Pathologic Nodal Upstaging Predictive Models for CT-based Clinical Node Negative Non-Small Cell Lung Cancer

Running head: Predicting cN0 NSCLC Upstaging

*Weelic Chong, MD-PhD candidate, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, 19107, USA; Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA 19107

wxc026@jefferson.edu

*Yang Hai, M.D. Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, 19107, USA

yxh019@jefferson.edu

Jian Zhou, M.D. Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, 610041, China

jianzhouscu@foxmail.com

Lun-xu Liu, Ph.D., M.D., FRCS. Department of Thoracic Surgery, West China Hospital, Western China Collaborative Innovation Center for Early Diagnosis and Multidisciplinary Therapy of Lung Cancer, Sichuan University, Chengdu 610041, China; Sichuan University, Chengdu, 610041, China

Lunxu_liu@outlook.com

*Weelic Chong and Yang Hai contribute equally to this study

Corresponding author: Weelic Chong

Address: 1025 Walnut Street, Rm727, Philadelphia, PA, 19107, USA

E-mail: wxc026@jefferson.edu
Author contributions: WC performed analysis and did primary writing of the abstract and manuscript. YH conducted initial study design, data collection and supervised study design, analysis, writing and editing of the manuscript. LL and JZ contributed to database creation and patient recruitment.

Abstract word count: 198 words

Manuscript word count: 2388 words
Abstract

Background: Accurate clinical nodal staging of non-small cell lung cancer (NSCLC) is essential for surgical management. Some clinical node negative cases diagnosed preoperatively by CT were later staged as pathological N1 (pN1) or pN2. Our study aimed to evaluate factors related to pathological nodal upstaging and develop statistical models for predicting upstaging.

Methods: We retrospectively reviewed 1,735 patients with clinical node negative NSCLC from 2011 to 2016 in the West China Lung Cancer database. Demographic and clinical data were analyzed via univariate and multivariate approaches. Predictive models were developed on a training set and validated with independent datasets.

Results: 171 (9.9%) clinical node negative patients have pathologic nodal upstaging to pN1. 191(11.0%) patients were upstaged to p(N1+N2). 91(5.2%) patients have pSN2 pathologic nodal upstaging. Preoperative factors were used to establish 3 statistical models for predicting pathological nodal upstaging. The area under the receiver operator characteristic (AUC) were 0.815, 0.768, and 0.726, for pN1, p(N1+N2) and pSN2 respectively.

Conclusion: Our models may help evaluate the possibility of nodal upstaging for clinical node negative NSCLC and enable surgeons to form appropriate plans preoperatively. External validation in a prospective multi-site study is needed before adoption into clinical practice.

Key Words: Non-small Cell Lung Cancer; Clinical Node Negative; Lymph Node; Upstaging; Diagnosis; Predictive Models
Introduction

Surgical resection is the primary and preferred treatment for suspected or confirmed Stage I and Stage II resectable non-small cell lung cancer (NSCLC) (1). Accurate Tumor Node Metastasis (TNM) staging is important for outcomes and treatment strategies (2). For example, N status is an important factor when surgeons make decisions on surgical methods, such as video-assisted thoracoscopic surgery (VATS) versus open thoracotomy or lobar versus limited resection, or stereotactic body radiotherapy (SBRT) for older patients (3–6). Meanwhile, studies have shown that neoadjuvant therapy improves the prognosis of patients with N2 stage IIIA disease (7,8).

To obtain more reliable clinical staging, there is an evolving array of procedures, each with distinct strengths – integrated positron emission tomography computed tomography (PET-CT), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), esophageal ultrasound-guided fine-needle aspiration (EUS-FNA), and mediastinoscopy (9–14). The use of more specific testing needs to be balanced with the additional financial cost to the patient and the cost in terms of time that further testing takes away from treatment (definitive surgery). Thus, there is potential value in using upstaging prediction models based on easily obtainable clinical parameters.

Despite the importance of N staging in NSCLC, clinical and pathological nodal staging is discordant in a small proportion of patients (15–19). In a prospective trial, the discordance between clinical and pathological staging was investigated by PET/CT (20). Unsuspected N2 disease was found in 9% of patients who were clinically staged I, and 26% of patients clinically staged II. In centers that only routinely conduct low-dose CT, rates of unsuspected pathological upstaging may be higher.

Many prior models of NSCLC nodal upstaging utilize a mix of peri-operative and pre-operative data (16,19,21–23). In the operating room, it is not ideal for surgeons to wait for the peri-operative histology, use that data as input in a model, calculate the risk likelihood, and then make a snap decision in the operating room while performing critical procedures. Thus, models that utilize only pre-operative (without considering peri-operative variables such as the degree of tumor differentiation) is more useful to surgeons (Personal Communication, open peer review of other works(18)).

Thus, we only used clinical factors, and only selected clinical N0 NSCLC patient records for creating...
and validating our pathological upstaging models. We created 3 different statistical models for estimating
the probability of nodal upstaging to pN1, p(N1+N2), and SN2 respectively.

