Journal of Cardiothoracic Surgery

RESEARCH

Open Access

# A novel nomogram based on PET/CT to predict lymph nodal metastasis for lung adenocarcinoma with normal size lymph node

Xinyu Zhu[1,2†], Xinyu Jia[1,2†], Shibing Teng[3†], Kai Fu[1,2], Jiawei Chen[1,2,4], Jun Zhao[1,2*] and Chang Li[1,2*]

## Abstract

**Background** A precise assessment of lymph nodal status is essential for guiding an individualized treatment plan in lung adenocarcinoma patients. A novel nomogram using easily accessible indicators was developed and validated in this study to predict CT-negative lymph nodal metastasis.

**Methods** Between September 2020 and December 2023, data from 132 consecutive patients diagnosed with lung adenocarcinoma who underwent lung resection with systemic lymph node dissection or sampling were retrospectively reviewed. Risk factors associated with lymph nodal metastasis were identified using univariable and multivariable logistic regression analyses. Subsequently, a nomogram was developed on basis of these identified parameters. The performance and validity of the nomogram were evaluated using the area under the receiver operating characteristic (ROC) curve, calibration curve, and bootstrap resampling techniques.

**Results** Four predictors (primary tumor location, primary tumor SUVmax value, N1 lymph node SUVmax, and N2 lymph node SUVmax) were identified and incorporated into the nomogram. The nomogram exhibited notable discrimination, evidenced by an area under the ROC curve of 0.825 (95% CI: 0.749–0.886, $P < 0.001$). Excellent concordance between the predicted and observed probabilities of lymph nodal involvement was demonstrated by the calibration curve. Furthermore, decision curve analysis indicated a net benefit associated with the use of our nomogram.

**Conclusion** The nomogram demonstrated efficacy and practicality in predicting CT-negative lymph node metastasis for lung adenocarcinoma patients. It holds potential to offer valuable treatment guidance for clinicians.

**Keywords** Positron emission tomography/Computed tomography (PET/CT), Lung adenocarcinoma, Lymph nodal metastasis, Nomogram

†Xinyu Zhu, Xinyu Jia and Shibing Teng contributed equally to this work.

*Correspondence:
Jun Zhao
junzhao@suda.edu.cn
Chang Li
cli@suda.edu.cn

[1]Department of Thoracic Surgery, The First Affiliated Hospital of Soochow University, Suzhou 215006, China
[2]Institute of Thoracic Surgery, The First Affiliated Hospital of Soochow University, Suzhou 215006, China
[3]Department of Thoracic Surgery, Suzhou Xiangcheng People's Hospital, Suzhou, China
[4]Department of Thoracic Surgery, Changshu Hospital, Nanjing University of Chinese Medicine, Nanjing, China

## Background

Lung cancer represents a leading cause of cancer-specific mortality globally [1–3]. Non-small cell lung cancer (NSCLC) constitutes approximately 80% of lung cancer cases, with adenocarcinoma (AC) being the most prevalent histological subtype within NSCLC [4, 5]. Accurate lymph node staging is essential in the comprehensive management of lung cancer patients, influencing both surgical decision-making and the administration of adjuvant therapies [6, 7]. Consequently, the development of an effective and practical method for predicting lymph nodal metastasis in patients with AC is of critical clinical significance.

Pathological biopsy, necessitating invasive techniques like endobronchial ultrasound-guided biopsies and mediastinoscopy, remains the gold-standard reference for determining lymph nodal status in the preoperative setting. However, the routine implementation of these procedures heightens the risk of futile diagnosis and appears to offer no additional benefits beyond confirming an N0 pathological state in patients without lymph nodal metastasis (LNM) [8]. Furthermore, the feasibility and precision of safely conducting an invasive procedure are constrained by the potential for additional costs, trauma, and complications, particularly in patients with substantial comorbidities and diminutive lymph nodes. Computed tomography (CT) and 18 F-fluorodeoxyglucose positron emission tomography/computed tomography (18 F-FDG PET/CT) serve as crucial non-invasive modalities for tumor detection, diagnosis, staging, and clinical decision-making in individuals with lung cancer. CT is capable of diagnosing lymph nodes based on their size; however, it lacks sufficient accuracy for evaluating lymph nodes with small lesions. PET/CT provides both anatomical and metabolic characteristics of lesions, yet its accuracy is not entirely reliable to eliminate the need for pathological confirmation of nodal metastases [9]. Moreover, infections and inflammatory processes can lead to false-positive results.

Nomograms, which integrate multiple risk factors rather than depending on a single variable, have been demonstrated to be a reliable and effective method for aiding surgeons in the formulation of more precise diagnostic, therapeutic, and prognostic strategies [10, 11]. Several models have been developed to predict lymph nodal metastasis in lung cancer patients using PET/CT- derived parameters [9, 12, 13]. However, predictive models for CT-negative patients with AC remain limited. Hence, this study sought to develop and validate a practical nomogram on basis of PET/CT to enhance noninvasive nodal evaluation in CT-negative patients with AC.

## Methods

### Patients

We conducted a retrospective enrollment of 132 consecutive patients diagnosed with lung adenocarcinoma who underwent lung resection accompanied by systemic lymph node dissection or sampling at the Thoracic Surgery Department of The First Affiliated Hospital of Soochow University (Suzhou, China) from September 2020 to December 2023. The inclusion criteria for this study were as follows: (1) Patients had undergone PET/CT imaging during their hospitalization prior to surgical operation, without evidence of distant metastasis detected; (2) No enlarged lymph nodes were identified on CT scans, with lymph nodes measuring less than 1 cm in the shortest dimension; (3) Patients were pathologically diagnosed with primary adenocarcinoma; (4) Necessary clinicopathological data of the patient were complete. The exclusion criteria were as follows: (1) PET/CT scanning was performed in other institution; (2) Pleural metastasis was revealed during surgery; (3) CT scan indicated that the short axis of the lymph node exceeded 1 cm; (4) Systematic dissection or sampling of hilar and mediastinal lymph nodes was not performed; (5) Final pathological diagnosis was not adenocarcinoma.

