95% CI, 0.79–0.98) and Brier score 0.13 in the validation dataset. The TREAT model had significantly higher accuracy ($p < 0.001$) and better calibration than the Mayo Clinic model (AUC = 0.80; 95% CI, 75–85; Brier score = 0.17).

Conclusion: The validated TREAT model had better diagnostic accuracy than the Mayo Clinic model in preoperative assessment of suspicious lung lesions in a population being evaluated for lung resection.

Key Words: Lung cancer, Diagnosis, Prediction models.

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Lung cancer is the leading cause of cancer-related mortality in the United States,[1,2] but early detection and treatment prolongs life. The National Lung Screening Trial found a 20% reduction in lung cancer mortality in high-risk patients screened with low-dose computed tomography (CT). Implementation of a screening regimen for lung cancer among the estimated 7.4 million eligible Americans[3] will greatly increase the number of lung nodules requiring evaluation and diagnosis. In addition, 39% of the patients screened with low-dose CT had at least one positive scan requiring additional diagnostic evaluations.[4] A diagnostic operation after nodule discovery and radiographic surveillance resulted in a benign diagnosis in 24% of the surgical procedures. Other studies describing resection for known or suspected lung cancer report benign disease rates as high as 40%.[5–9]

Existing lung cancer prediction models are designed to either determine which high-risk populations would most benefit from screening[10–13]; or estimate the likelihood of cancer, once a lesion is discovered.[14–16] Current guidelines from the American College of Chest Physicians recommend that clinicians use a validated prediction model, such as the model developed in the Mayo Clinic, or their clinical expertise to estimate the probability of cancer in a suspicious lung lesion.[17] The Mayo Clinic model contains six variables (age, smoking history, previous cancer, lesion size, spiculated edge, and location) and was designed to evaluate nodules in patients selected from a general population who had a lesion found on imaging. Our previous work demonstrated that the Mayo Clinic model has poor calibration in patients referred for surgical evaluation.[18] Currently, no models exist to estimate the lesion's probability of malignancy at the point of surgical evaluation.

Patients evaluated by surgeons usually have a significant body of diagnostic information compiled from previous medical specialists such as multiple radiographic scans, biopsy results, and pulmonary function. Surgeons need an accurate and well calibrated predictive model to help diagnose a

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suspected lung cancer without missing early stage disease; no models exist which integrate this additional information.[19] We developed and validated the Thoracic Research Evaluation And Treatment (TREAT) lung cancer prediction model and compared the performance of the TREAT model to the Mayo Clinic model in two populations being evaluated for lung resection.

METHODS

Study Population

The TREAT model was developed in the Vanderbilt University Medical Center (VUMC) Lung Cancer Cohort and to examine the generalizability of the TREAT model, it was validated in the Tennessee Valley Veterans Affairs (VA) cohort. The Vanderbilt cohort was composed of patients identified from two separate sources. Using VUMC's Thoracic Surgery Quality Improvement database and clinic records, 606 patients were identified who received an evaluation of a lung nodule or mass by a thoracic surgeon for known or suspected non–small-cell lung cancer from January, 2005 to October, 2010 (Fig. 1). Demographic and clinical data for each procedure were abstracted using the Society of Thoracic Surgeons National Database for General Thoracic Surgery specifications and guidelines.[20] Imaging data were abstracted from radiologist reports or from original scans of the most recent preoperative CT scans for lesion growth, edge characteristics, and F18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) avidity by experienced medical reviewers.[5,18,21,22] Lesion edge characteristics defined by the terms smooth, lobulated, lobular, lobed, irregular, ground glass opacity, ground glass nodule, spiky, or spiculated in the radiologists' reports were designated by medical reviewers as either smooth, lobulated, ground glass opacity, spiculated, or indeterminate. The growth on serial radiographs occurring at least 60 days apart is defined as an increase in the mean diameter of 2 mm for nodules initially less than 15 mm in size and an increase of at least 15% compared with a baseline scan for lesions more than 15 mm in size at baseline.[23] For cases with one preoperative radiograph or whose subsequent radiograph was fewer than 60 days and deemed too short a time span to record lesion growth, the case was designated as "insufficient data." FDG-PET avidity was determined by either physician report or by maximum standard uptake value (SUV). Not avid was coded if the radiologist report used the terminology: not avid, not cancerous, low avidity, not likely cancerous or reported a SUV less than 2.5. Avidity was coded if the radiologist used the terminology: avid, likely cancerous, highly avid, cancerous or reported a SUV of 2.5 or greater. Any radiological reports of insufficient quality to determine diagnosis, shape characteristics, or FDG-PET avidity by chart review were reviewed for determination by a thoracic surgeon. If no designation could be made, then the original scans were reviewed by a thoracic radiologist blinded to clinical pretest data and pathological outcome. Diagnosis was confirmed by the pathologic examination after thoracotomy, thoracoscopy, mediastinoscopy, bronchoscopy with biopsy (N = 523) or by radiographic surveillance among patients not undergoing a procedural biopsy (N = 83). Preoperative symptoms were defined as any documented evidence in the medical record of the following: hemoptysis, shortness of breath, unplanned weight loss, fatigue, pain, or pneumonia. Preoperative predicted forced expiratory volume in 1 second (FEV_1) was a continuous variable based on the most recent pulmonary function test prior to their thoracic operation.

Individuals with multiple nodules or who had the evidence for benign diseases (e.g., benign calcification, infiltrates, bronchiolitis obliterans organizing pneumonia, or empyema) were excluded (N = 39). Also, individuals receiving an operation for a known malignancy after initial chemo-radiation therapy (N = 13), who had no preoperative radiographic

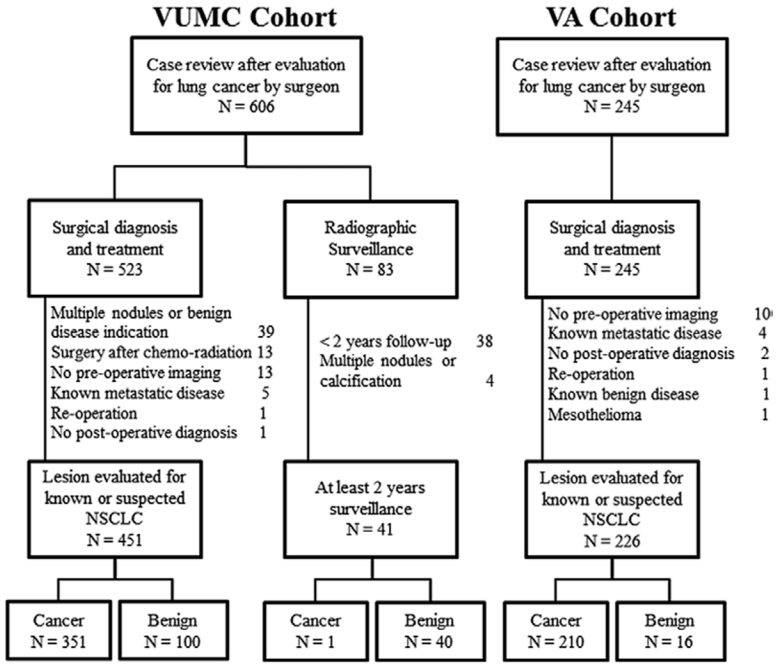

FIGURE 1. Consort diagram of VUMC and Tennessee Valley Healthcare System VA cohort. VUMC, Vanderbilt University Medical Center cohort; VA, Veteran Affairs; NSCLC, non–small-cell lung cancer.