Material and Methods

Patient population

A total of 4,336 patients who underwent surgical resection for primary lung cancer at West China Hospital,
Sichuan University from January 2011 to December 2016 were reviewed retrospectively. All data were
retrieved from Western China Lung Cancer database (WCLC). All patients were >18 years old with
pathologically confirmed NSCLC after surgery. The eligibility criteria were: 1) clinical N0 NSCLC; 2)
lobectomy or sublobar resection without microscopic residual tumor; 3) systematic lymph node dissection;
4) no previous history of other malignancies or received neoadjuvant chemotherapy or radiotherapy. 2,086
patients with cN0 NSCLC met our criteria above. We excluded patients with incomplete
clinicopathological data, had no detailed records of preoperative examination, or had received
chemotherapy/radiotherapy prior to surgery. Finally, 1,735 records were included for this study.

Preoperative Evaluation

Preoperative assessment included physical examination, routine blood work, chest X-ray and computed
tomography (CT), abdominal CT, brain magnetic resonance imaging (MRI), bone scintigraphy and/or
bronchoscopy as necessary. CT was performed in all patients and interpreted independently by one
radiologist and one surgeon. Surgery was conducted 1 to 2 weeks after CT was performed. Pre-operative
clinical lung cancer staging was based on the 8th edition of TNM classification(25), with the modification
that staging based on ground-glass opacity, i.e. staging as tumor in-situ or T1mi, was not conducted.
Positive clinical nodal stage was defined by size >=1cm, or greater in the short-axis dimension. A central
tumor was defined by a tumor visible by bronchoscopy while a peripheral tumor was defined by not
visiblex. PET-CT is expensive and not covered by public medical insurance in China, so patients
underwent PET-CT only if they are willing to afford the scan out-of-pocket.

Pathology Evaluation
In the hospital, we routinely conduct an intraoperative frozen section (FS) to get an initial impression of the tumor and the lymph nodes. The intraoperative pathological findings were in the raw data, but not used for the univariate analysis or the predictive models.

Confirmatory postoperative histological classification was made with reference to the latest WHO guideline(24). The distribution of the positive nodes were based on final pathology reports of post-operative pathological nodal staging, as follows: (1) pN0 group; (2) pN1 (involving only N1 lymph nodes); (2) p(N1+N2) group (involving both N1 and N2 lymph nodes); and (3) pSN2 (skip nodal metastasis, in which there is direct metastasis to N2 station with no involvement of N1 lymph nodes).

**Statistical Analysis**

Statistical analysis was performed using SPSS (Version 26.0, Chicago, IL, USA) and R 3.6.0 software (Institute for Statistics and Mathematics; www.r-project.org). Based on patient pathological nodal status, data was separated into 4 groups: pN0, pN1, p(N1+N2), and pSN2. Univariate analysis was conducted to identify clinicopathological characteristics that differ between the pN0 group and the upstaged groups. For univariate analysis of categorical variables, Fisher’s exact test (for N < 30) or χ²-test (for all other N) were used, while Student’s t-test was used for continuous variables. All P values were two-tailed with <0.05 considered to be statistically significant. For variable selection, a correlation matrix was created to visualize potential statistically significant differences. The identified independent variables were further manually selected for logistic regression. Before logistic regression was performed, the dataset was split into a training dataset and a test dataset in a 80:20 ratio. The training dataset was used for creating the logistic regression. The model was then tested in the testing dataset. Due to the unbalanced nature of the datasets (i.e. nodal upstaging is rare), accuracy was not used for determining the cut-off for the model. Instead, the optimal cut-off for the regression model was calculated using a cost function(26). For pN1 and p(N1+N2), the cost of a false negative (FN) was set to 100 and the cost of a false positive (FP) was set to 200. For pSN2, FN was set to 100 and FP was set to 600. The concordance between predicted and actually observed probabilities was examined with a confusion matrix. Nomograms for each model was created with rms 5.1 package in R(27). Area under the receiver operating characteristic curve (AUROC) analysis
was performed to evaluate the discriminative capability of the model with pROC 1.16.1 (28). An exploratory validation using an external data set was also performed(18). Detailed statistical analyses are found in the supplementary text.

Results

Patient Characteristics

A total of 1,735 patients were enrolled, with 948(54.6%) males and 788(45.4%) females. The average age and standard deviation were 58.6 and 9.9, respectively. In our study, 1,053(60.7%) patients never smoked, 277(16.0%) patients had less than 30 pack-years, and 405(23.3%) patients had 30 or more pack-years. According to preoperative CT, 569(32.9%) tumors were located in the right upper lobe(RUL), 188(10.8%) tumors were in the right middle lobe(RML), and 299(17.2%) tumors were in the right lower lobe(RLL); 384(22.1%) tumors were in the left upper lobe(LUL), and 295(17.0%) tumors were in the left lower lobe(LLL). Centrally located tumors were found in 374(21.6%) cases by bronchoscopy. For clinical T stage based on CT findings, there were 107(6.2%) cases with T1a, 298(17.2%) cases with T1b, 222(12.8%) cases with T1c, 765(44.1%) cases with T2a, 177(10.2%) cases with T2b, 155(8.9%) cases with T3, and 11(0.6%) cases with T4. Visceral pleural involvement was found in 819(47.2%) cases, and tumors with solid components were identified in 1,284(74.1%) cases while pure ground-glass opacity (GGO) were found in 451(25.9%) cases. Video-assisted thoracic surgery (VATS) was performed in 1,300(75.0%) patients compared with thoracotomy in 435(25.0%) patients. Specimens were histologically proven to be lung adenocarcinoma in 1,345(77.5%) patients, squamous cell carcinoma in 345(19.9%) patients, or other NSCLC subtypes in 45(2.6%). As for the degree of differentiation, 22(1.3%) cases were well, 94(5.4%) cases were well-moderate, 1,135(65.4%) cases were moderate, 330(19.0%) were moderate-poor, and 154(8.9%) cases had poor differentiation. Details are presented in Table 1.