Baseline clinicopathological data, encompassing age, gender, smoking history, peripheral blood cell parameters, pathological findings, and initial PET/CT data, were extracted from the HaiTai electronic medical record system (Nanjing, Jiangsu, China). Primary tumors situated within the proximal third of the hemithorax were classified as central-type tumors, whereas those located beyond the proximal third of the hemithorax were categorized as peripheral-type tumors [14].

This study was retrospectively conducted following the principles delineated in the Declaration of Helsinki (as revised in 2013) and received approval from the ethical committee and institutional review board of The First Affiliated Hospital of Soochow University (No. 2024349). Individual consent was waived for this retrospective analysis. All data were anonymized to ensure the protection of personal privacy.

### $^{18}$F-FDG PET/CT examination

All patients underwent integrated FDG PET/CT imaging prior to surgical operation. Patients fasted for a minimum of 6 h to ensure their blood glucose levels were below 11 mmol/L before receiving an 18 F-FDG injection, with a dosage ranging from 4.07 to 5.55 MBq/kg. Approximately 40 to 60 min post-injection, PET/CT scans were conducted from the base of the skull to the mid-thigh region, with an acquisition time of 2 to 3 min per bed position. The ordered subset expectation-maximization algorithm was used to conduct image reconstruction. The imaging was carried out using a Discovery PET/CT system

(General Electric Medical Systems, Milwaukee, WI, USA) with low-dose CT parameters set at 140 kV, 120 mA, a transaxial field of view of 70 cm, and a slice thickness of 3.75 mm. The maximum standardized uptake value (SUVmax) of the tumor and suspected lymph nodes was ascertained by delineating a region of interest around each respective area. For part-solid tumors, tumor size was determined by measuring the solid component of the lesion. Final pathological findings were utilized as the gold standard to compare with PET/CT results.

#### Blood parameters

Each patient received a routine blood test during the week preceding surgery. The quantities of monocytes, neutrophils, platelets, and lymphocytes were measured. Subsequently, the ratios of neutrophils to lymphocytes (NLR), lymphocytes to monocytes (LMR), and platelets to lymphocytes (PLR) were individually calculated.

#### Lymph nodal staging

Tumor staging was assessed following the 8th edition of the TNM classification for lung cancer [15]. Clinically, lymph nodes were deemed positive if they exceeded 1 cm in the shortest dimension on CT or exhibited an SUVmax greater than 2.5 PET/CT [16].

#### Surgical procedures

Generally, lung cancer is typically excised via wedge resection, segmentectomy, lobectomy, or bilobectomy, accompanied by systemic lymph node dissection or sampling. Complete resection is characterized by the achievement of both macroscopic and microscopic tumor-free margins. At least 1 N1 (hilar) station and 3 N2 (mediastinal) stations including the subcarinal station were excised.

#### Statistical analysis

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET/CT for the evaluation of lymph nodal metastasis were assessed using histological results as the reference standard. Continuous variables with non-normal distributions were reported as medians (range) and analyzed using the Mann–Whitney U test. Categorical variables were expressed as numbers (rates) and analyzed using the $\chi^2$ test or Fisher's exact test. Univariable and multivariable binary logistic regression analyses were conducted to identify independent risk factors for lymph nodal metastasis. Variables with $p<0.05$ in univariable analyses were included in multivariable analyses, which were subsequently used to construct a nomogram. The value of each indicator was given a score on the point scale axis. The total points could be calculated by adding every single point. By projecting the total points to the probability of the LNM axis, we could easily estimate the probability of lymph node metastasis in the patients. ROC curves were generated using MedCalc, and the area under the curves (AUC) was calculated to demonstrate the predictive accuracy of the nomogram. Internal validation of the nomogram was performed with 1000 bootstrap resamples. Harrell's C-index was employed to evaluate the discrimination performance. Calibration plots and decision curve analysis (DCA) were utilized to assess the calibration and clinical utility of the nomogram. Clinical baseline data analysis was conducted using the SPSS statistical package (version 26.0, IBM Corp., Armonk, NY, USA). The nomogram, calibration plot, and DCA curve were generated using R software version 4.4.1. Two-sided $p<0.05$ was considered statistically significant.

## Results

From September 2020 to December 2023, a total of 132 lung adenocarcinoma patients consisting of 54 males and 78 females were enrolled in the study. All patients underwent integrated FDG PET/CT before pulmonary resection and were at least diagnosed with CT negative (the shortest dimension of lymph nodes less than 1 cm). Table 1 presents the diagnostic performance of PET-CT lymph nodal staging in lung adenocarcinoma patients. The sensitivity and specificity for N1 lymph nodes were 34.6% and 91.5%, respectively; for N2 lymph nodes, 50% and 99.1%, respectively; and for the overall patient cohort, 45.2% and 90.1%, respectively. The overall diagnostic accuracy was 79.5%. In all patients, the incidence of lymph nodal metastasis was 23.5% (31/132). Among these patients, 90 were classified as cT1 stage, 37 as cT2 stage, 4 as cT3 stage, and 1 as cT4 stage. Besides, 26 patients had N1 LNM and 18 patients had N2 LNM. Of all the patients, 6 underwent wedge resection due to poor pulmonary functional reserve, 3 underwent segmentectomy, 120 underwent lobectomy and 3 underwent bilobectomy.

**Table 1** Overview of FDG-PET/CT in diagnosing LNM ($n=132$)

| | Sensitivity % (*n*) | Specificity % (*n*) | Positive predictive value % (*n*) | Negative predictive value % (*n*) | Accuracy % (*n*) |
|---|---|---|---|---|---|
| N1 LNM | 34.6(9/26) | 91.5(97/106) | 50(9/18) | 85.1(97/114) | 80.3(106/132) |
| N2 LNM | 50(9/18) | 99.1(113/114) | 90(9/10) | 92.6(113/122) | 92.4(122/132) |
| Overall LNM | 45.2(14/31) | 90.1(91/101) | 58.3(14/24) | 84.3(91/108) | 79.5(105/132) |

Abbreviations: LNM, lymph nodal metastasis

### Clinicopathological features and nomogram construction

All patients' data including demographic, imaging, and pathological characteristics are summarized in Table 2. The distribution of these characteristics was compared between the lymph nodes negative (LN-) group and the lymph nodes positive (LN+) group. Compared to LN- patients, LN + patients exhibited a larger tumor size (29 vs. 23; $P = 0.018$) and higher tumor SUVmax value (7.3 vs. 2.9; $P < 0.001$). More patients in the LN + group had a central-type tumor (35.5% vs. 13.9%; $P = 0.007$), a pure solid nodule (90.3% vs. 71.3%; $P = 0.031$), and were with N1 LN SUVmax value ≥ 2.5 (29% vs. 8.9%; $P = 0.011$), N2 LN SUVmax value ≥ 2.5 (29% vs. 1%; $P < 0.001$), poor tumor grade (29% vs. 11.9%; $P = 0.045$), solid pattern (58.1% vs. 30.7%; $P = 0.006$). However, no statistically significant differences were observed in peripheral blood cell parameters. Independent risk factors for LNM were identified through univariable and multivariable binary logistic regression analyses (Table 3). Ultimately, tumor location (OR, 3.90; 95% CI, 1.21–12.53; $P = 0.022$), tumor SUVmax value (OR, 1.16; 95% CI, 1.0-1.35; $P = 0.049$), N1 LN SUVmax value (OR, 5.25; 95% CI, 1.37–20.04; $P = 0.015$) and N2 LN SUVmax value (OR, 21.89; 95% CI, 2.27-210.86; $P = 0.008$) were identified for the construction of the nomogram (Figure 1).

### Nomogram evaluation

Our model demonstrated robust discrimination, evidenced by a C-index of 0.810 for LNM when evaluated using 1000 bootstrap resamples. Internal validation further corroborated this performance, yielding a high C-index value of 0.825. Calibration curves shown in Figure 2 indicated strong concordance between the predicted and actual probabilities of LNM. Decision curve analysis revealed that, for patients with a threshold probability exceeding 10%, the nomogram provided greater clinical benefit compared to both the treat-all and treat-none strategies (Figure 3). Additionally, the area under the ROC curve was 0.825 (95% CI 0.749–0.886, $P < 0.001$) (Figure 4), signifying a notable discrimination capability.

**Table 2** Clinicopathological variables in lung adenocarcinoma patients with (LN+) and without (LN-) lymph nodal metastasis

| Variables | LN(-) cohort ($n = 101$) | LN(+) cohort ($n = 31$) | *P* value |
|---|---|---|---|
| Age, years (Median, range) | 64(37–85) | 66(34–77) | 0.711 |
| Gender, *n* (%) | | | |
| Female/Male | 61(60.4)/40(39.6) | 17(54.8)/14(45.2) | 0.582 |
| Smoking history, *n* (%) | | | |
| Never/Ever | 83(82.2)/18(17.8) | 29(93.5)/2(6.5) | 0.208 |
| PLR (Median, range) | 109.3(8.7-318.8) | 119.6(43.1-293.5) | 0.673 |
| NLR (Median, range) | 1.8(0.1–9.5) | 1.8(0.5–4.8) | 0.741 |
| LMR (Median, range) | 4(0.5–33.7) | 3.5(1.6–8.9) | 0.492 |
| Tumor size, mm (Median, range) | 23(10–84) | 29(13–61) | 0.018* |
| Tumor side, *n* (%) | | | |
| Left/Right | 45(44.6)/56(55.4) | 16(51.6)/15(48.4) | 0.490 |
| Tumor location, *n* (%) | | | |
| Central/Peripheral | 14(13.9)/87(86.1) | 11(35.5)/20(64.5) | 0.007* |
| Pure solid nodule, *n* (%) | | | |
| Yes/No | 72(71.3)/29(28.7) | 28(90.3)/3(9.7) | 0.031* |
| Tumor SUVmax value (Median, range) | 2.9(0-17.8) | 7.3(1.7–18.5) | 0.000* |
| N1 LN SUVmax value, *n* (%) | | | |
| ≥ 2.5/<2.5 | 9(8.9)/92(91.1) | 9(29)/22(71) | 0.011* |
| N2 LN SUVmax value, *n* (%) | | | |
| ≥ 2.5/<2.5 | 1(1)/100(99) | 9(29)/22(71) | 0.000* |
| Tumor grade, *n* (%) | | | |
| Well or Moderate/Poor | 89(88.1)/12(11.9) | 22(71)/9(29) | 0.045* |
| Pathological subtype | | | |
| Absent/Present, *n* (%) | | | |
| Lepidic pattern | 83(82.2)/18(17.8) | 28(90.3)/3(9.7) | 0.422 |
| Acinar pattern | 9(8.9)/92(91.1) | 7(22.6)/24(77.4) | 0.084 |
| Papillary pattern | 27(26.7)/74(73.3) | 9(29)/22(71) | 0.801 |
| Micropapillary pattern | 45(44.6)/56(55.4) | 12(38.7)/19(61.3) | 0.566 |
| Solid pattern | 70(69.3)/31(30.7) | 13(41.9)/18(58.1) | 0.006* |
| Mucinous pattern | 98(97)/3(3) | 30(96.8)/1(3.2) | 1.000 |