Postoperative nodal status among patients with cN0 NSCLC

453(26.1%) cases were found to have positive nodes based on final pathology reports. 1282 patients (73.9%) were node negative. Of the 1735 cN0 cases, the rate of upstaging to pN1, p(N1+N2), and SN2
were 9.8%, 11.0%, and 5.2%. Out of the nodal upstaging cases, 171 (37.7%), 191 (41.2%), and 91 (20.1%) cases were diagnosed as pN1, p(N1+N2), and SN2, respectively.

Risk Factors Predicting Nodal Upstaging to pN1

For the pN1 group, univariate analysis identified the following factors as significant predictors: male sex (P<0.001), smoking history (pack-years >=30) (P<0.001), tumor located in LLL (P<0.001), centrally located tumor (P<0.001), clinical T staging based on CT (P<0.001), visceral pleural involvement (P<0.001) and consolidation with solid component (P<0.001) as significant risk factors in univariate analysis (Table 2). Multivariate logistic regression identified male sex (odds ratio[OR], 1.83; P<0.01), tumor located in LLL (OR, 2.02; P=0.003), centrally located tumor (OR, 2.35; P<0.001), visceral pleural involvement (OR, 3.28; P<0.001), tumor with solid component (OR, 3.89; P<0.001) and tumor size (OR, 1.40; P<0.001) to be statistically significant (Table 4).

Risk Factors Predicting Nodal Upstaging to p(N1+N2)

For the p(N1+N2) group, centrally located tumor (P<0.001), clinical T staging (P<0.001), visceral pleural involvement (P<0.001), tumors greater than 2.0 cm (P<0.001), and consolidation with solid component (P<0.001) as significant risk factors in univariate analysis (Table 3). Multivariate logistic regression identified tumor size (OR, 1.34; P<0.001), visceral pleural involvement (OR, 2.78; P<0.001) and consolidation with solid component (OR, 5.38; P<0.001) to be statistically significant (Table 4).

Risk Factors Predicting Nodal Upstaging to SN2

For the SN2 group, univariate analysis showed RUL-located tumors (P=0.041), clinical T stage (P<0.001), visceral pleural involvement (P<0.001), consolidation with solid component (P<0.001) as significant risk factors (Table 3). We also found tumors greater than 2.0 cm was a predictive risk factor (P<0.001). Using multivariate analysis, the following 4 factors were found with statistical significance: tumor located in RUL (OR, 1.64; P=0.048), tumor size>2.0cm (OR, 2.77; P<0.001), visceral pleural involvement (OR, 2.71; P<0.001) and consolidation with solid component (OR, 2.71; P=0.005) (Table 4).
Predictive models and validation

We identified pre-operative variables that were significant in the univariate test and in the correlation matrix (Figs 1a, 2a, 3a). From these, we only selected relevant pre-operative variables. We performed logistic regression on the selected variables and the binary nodal upstaging outcome to obtain three regression models: pN1 (Fig 1), p(N1+N2) (Fig 2), and pSN2 (Fig 3). The formulas are presented in Table 5. Internal validation was performed with the validation set, with similar performance obtained from the training and validation sets (Fig 1b, 2b, 3b). The cut-off was selected using a cost function that includes the cost of a false negative (i.e. patient with unsuspected upstaging), and the cost of a false positive (i.e. patient that has no upstaging, falsely predicted to have upstaging) (Figs 1c, 2c, 3c). The models’ predictions were compared to the actual result and displayed in a confusion matrix (Figs 1d, 2d, 3d). Static nomograms are presented in Figs 1e, 2e, 3e. The AUC for the pN1 model was 0.815, p(N1+N2) was 0.768, and pSN2 was 0.726 (Figs 1f, 2f, 3f), indicating that all three models have good discriminatory ability, especially the pN1 model. We also conducted an exploratory external validation using data from an independent, previously published dataset from another institution, obtaining an AUC of 0.635 (Supplementary Fig 1).

Discussion

There are many reports of discordance between clinical and pathological staging for early-stage NSCLC. Bott et al. reported 9,530/55,653 (17%) patients with more advanced staging on final pathologic review (15). D’Cunha et al. conducted a multicenter prospective trial (GALGA 9761) for clinical stage 1 NSCLC, and reported 14% of patients with pathological stage 2 disease, 13.5% with stage 3 disease, and 0.9% with stage 4 disease (29). Decaluwé et al. reported nodal pN1 and pN2 upstaging in 13.3% and 8.2% of their cohort (30). In our study, among 1,735 patients who were preoperative diagnosed with cN0 disease, 171 (9.9%) patients had pN1, 191 (11.0%) had p(N1+N2), and 91 (5.2%) patients had SN2 postoperatively.