Abbreviations: LN lymph node; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SUVmax: maximum standardized uptake value. *$p < 0.05$

**Table 3** Univariable and multivariable analysis of predictors of lymph nodal metastasis in 132 patients with lung adenocarcinoma

| Variables | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | *P* value | OR | 95%CI | *P* value |
| Tumor size, mm | 1.03 | 1.0-1.07 | 0.051 | | | |
| Tumor location | | | | | | |
| Peripheral vs. Central | 3.42 | 1.35–8.64 | 0.009* | 3.90 | 1.21–12.53 | 0.022* |
| Pure solid nodule | | | | | | |
| No vs. Yes | 3.76 | 1.06–13.33 | 0.04* | 1.06 | 0.24–4.61 | 0.94 |
| Tumor SUVmax value | 1.26 | 1.12–1.41 | 0.000* | 1.16 | 1.0-1.35 | 0.049* |
| N1 LN SUVmax value | | | | | | |
| <2.5 vs. ≥ 2.5 | 4.182 | 1.49–11.77 | 0.007* | 5.25 | 1.37–20.04 | 0.015* |
| N2 LN SUVmax value | | | | | | |
| <2.5 vs. ≥ 2.5 | 40.91 | 4.93-339.77 | 0.001* | 21.89 | 2.27-210.86 | 0.008* |
| Tumor grade | | | | | | |
| Well or Moderate vs. Poor | 3.03 | 1.14–8.10 | 0.027* | 1.512 | 0.34–6.74 | 0.59 |
| Solid pattern | | | | | | |
| Absent vs. Present | 3.13 | 1.34–7.17 | 0.007* | 2.29 | 0.71–7.37 | 0.16 |

Abbreviations: CI: confidence interval; OR: odds ratio. *$p$ <0.05

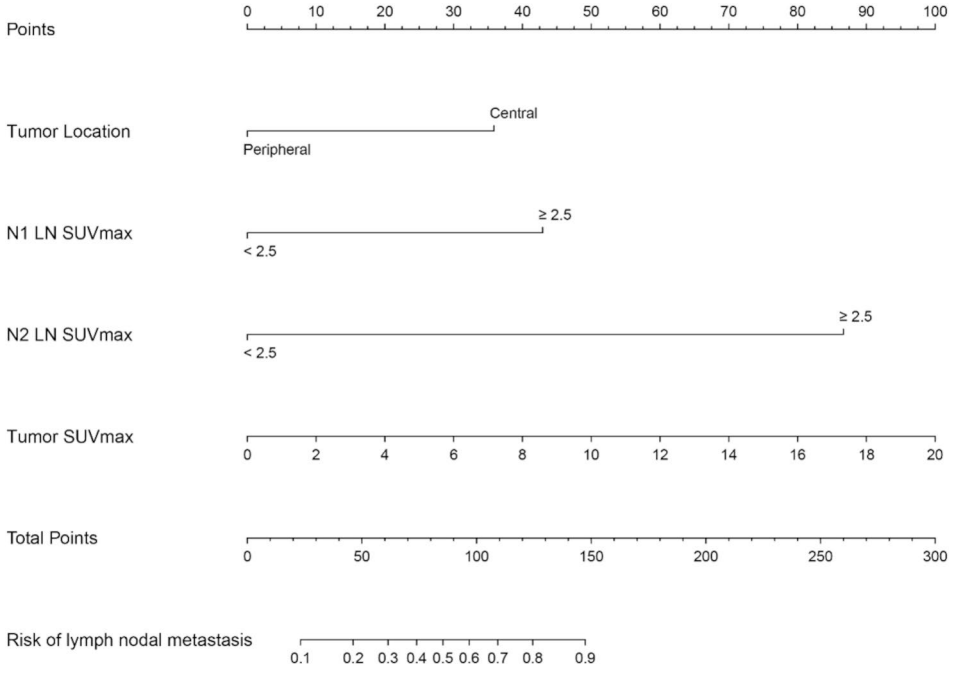


**Fig. 1** Nomogram to predict the probability of lymph nodal metastasis in patients with lung adenocarcinoma. Each indicator is assigned a score based on a point scale. The total score is obtained by summing the individual scores. We can estimate the probability of lymph nodal metastasis by projecting the total score to the lower total point scale

## Discussion

A novel nomogram was developed and validated in this retrospective study to predict the incidence of lymph node metastasis in patients with lung adenocarcinoma, utilizing readily accessible PET/CT indicators. The analysis identified primary tumor location, tumor SUVmax, N1 lymph node SUVmax ≥ 2.5, and N2 lymph node SUVmax ≥ 2.5 as independent risk factors. Our nomogram indicated that patients with central-type lung adenocarcinoma, elevated tumor SUVmax, and N1 and N2 lymph node SUVmax ≥ 2.5 are at a higher risk of lymph nodal involvement. The model demonstrated robust discrimination and calibration. Hence, it might possess potential clinical utility to evaluate preoperative lymph nodal status in lung adenocarcinoma patients and might provide clinicians with valuable treatment guidance.

Clinicians predominantly depend on specific clinical features, particularly imaging characteristics, to assess the risk of LNM in lung cancer during routine practice. Several studies have suggested that metabolic and

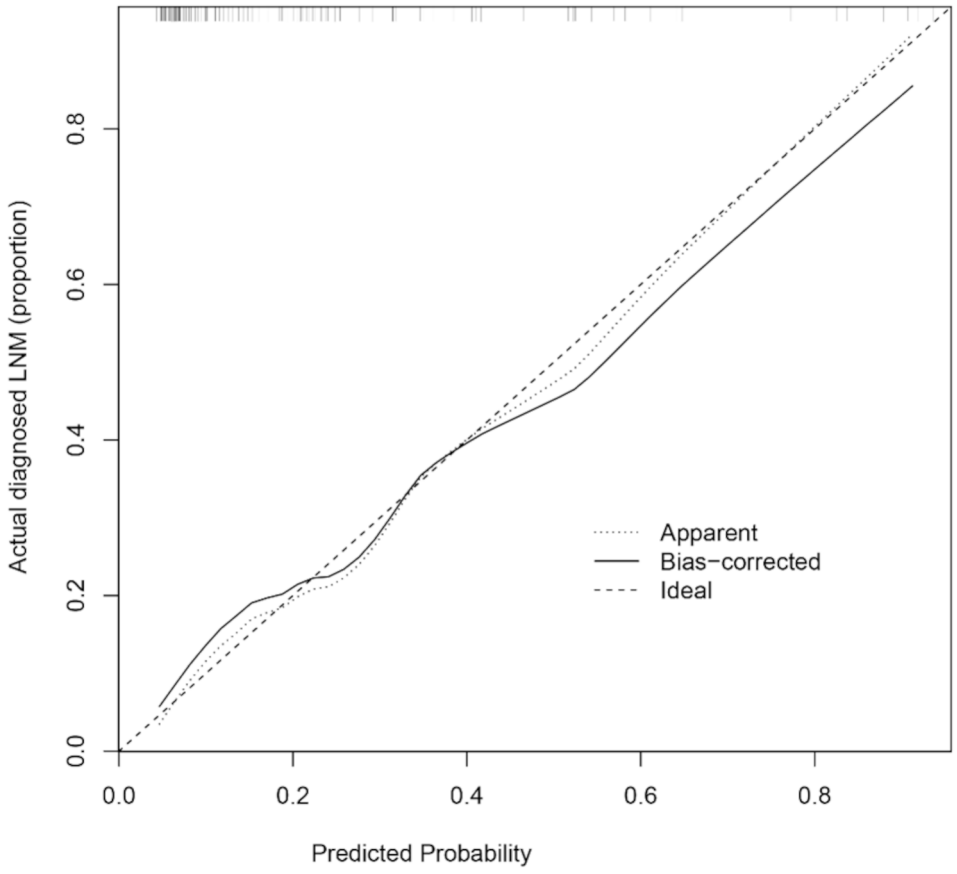


**Fig. 2** Calibration curve of the nomogram. The x-axis shows the predicted probability, while the y-axis shows the actual probability of lymph nodal metastasis

morphologic parameters observed in PET/CT scans, such as tumor size, tumor location, consolidation ratio, and metabolic value, may offer valuable insights into the likelihood of LNM [8, 17–19]. Nevertheless, this subjective evaluation is limited in its ability to comprehensively estimate the probability of LNM due to the variability in clinicians' experiences. This limitation has direct implications for the management strategies employed for individual patients. Therefore, various models utilizing PET/CT have been developed and validated to predict lymph nodal involvement in NSCLC [9, 11–13]. Whereas, to the best of our knowledge, there are limited studies specifically aimed at constructing prediction models for LNM in lung adenocarcinoma. Consistent with previous studies, factors such as tumor location, the SUVmax of the primary tumor, and suspicious lymph nodes have been identified as significant risk factors for lymph nodal metastasis [11–13, 20]. Notably, central lung cancer characterized by a high SUVmax value of both the primary tumor and suspicious lymph nodes exhibits a markedly higher prevalence of lymph nodal metastasis. Given that our model was designed for lung adenocarcinoma patients, which could be confirmed by preoperative biopsy or intraoperative frozen section, we incorporated the precise SUVmax of the primary tumor into our model to minimize measurement error. However, for the suspicious lymph nodes, 2.5 was used as the cut-off value associated with positive lymph nodes, which is more pragmatic and consistent with current clinical habits [21, 22]. We exclusively utilized the lymph node station with the highest SUVmax, despite the potential inaccuracy arising from the possibility that a single individual may present with multiple lymph nodes exhibiting abnormal SUVmax. This approach is justifiable for two reasons: firstly, our study aimed to evaluate overall lymph nodal involvement rather than the risk associated with specific lymph nodal stations; secondly, distinguishing between metastatic hilar and interlobar lymph nodes and those that are non-metastatic is challenging due to their proximity to the bronchus and similar soft tissue characteristics [11, 23]. Thus, both N1 and N2 lymph node SUVmax were included in our model, with the latter demonstrating a more substantial contribution to the risk of LNM. Fundamentally, the identification of LNM and improvement of staging accuracy is determined depending on