Previous studies have identified the following significant associations for nodal upstaging: non-upper located tumors (22), tumor size (31), consolidation with solid component (32), visceral pleural involvement (33), positive tumor markers (34), and tumors with poor differentiation (21, 35). Despite this,
results from individual studies are not generalizable to other clinics. The large variation in different studies’ models reflects variation in the clinical variables recorded for each patient, variation in criteria for selection of patients, variation in nodal dissection expertise, among other variations. Until pre-specified risk stratification and algorithm are tested in a multi-center prospective trial, this work (and others before it) cannot be used to guide management.

**What does this work add to the field?** Unbalanced datasets are not unique to upstaging models, but the challenges to data analysis have been largely disregarded in prior papers. Using a unique data analysis approach, we improved the characterization of the models, applying 3 equations to model 3 possible outcomes from these patients. Since patients’ selection criteria was specific to cN0 rather than overall stage, this dataset thereby included patients with larger tumor sizes, which allowed us to use tumor size as an independent variable in the model. The variables in the dataset are obtained from low-dose CT imaging and demographic findings, which enable the use of our predictive model in low-resource settings.

**Is there anything that we need to do as clinicians and surgeons for case management?** We hope clinicians will be able to estimate nodal upstaging risk for each clinical nodal negative patient using preoperative parameters, and through this, avoid unnecessary invasive procedure for low risk patients, and also consider more comprehensive nodal dissection for higher risk patients.

The current study has several limitations. The retrospective nature of the dataset limits the number of clinical variables that could be potentially be collected on the patients. Similarly, promising biomarkers could not be tested in a retrospective study. Prospective studies that systematically test the utility of individualized risk assessment for selecting biopsies in cN0 NSCLC patients would be welcome. We welcome collaborations with other centers. Finally, due to the indolent nature of early-stage NSCLC, a long follow-up is needed, and we could not perform a survival analysis at this time.

**Conclusion**

In a large retrospective single-institution dataset of 1735 cN0 NSCLC patients, we report an overall 26.1% nodal upstaging rate. 9.9% to pN1, 11.0% to p(N1+N2) and 5.2% to pSN2. After a thorough analysis of multiple clinical factors, we established 3 accurate and easy-to-use predictive models for specific pN upstaging. The predictive models can stratify cN0 NSCLC patients into different risk groups, which can
aid clinical management. External validation in a prospective multi-site study is needed before adoption into clinical practice.
ACKNOWLEDGEMENTS

Funding: No external funding was directly used for this study. LL was supported by Key Science and Technology Program of Sichuan Province, China (2016FZ0118). WC is supported by the Dubbs MDPHD scholarship award from Thomas Jefferson University. Publication is made possible in part by support from the Thomas Jefferson University + Philadelphia University Open Access Fund.

Competing interests: The authors declare that they have no conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

IRB approval: Approval for this retrospective chart review was granted by the Institutional Review Board at the West China Hospital, Sichuan University.
Table 1 Demographic Characteristics (N=1735)

| Variables                                   | N (%)  |
|---------------------------------------------|--------|
| Gender                                      |        |
| Male                                        | 948(54.6) |
| Female                                      | 788(45.4) |
| Age (mean± SD)                              |        |
| 58.6± 9.9                                   |        |
| Smoking status (pack-years)                 |        |
| 0 (Never smoked)                            | 1053(60.7) |
| <30                                         | 277(16.0) |
| >=30                                        | 405(23.3) |
| Location                                    |        |
| RUL                                         | 569(32.9) |
| RML                                         | 188(10.8) |
| RLL                                         | 299(17.2) |
| LUL                                         | 384(22.1) |
| LLL                                         | 295(17.0) |
| Central/Peripheral                          |        |
| Central                                     | 374(21.6) |
| Peripheral                                  | 1361(78.4) |
| T stage                                     |        |
| T1a                                         | 107(6.2) |
| T1b                                         | 298(17.2) |
| T1c                                         | 222(12.8) |
| T2a                                         | 765(44.1) |
| T2b                                         | 177(10.2) |
| T3                                          | 155(8.9) |
| T4                                          | 11(0.6) |
| Visceral pleura involvement                 |        |
| Yes                                         | 819(47.2) |
| No                                          | 916(52.8) |
| Consolidation                               |        |
| Solid                                       | 1284(74.0) |
| GGO                                         | 451(26.0) |
| Surgical procedure                          |        |
| VATS                                        | 1300(75.0) |
| Thoracotomy                                 | 435(25.0) |
| Histology                                   |        |
| Adenocarcinoma                              | 1345(77.5) |
| Squamous cell carcinoma                     | 345(19.9) |
| Others                                      | 45(2.6) |
| Differentiation                             |        |
| Well                                        | 22(1.3) |
| Well-moderate                               | 94(5.4) |
| Moderate                                    | 1135(65.4) |
| Moderate-poor                               | 330(19.0) |
| Poor                                        | 154(8.9) |

NSCLC, non-small cell lung cancer; N(%), cases sample size and percentage; SD, standard deviation;

Brinkman index: the number of cigarettes smoked per day multiplied by the number of years of smoking.
T stage, tumor; GGO, ground glass opaque; VATS, Video-assisted thoracoscopic surgery;
RUL, right upper lobe; RML, right medial lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe
Table 2 Univariate Analysis for the Prevalence of pN1

| Variables                        | pN0   | pN1   | P value$^a$ |
|----------------------------------|-------|-------|------------|
|                                  | Number of patients (%) |       |            |
|                                  | 1282(88.2) | 171 (11.8) |          |
| Gender                           |       |       | <0.001     |
| Male                             | 658(51.3) | 129(75.4) |            |
| Female                           | 624(48.7) | 42(24.6) |            |
| Age (mean± SD)                   | 58.8± 10.0 | 59.3± 8.4 | 0.549      |
| Smoking status (pack-years)      |       |       | <0.001     |
| 0 (Never smoked)                 | 817 (63.7) | 68 (39.8) |            |
| 0-30                             | 201 (15.7) | 29 (17.0) |            |
| >=30                             | 264 (20.6) | 74 (43.3) |            |
| Location                         |       |       | <0.001     |
| RUL                              | 433(33.8) | 40(23.4) |            |
| RML                              | 140(10.9) | 23(13.5) |            |
| RLL                              | 226(17.6) | 24(14.0) |            |
| LUL                              | 280(21.8) | 34(19.9) |            |
| LLL                              | 203(15.8) | 50(29.2) |            |
| Central/Peripheral               |       |       | <0.001     |
| Central                          | 219(17.1) | 81(47.4) |            |
| Peripheral                       | 1063(82.9) | 90(52.6) |            |
| T stage                          |       |       | <0.001     |
| T1a                              | 105(8.2) | 0(0.0) |            |
| T1b                              | 271(21.1) | 7(4.1) |            |
| T1c                              | 185(14.4) | 13(7.6) |            |
| T2a                              | 523(40.8) | 81(47.4) |            |
| T2b                              | 105(8.2) | 32(18.7) |            |
| T3                               | 83(6.5) | 38(22.2) |            |
| T4                               | 10(0.8) | 0(0.0) |            |
| Visceral pleura involvement      |       |       | <0.001     |
| Yes                              | 515(40.2) | 116(67.8) |            |
| No                               | 767(59.8) | 55(32.2) |            |
| Consolidation                    |       |       | <0.001     |
| Solid                            | 872(68.0) | 157(91.8) |            |
| GGO                              | 410(32.0) | 14(8.2) |            |
| Histology                        |       |       | <0.001     |
| Adenocarcinoma                   | 1019(79.5) | 99(57.9) |            |
| Squamous cell carcinoma          | 235(18.3) | 64(37.4) |            |
| Others                           | 28(2.2) | 8(4.7) |            |

NSCLC, non-small cell lung cancer; N(%), cases sample size and percentage; SD, standard deviation; N stage, node; T stage, tumor; GGO, ground glass opaque; RUL, right upper lobe; RML, right medial lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe

$^a$Significance of Fisher’s exact test, $\chi^2$-test or t-test. $P<0.05$ was considered statistically significant.
Table 3 Univariate Analysis for the Prevalence of p(N1+N2) and SN2

| Variables                  | pN0          | pN1+N2         | P value | pN0          | SN2          | P value |
|----------------------------|--------------|----------------|---------|--------------|--------------|---------|
|                            | Number of patients (%) |                 |         | Number of patients (%) |                 |         |
| Gender                     |              |                |         |              |              |         |
| Male                       | 658(51.3)    | 110(42.4)      | 0.106   | 658(51.3)    | 51(56.0)     | 0.384   |
| Female                     | 624(48.7)    | 81(57.6)       |         | 624(48.7)    | 40(44.0)     |         |
| Age (mean±SD)              | 58.8±10.0    | 56.4±9.8       | 0.823   | 58.8±10.0    | 56.9±10.1    | 0.956   |
| Smoking status (pack-years)|              |                |         |              |              |         |
| 0 (never smoked)           | 817(63.7)    | 108(56.5)      | 0.09    | 817(63.7)    | 60(65.9)     | 0.617   |
| 0-30                       | 201 (15.7)   | 31(16.2)       |         | 201 (15.7)   | 16 (17.6)    |         |
| >= 30                      | 264 (20.1)   | 52 (27.2)      |         | 264 (20.1)   | 15 (16.5)    |         |
| Location                   |              |                | 0.694   |              |              | 0.236   |
| RUL                        | 433(33.8)    | 57(29.8)       |         | 433(33.8)    | 39(42.9)     |         |
| RML                        | 140(10.9)    | 19(9.9)        |         | 140(10.9)    | 6(6.6)       |         |
| RLL                        | 226(17.6)    | 33(17.3)       |         | 226(17.6)    | 16(17.6)     |         |
| LUL                        | 280(21.8)    | 49(25.7)       |         | 280(21.8)    | 21(23.1)     |         |
| LLL                        | 203(15.8)    | 33(17.3)       |         | 203(15.8)    | 9(9.9)       |         |
| Central/Peripheral         |              |                | <0.001  |              |              | 0.903   |
| Central                    | 219(17.1)    | 58(30.4)       |         | 219(17.1)    | 16(17.6)     |         |
| Peripheral                 | 1063(82.9)   | 133(69.6)      |         | 1063(82.9)   | 75(82.4)     |         |
| T stage                    |              |                | <0.001  |              |              | <0.001  |
| T1a                        | 105(8.2)     | 2(1.0)         |         | 105(12.0)    | 0(0.0)       |         |
| T1b                        | 271(21.1)    | 12(6.3)        |         | 271(32.8)    | 8(8.8)       |         |
| T1c                        | 185(14.4)    | 13(6.8)        |         | 185(25.4)    | 11(12.1)     |         |
| T2a                        | 523(40.8)    | 103(53.9)      |         | 523(14.4)    | 58(63.7)     |         |
|        | N  | %   |        | N  | %   |
|--------|----|-----|--------|----|-----|
| T2b    | 105(8.2) | 33(17.3) | 105(8.2) | 7(7.7) |
| T3     | 83(6.5)    | 27(14.1)    | 83(6.5)    | 7(7.7)    |
| T4     | 10(0.8)    | 1(0.5)      | 10(0.8)    | 0(0.0)    |
| Visceral pleura involvement | <0.001      | <0.001      |
| Yes    | 515(40.2)  | 126(66.0)   | 515(40.2)  | 62(68.1)   |
| No     | 767(59.8)  | 65(34.0)    | 767(59.8)  | 29(31.9)   |
| Consolidation | <0.001      | <0.001      |
| Solid  | 872(68.0)  | 176(92.1)   | 872(68.0)  | 79(86.8)   |
| GGO    | 410(32.0)  | 15(7.9)     | 410(32.0)  | 12(13.2)   |
| Histology | 0.333      | 0.984       |
| Adenocarcinoma | 1019(79.5) | 154(80.6)  | 1019(79.5) | 73(80.2)   |
| Squamous cell carcinoma | 235(18.3)  | 30(15.7)   | 235(18.3)  | 16(17.6)   |
| Others | 28(2.2)    | 7(3.7)      | 28(2.2)    | 2(2.2)     |