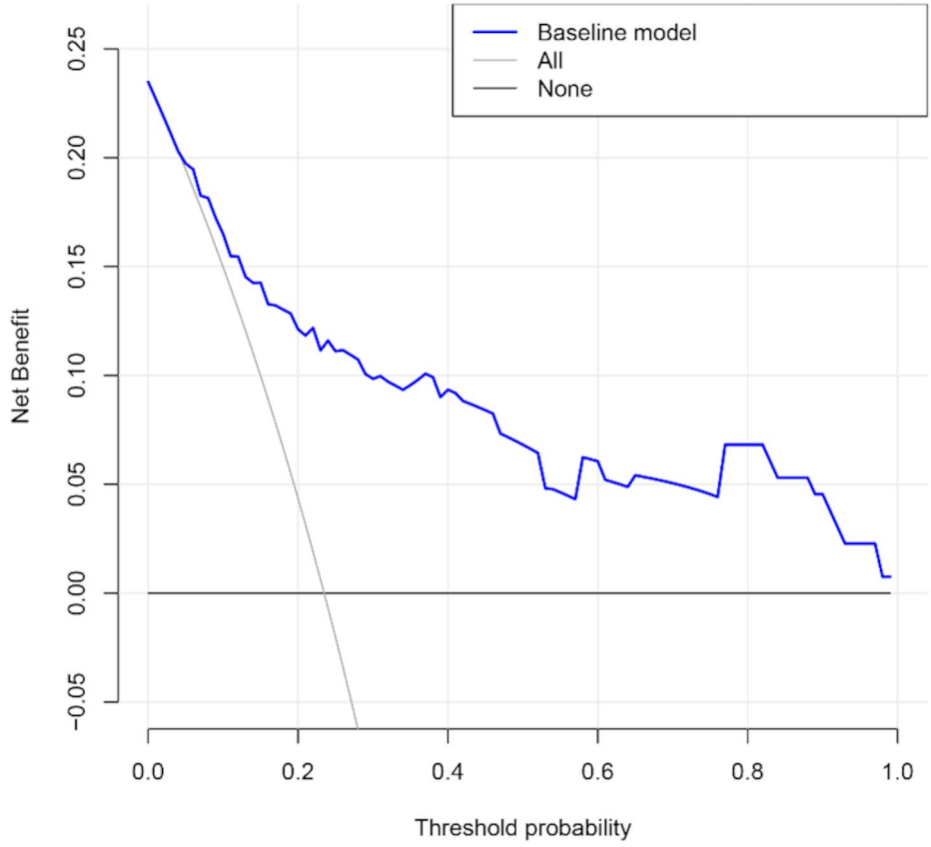


**Fig. 3** DCA for the nomogram. The x-axis shows the threshold probability. The y-axis shows the net benefit. The blue line represents the nomogram, the grey line assumes all patients have lymph nodal metastasis, and the black line assumes none do. The net benefit is calculated by subtracting the false positive rate from the true positive rate. DCA, decision curve analysis

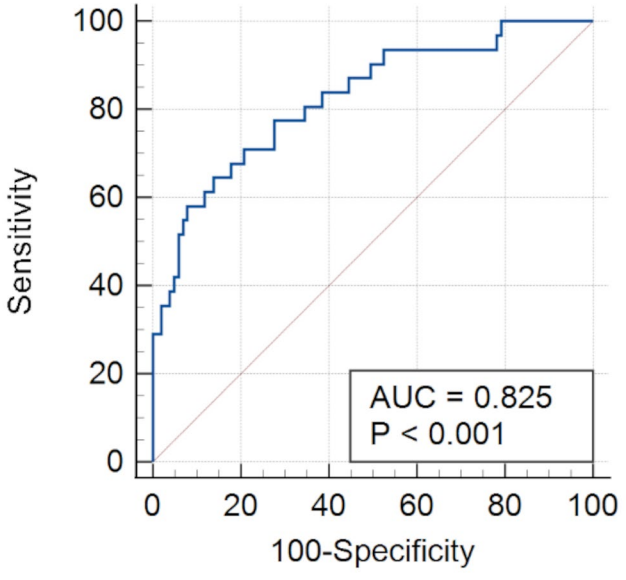


**Fig. 4** ROC curve of the nomogram in the prediction of lymph nodal metastasis in lung adenocarcinoma patients. The area under the ROC curve was 0.825 (95% CI 0.749–0.886, $P < 0.001$), indicating certain discrimination ability. ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval

complete and en bloc resection of each lymph node station [24, 25].

In consideration of the importance of inflammation in tumor initiation, progression, and metastasis, Wei, Chen, and Wang reported that peripheral blood cell parameters such as NLR and PLR were significantly elevated in LNM patients [13, 26, 27]. However, no statistical difference was found in our cohort. This may be derived from the different biological characteristics of adenocarcinoma and other types of NSCLC. Additionally, micropapillary and/or solid subtypes of lung adenocarcinoma have been demonstrated to correlate with LNM and poor prognosis [28, 29]. While the pathological subtype significantly influenced the risk of lymph node metastasis in univariable analysis, it was not identified as an independent predictor in our multivariable analysis. This may be because previous studies did not incorporate both PET/CT-related parameters and clinicopathological features simultaneously. Thus, these intriguing findings require to be validated by further studies with a larger sample size. Notably, some clinicopathologic factors such as vascular invasion, pleural invasion, and the existence of tumor spread through air spaces (STAS) were not incorporated

into our prediction model, despite numerous studies reporting the potential increase of LNM in lung adenocarcinoma patients presenting with these characteristics [29–31]. For the moment, the determination of these pathological characteristics by preoperative biopsy or intraoperative FS is challenging for most pathologists due to limited access to the tissue and detection techniques, causing relatively low accuracy.

Nodal biopsy is considered the gold standard for lymph node staging in the preoperative setting, but the potential risk of invasive procedures cannot be ignored. It is thus necessary to balance the advantages and disadvantages of this dual-nature procedure to individualize the lymph node staging for lung cancer patients [32, 33]. Besides, in surgical decision-making, sublobar resection and lobe-specific lymph node dissection are increasingly utilized for the surgical treatment of early-stage NSCLC due to more lung parenchyma preservation and less surgical trauma. However, lobectomy with systematic lymph node dissection is still the more appropriate choice if LNM occurs [34, 35]. Therefore, it is advisable to recommend more aggressive diagnostic and therapeutic strategies for patients predicted by the model to have a high incidence of lymph node metastasis. Ultimately, our model may aid in identifying patients at high risk for lymph node involvement, thereby preventing missed opportunities for perioperative adjuvant therapy.

Several limitations of this study warrant acknowledgment. Firstly, selection bias was unavoidable in this single-center retrospective study, raising questions about the generalizability of our findings to other populations. There still exists some unknown potential biases between the groups although multivariable analysis was conducted to balance the apparent biases. Secondly, all included cases were adenocarcinomas. Different histological types exhibit distinct radiological phenotypes and tumor aggressiveness, which contribute to heterogeneity in metastatic behavior. Consequently, patients were divided into two groups based solely on lymph node metastasis status, a constraint necessitated by the small sample size. Additionally, PET/CT imaging is not a mandatory preoperative procedure for every patient within our department. Consequently, our analysis was limited to the subset of patients who had undergone this imaging modality. Despite conducting internal validation to mitigate adverse influence and calibrate the model, considering the SUVmax in PET may vary greatly in value among different models, timing of imaging, and institution, external validation using data from other centers is necessary to ensure the generalizability of this nomogram.