NSCLC, non-small cell lung cancer; N(%), cases sample size and percentage; SD, standard deviation; Brinkman index: the number of cigarettes smoked per day multiplied by the number of years of smoking; N stage, node; T stage, tumor; GGO, ground glass opaque; VATS, Video-assisted thoracoscopic surgery; RUL, right upper lobe; RML, right medial lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

aSignificance of Fisher’s exact test, χ²-test or t-test. P<0.05 was considered statistically significant.
Table 4 Multivariate Analysis for Prevalence of nodal upstaging

| Variable                          | Reference            | OR (95% CI)   | P     |
|-----------------------------------|----------------------|---------------|-------|
| **p(N1)**                         |                      |               |       |
| Male gender                       | Female               | 1.74 (1.11-2.73) | 0.016 |
| Tumor location LLL                | All other locations  | 2.02 (1.26-3.23) | <0.01 |
| Central tumor location            | Other locations by CT| 2.42 (1.58-3.70) | <0.001|
| Visceral pleural involvement      | No involvement       | 3.31 (2.18-5.02) | <0.001|
| Solid consolidation               | GGO                  | 3.99 (2.08-7.67) | <0.001|
| Tumor size                        | -- (continuous)      | 1.40 (1.25-1.58) | <0.001|
| **p(N1+N2)**                      |                      |               |       |
| Heavy smoker>30 pack-years        | Light or non-smoker  | 1.13 (0.73-1.75) | NS    |
| Age                               | -- (continuous)      | 0.97 (0.95- 0.99) | 0.01  |
| Tumor size                        | -- (continuous)      | 1.34 (1.21-1.48) | <0.001|
| Visceral pleural involvement      | No involvement       | 2.78 (1.91-4.05) | <0.001|
| Solid consolidation               | GGO                  | 5.38 (2.84-10.19) | <0.001|
| **SN2**                           |                      |               |       |
| Tumor location RUL                | All other locations  | 1.64 (1.00-2.70) | 0.048 |
| Solid consolidation               | GGO                  | 2.71 (1.36-5.40) | <0.01 |
| Tumor size >2.0cm                  | <2.0cm               | 2.77 (1.53-4.98) | <0.001|
| Visceral pleural involvement      | No involvement       | 2.49 (1.50-4.14) | <0.001|

NSCLC, non-small cell lung cancer; OR, Odds ratio; CI, confidence interval
N stage, node; RUL, right upper lobe; LLL, left lower lobe
P < 0.05 is considered statistically significant.
Table 5 Summary of Logistic Regression Models

| Variable | Equation |
|----------|----------|
| **General equation for a binary logistic regression model** | \[ l = log_e \left( \frac{\pi}{1 - \pi} \right) = \beta_0 + \beta_1 x_1 + \cdots + \beta_{p-1} x_{p-1} \] |
| \( pN1 \) | \[ \log \left( \frac{\pi}{1 - \pi} \right) = -5.68 + 0.70 \times LLL + 0.86 \times central \\
+0.33 \times size + 1.19 \times visceral + 1.36 \times consolidation \\
+0.60 \times gender \] |
| \( p(N1+N2) \) | \[ \log \left( \frac{\pi}{1 - \pi} \right) = -4.76 + 0.30 \times size \\
0.99 \times visceral + 1.69 \times consolidation \] |
| \( pSN2 \) | \[ \log \left( \frac{\pi}{1 - \pi} \right) = -4.80 + 0.50 \times RUL + 1.02 \times T2plus \\
+0.91 \times visceral + 1.00 \times consolidation \] |

List of variable abbreviations:
- central: presence of tumor by bronchoscopy (1), absence (0)
- size: size of tumor from CT (in cm). continuous variable
- visceral: visceral pleural involvement identified by CT (1), absence (0)
- consolidation: solid component identified by CT (1), ground-glass opacity on CT (0)
- gender: male (1), female (0)
- RUL: tumor located in right-upper lobe on CT (1), other locations (0)
- T2plus: Tumor size is greater than 2.0cm (1), else equal to or less than 2.0 cm (0)
ABBREVIATION LIST

NSCLC: non-small cell lung cancer
pN: pathological node stage
cN: clinical node stage
CT: computed tomography
PET-CT: positron emission tomography-computed tomography
VATS: video-assisted thoracic surgery
FS: frozen specimen
AUC: area under the curve
RUL: right upper lobe
RML: right middle lobe
RLL: right lower lobe
LUL: left upper lobe
LLL: left lower lobe
GGO: ground-glass opacity
OR: odds ratio
CI: confidence interval
EBUS-TBNA: endobronchial ultrasound-transbronchial needle aspiration
EUB-FNA: endoscopic ultrasound-fine needle aspiration
FIGURE LEGENDS

**Figure 1:** pN1 upstaging model from 1282 pN0 and 171 pN1 cases. (a) Correlation matrix identifies variables that are associated with upstaging (b) Accuracy measurements for training set and test set at different cutoffs. Accuracy does not have defined peak, showing it cannot be used to determine cutoff values in unbalanced datasets (c) Application of a cost function for determining the cutoff value. 0.17 is the optimal cutoff identified. (d) Confusion matrix at the cutoff in 1(c), symbolized by the horizontal line in blue. Points on the upper left are true positives, bottom left are false negatives, upper right are false positives, and bottom right are true negatives. (d) nomogram of the upstaging model (e) ROC (Receptor Operating Characteristic) curve. Area under the curve is 0.8145.

**Figure 2:** p(N1+N2) upstaging model from 1282 pN0 and 191 p(N1+N2) cases. (a) Correlation matrix identifies variables that are associated with upstaging (b) Accuracy measurements for training set and test set at different cutoffs. Accuracy does not have defined peak, showing it cannot be used to determine cutoff values in unbalanced datasets (c) Application of a cost function for determining the cutoff value. 0.29 is the optimal cutoff identified. (d) Confusion matrix at the cutoff in 2(c), symbolized by the horizontal line in blue. Points on the upper left are true positives, bottom left are false negatives, upper right are false positives, and bottom right are true negatives. (d) nomogram of the upstaging model (e) ROC (Receptor Operating Characteristic) curve. Area under the curve is 0.7675.

**Figure 3:** p(N1+N2) upstaging model from 1282 pN0 and 91 pSN2 cases. (a) Correlation matrix identifies variables that are associated with upstaging (b) Accuracy measurements for training set and test set at different cutoffs. Accuracy does not have defined peak, showing it cannot be used to determine cutoff values in unbalanced datasets (c) Application of a cost function for determining the cutoff value. 0.13 is the optimal cutoff identified. (d) Confusion matrix at the cutoff in 3(c), symbolized by the horizontal line in blue. Points on the upper left are true positives, bottom left are false negatives, upper right are false positives, and bottom right are true negatives. (d) nomogram of the upstaging model (e) ROC (Receptor Operating Characteristic) curve. Area under the curve is 0.726.
Bibliography

1. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II 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 May;143(5 Suppl):e278S–e313S.

2. Thomas KW, Gould MK. Tumor, Node, Metastasis (TNM) staging system for lung cancer. In: Ted W Post, editor. UpToDate [Internet]. 2020 [cited 2020 Feb 2]. Available from: https://www.uptodate.com/contents/tumor-node-metastasis-tnm-staging-system-for-lung-cancer

3. Whitson BA, Andrade RS, Boettcher A, Bardales R, Kratzke RA, Dahlberg PS, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. Ann Thorac Surg. 2007 Jun;83(6):1965–70.

4. Nakayama H, Yamada K, Saito H, Oshita F, Ito H, Kameda Y, et al. Sublobar resection for patients with peripheral small adenocarcinomas of the lung: surgical outcome is associated with features on computed tomographic imaging. Ann Thorac Surg. 2007 Nov;84(5):1675–9.

5. Cao C, Zhu Z-H, Yan TD, Wang Q, Jiang G, Liu L, et al. Video-assisted thoracic surgery versus open thoracotomy for non-small-cell lung cancer: a propensity score analysis based on a multi-institutional registry. Eur J Cardiothorac Surg. 2013 Nov;44(5):849–54.

6. Chua GWY, Chua KLM. Which patients benefit most from stereotactic body radiotherapy or surgery in medically operable non-small cell lung cancer? An in-depth look at patient characteristics on both sides of the debate. Thorac Cancer. 2019 Oct;10(10):1857–67.

7. Koshy M, Fedewa SA, Malik R, Ferguson MK, Vigneswaran WT, Feldman L, et al. Improved survival associated with neoadjuvant chemoradiation in patients with clinical stage IIIA(N2) non-small-cell lung cancer. J Thorac Oncol. 2013 Jul;8(7):915–22.

8. Lewis J, Gillaspie EA, Osmundson EC, Horn L. Before or After: Evolving Neoadjuvant Approaches to Locally Advanced Non-Small Cell Lung Cancer. Front Oncol. 2018 Jan 23;8:5.

9. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg. 2011 Dec;142(6):1393–400.e1.