## Conclusions

Overall, the nomogram is a promising tool for predicting lymph nodal metastasis for lung adenocarcinoma with normal size lymph node due to the good calibration and net benefit. It holds potential to offer valuable treatment guidance for clinicians.

### Abbreviations

| | |
|---|---|
| ROC | Receiver operating characteristic |
| PET/CT | Positron emission tomography/computed tomography |
| NSCLC | Non-small cell lung cancer |
| AC | Adenocarcinoma |
| LNM | Lymph nodal metastasis |
| CT | Computed tomography |
| 18 F-FDG PET/CT | 18 F-fluorodeoxyglucose positron emission tomography/computed tomography |
| SUVmax | Maximum standardized uptake value |
| NLR | Neutrophils to lymphocytes |
| LMR | Lymphocytes to monocytes |
| PLR | Platelets to lymphocytes |
| AUC | Area under the curves |
| DCA | Decision curve analysis |

### Author contributions

Design: XZ, XJ and CL. Collection of statistics: ST. Statistical analysis: JC and KF. Manuscript writing: XZ, JZ and CL.

### Funding

This work was supported by the grants from National Natural Science Foundation of China (81873417).

### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

This study was retrospectively conducted following the principles delineated in the Declaration of Helsinki (as revised in 2013) and received approval from the ethical committee and institutional review board of The First Affiliated Hospital of Soochow University (No. 2024349).

### Conflicts of interest

The authors declare no conflict of interest.

Received: 28 October 2024 / Accepted: 6 April 2025
Published online: 16 April 2025

### References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63. https://doi.org/10.3322/caac.21834
2. Han B, Zheng R, Zeng H, Wang S, Sun K, Chen R, et al. Cancer incidence and mortality in China, 2022. J Natl Cancer Cent. 2024;4(1):47–53. https://doi.org/10.1016/j.jncc.2024.01.006
3. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49. https://doi.org/10.3322/caac.21820
4. Arbour KC, Riely GJ. Systemic therapy for locally advanced and metastatic Non-Small cell lung cancer: A review. JAMA. 2019;322(8):764–74. https://doi.org/10.1001/jama.2019.11058
5. Wang S, Yu Y, Xu W, Lv X, Zhang Y, Liu M. Dynamic nomograms combining N classification with ratio-based nodal classifications to predict long-term survival for patients with lung adenocarcinoma after surgery: a SEER population-based study. BMC Cancer. 2021;21(1):653. https://doi.org/10.1186/s12885-021-08410-6