10. Gonzalez-Stawinski GV, Lemaire A, Merchant F, O’Halloran E, Coleman RE, Harpole DH, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. J Thorac Cardiovasc Surg. 2003 Dec;126(6):1900–5.

11. Kandathil A, Kay FU, Butt YM, Wachsmann JW, Subramaniam RM. Role of FDG PET/CT in the Eighth Edition of TNM Staging of Non-Small Cell Lung Cancer. Radiographics. 2018 Dec;38(7):2134–49.

12. Kaseda K, Watanabe K-I, Asakura K, Kazama A, Ozawa Y. Identification of false-negative and false-positive diagnoses of lymph node metastases in non-small cell lung cancer patients staged by integrated (18F)-fluorodeoxyglucose-positron emission tomography/computed tomography: A retrospective cohort study. Thorac Cancer. 2016 Jul;7(4):473–80.

13. Chung F-T, Kuo C-H, Chen H-C, Feng P-H, Lin S-M, Yu C-T, et al. Roles of EBUS-TBNA in non-small cell lung cancer. Thorac Cancer. 2012 May;3(2):182–7.

14. Nasir B, Cerfolio RJ, Bryant AS. Endobronchial ultrasound (EBUS) with tranbronchial needle aspiration (TBNA) versus mediastinoscopy for mediastinal staging in non-small cell lung cancer
15. Bott MJ, Patel AP, Crabtree TD, Colditz GA, Kreisel D, Krupnick AS, et al. Pathologic Upstaging in Patients Undergoing Resection for Stage I Non-Small Cell Lung Cancer: Are There Modifiable Predictors? Ann Thorac Surg. 2015 Dec;100(6):2048–53.

16. Jiang L, Jiang S, Lin Y, Yang H, Xie Z, Lin Y, et al. Nomogram to predict occult N2 lymph nodes metastases in patients with squamous non-small cell lung cancer. Medicine. 2015 Nov;94(46):e2054.

17. Caldarella A, Crocetti E, Comin CE, Janni A, Pegna AL, Paci E. Prognostic variability among non-small cell lung cancer patients with pathologic N1 lymph node involvement. Epidemiological figures with strong clinical implications. Cancer. 2006 Aug 15;107(4):793–8.

18. Zhao F, Zhou Y, Ge P-F, Huang C-J, Yu Y, Li J, et al. A prediction model for lymph node metastases using pathologic features in patients intraoperatively diagnosed as stage I non-small cell lung cancer. BMC Cancer. 2017 Apr 13;17(1):267.

19. Cho S, Song IH, Yang HC, Kim K, Jheon S. Predictive factors for node metastasis in patients with clinical stage I non-small cell lung cancer. Ann Thorac Surg. 2013 Jul;96(1):239–45.

20. Cerfolio RJ, Bryant AS, Ojha B, Eloubeidi M. Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. Ann Thorac Surg. 2005 Oct;80(4):1207–13; discussion 1213.

21. Koike T, Koike T, Yamato Y, Yoshiya K, Toyabe S-I. Predictive risk factors for mediastinal lymph node metastasis in clinical stage IA non-small-cell lung cancer patients. J Thorac Oncol. 2012 Aug;7(8):1246–51.

22. Bao F, Yuan P, Yuan X, Lv X, Wang Z, Hu J. Predictive risk factors for lymph node metastasis in patients with small size non-small cell lung cancer. J Thorac Dis. 2014 Dec;6(12):1697–703.

23. Farjah F, Lou F, Sima C, Rusch VW, Rizk NP. A prediction model for pathologic N2 disease in lung cancer patients with a negative mediastinum by positron emission tomography. J Thorac Oncol. 2013 Sep;8(9):1170–80.

24. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 world health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 2015 Sep;10(9):1243–60.

25. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010 Jun;17(6):1471–4.

26. Liu E. Choosing Logistic Regression’s Cutoff Value for Unbalanced Dataset [Internet]. Choosing Logistic Regression’s Cutoff Value for Unbalanced Dataset. 2015 [cited 2019 Dec 30]. Available from: http://ethen8181.github.io/machine-learning/unbalanced/unbalanced.html#content
location should be considered when comparing N1 upstaging between thoracoscopic and open surgery for clinical stage I non-small-cell lung cancer. Eur J Cardiothorac Surg. 2016 Jul;50(1):110–7.

31. Flieder DB, Port JL, Korst RJ, Christos PJ, Levin MA, Becker DE, et al. Tumor size is a determinant of stage distribution in t1 non-small cell lung cancer. Chest. 2005 Oct;128(4):2304–8.

32. Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M, et al. Prediction of pathologic node-negative clinical stage IA lung adenocarcinoma for optimal candidates undergoing sublobar resection. J Thorac Cardiovasc Surg. 2012 Dec;144(6):1365–71.

33. Yu X, Li Y, Shi C, Han B. Risk factors of lymph node metastasis in patients with non-small cell lung cancer ≤ 2 cm in size: A monocentric population-based analysis. Thorac Cancer. 2018;9(1):3–9.

34. Zang R-C, Qiu B, Gao S-G, He J. A Model Predicting Lymph Node Status for Patients with Clinical Stage T1aN0-2M0 Nonsmall Cell Lung Cancer. Chin Med J. 2017 Feb 20;130(4):398–403.

35. Schwartz AM, Rezaei MK. Diagnostic surgical pathology in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e251S–e262S.