6. Ran J, Cao R, Cai J, Yu T, Zhao D, Wang Z. Development and validation of a nomogram for preoperative prediction of lymph node metastasis in lung adenocarcinoma based on radiomics signature and deep learning signature. Front Oncol. 2021;11:585942. https://doi.org/10.3389/fonc.2021.585942
7. Kim ES, Bosquée L. The importance of accurate lymph node staging in early and locally advanced non-small cell lung cancer: an update on available techniques. J Thorac Oncol. 2007;2(Suppl 2):S59–67.
8. Zhong Y, Cai C, Chen T, Gui H, Deng J, Yang M, et al. PET/CT based cross-modal deep learning signature to predict occult nodal metastasis in lung cancer. Nat Commun. 2023;14(1):7513. https://doi.org/10.1038/s41467-023-42811-4
9. Mattes MD, Weber WA, Foster A, Moshchinsky AB, Ahsanuddin S, Zhang Z, et al. A predictive model for lymph node involvement with malignancy on PET/CT in Non-Small-Cell lung cancer. J Thorac Oncol. 2015;10(8):1207–12. https://doi.org/10.1097/JTO.0000000000000601
10. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than Meets the eye. Lancet Oncol. 2015;16(4):e173–80. https://doi.org/10.1016/s1470-2045(14)71116-7
11. Fu Y, Xi X, Tang Y, Li X, Ye X, Hu B, et al. Development and validation of tumor-to-blood based nomograms for preoperative prediction of lymph node metastasis in lung cancer. Thorac Cancer. 2021;12(15):2189–97. https://doi.org/10.1111/1759-7714.14066
12. Lv X, Wu Z, Cao J, Hu Y, Liu K, Dai X, et al. A nomogram for predicting the risk of lymph node metastasis in T1-2 non-small-cell lung cancer based on PET/CT and clinical characteristics. Transl Lung Cancer Res. 2021;10(1):430–8. https://doi.org/10.21037/tlcr-20-1026
13. Wei B, Jin X, Lu G, Zhao T, Xue H, Zhang Y. A novel nomogram to predict lymph node metastasis in cT1 non-small-cell lung cancer based on PET/CT and peripheral blood cell parameters. BMC Pulm Med. 2023;23(1):44. https://doi.org/10.1186/s12890-023-02341-7
14. Jin C, Cao J, Cai Y, Wang L, Liu K, Shen W, et al. A nomogram for predicting the risk of invasive pulmonary adenocarcinoma for patients with solitary peripheral subsolid nodules. J Thorac Cardiovasc Surg. 2017;153(2):462–e91. https://doi.org/10.1016/j.jtcvs.2016.10.019
15. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11(1):39–51. https://doi.org/10.1016/j.jtho.2015.09.009
16. Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abraira V, Roqué I, Figuls M. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. Cochrane Database Syst Rev. 2014;2014(11):CD009519. https://doi.org/10.1002/14651858.CD009519.pub2
17. Kameyama K, Imai K, Ishiyama K, Takashima S, Kuriyama S, Atari M, et al. New PET/CT criterion for predicting lymph node metastasis in resectable advanced (stage IB-III) lung cancer: the standard uptake values ratio of Ipsilateral/contralateral hilar nodes. Thorac Cancer. 2022;13(5):708–15. https://doi.org/10.1111/1759-7714.14302
18. Kagimoto A, Tsutani Y, Izaki Y, Handa Y, Mimae T, Miyata Y, et al. Prediction of lymph node metastasis using semiquantitative evaluation of PET for lung adenocarcinoma. Ann Thorac Surg. 2020;110(3):1036–42. https://doi.org/10.1016/j.athoracsur.2020.03.032
19. Nie P, Yang G, Wang N, Yan L, Miao W, Duan Y, et al. Additional value of metabolic parameters to PET/CT-based radiomics nomogram in predicting lymphovascular invasion and outcome in lung adenocarcinoma. Eur J Nucl Med Mol Imaging. 2021;48(1):217–30. https://doi.org/10.1007/s00259-020-04747-5
20. Kawamoto N, Tsutani Y, Kamigaichi A, Ohsawa M, Mimae T, Miyata Y, et al. Tumour location predicts occult N1 nodal metastasis in clinical stage I non-small-cell lung cancer. Eur J Cardiothorac Surg. 2023;63(2). https://doi.org/10.1093/ejcts/ezac575
21. Kaseda K, Watanabe K, 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;7(4):473–80. https://doi.org/10.1111/1759-7714.12358
22. Miyasaka Y, Suzuki K, Takamochi K, Matsunaga T, Oh S. The maximum standardized uptake value of Fluorodeoxyglucose positron emission tomography of the primary tumour is a good predictor of pathological nodal involvement in clinical N0 non-small-cell lung cancer. Eur J Cardiothorac Surg. 2013;44(1):83–7. https://doi.org/10.1093/ejcts/ezs604
23. Dyas AR, King RW, Ghanim AF, Cerfolio RJ. Clinical misstagings and risk factors of occult nodal disease in Non-Small cell lung cancer. Ann Thorac Surg. 2018;106(5):1492–8. https://doi.org/10.1016/j.athoracsur.2018.05.045
24. Doddoli C, Aragon A, Barlesi F, Chetaille B, Robitail S, Giudicelli R, et al. Does the extent of lymph node dissection influence outcome in patients with stage I non-small-cell lung cancer? Eur J Cardiothorac Surg. 2005;27(4):680–5. https://doi.org/10.1016/j.ejcts.2004.12.035
25. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American college of surgery oncology group Z0030 trial. J Thorac Cardiovasc Surg. 2011;141(3):662–70. https://doi.org/10.1016/j.jtcvs.2010.11.008
26. Chen JL, Wu JN, Lv XD, Yang QC, Chen JR, Zhang DM. The value of red blood cell distribution width, neutrophil-to-lymphocyte ratio, and hemoglobin-to-red blood cell distribution width ratio in the progression of non-small cell lung cancer. PLoS ONE. 2020;15(8):e0237947. https://doi.org/10.1371/journal.pone.0237947
27. Wang Y, Zhou N, Zhu R, Li X, Sun Z, Gao Y, et al. Circulating activated immune cells as a potential blood biomarkers of non-small cell lung cancer occurrence and progression. BMC Pulm Med. 2021;21(1):282. https://doi.org/10.1186/s12890-021-01636-x
28. Zhao Y, Wang R, Shen X, Pan Y, Cheng C, Li Y, et al. Minor components of micropapillary and solid subtypes in lung adenocarcinoma are predictors of lymph node metastasis and poor prognosis. Ann Surg Oncol. 2016;23(6):2099–105. https://doi.org/10.1245/s10434-015-5043-9
29. Hung JJ, Yeh YC, Jeng WJ, Wu YC, Chou TY, Hsu WH. Factors predicting occult lymph node metastasis in completely resected lung adenocarcinoma of 3 cm or smaller. Eur J Cardiothorac Surg. 2016;50(2):329–36. https://doi.org/10.1093/ejcts/ezv485
30. Moon Y, Kim KS, Lee KY, Sung SW, Kim YK, Park JK. Clinicopathologic factors associated with occult lymph node metastasis in patients with clinically diagnosed N0 lung adenocarcinoma. Ann Thorac Surg. 2016;101(5):1928–35. https://doi.org/10.1016/j.athoracsur.2015.11.056
31. Vaghjiani RG, Takahashi Y, Eguchi T, Lu S, Kameda K, Tano Z, et al. Tumor spread through air spaces is a predictor of occult lymph node metastasis in clinical stage IA lung adenocarcinoma. J Thorac Oncol. 2020;15(5):792–802. https://doi.org/10.1016/j.jtho.2020.01.008
32. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA, American College of Chest P. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):S202–20. https://doi.org/10.1378/chest.07-1362
33. Czarnecka-Kujawa K, Yasufuku K. The role of endobronchial ultrasound versus mediastinoscopy for non-small cell lung cancer. J Thorac Dis. 2017;9(Suppl 2):S83–97. https://doi.org/10.21037/jtd.2017.03.102
34. Dezube AR, Mazzola E, Deeb A, Wiener DC, Marshall MB, Rochefort MW, et al. Mandatory nodal evaluation during resection of clinical T1a Non-Small cell lung cancers. Ann Thorac Surg. 2022;113(5):1583–90. https://doi.org/10.1016/j.athoracsur.2021.06.078
35. Zhao ZR, Situ DR, Lau RWH, Mok TSK, Chen GG, Underwood MJ, et al. Comparison of segmentectomy and lobectomy in stage IA adenocarcinomas. J Thorac Oncol. 2017;12(5):890–6. https://doi.org/10.1016/j.jtho.2017.01.012


## Publisher's note