

# A Model Predicting Lymph Node Status for Patients with Clinical Stage T1aN0-2M0 Nonsmall Cell Lung Cancer

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## Abstract

**Background:** Lymph node status of patients with early-stage nonsmall cell lung cancer has an influence on the choice of surgery. To assess the lymph node status more correspondingly and accurately, we evaluated the relationship between the preoperative clinical variables and lymph node status and developed one model for predicting lymph node involvement.

**Methods:** We collected clinical and dissected lymph node information of 474 patients with clinical stage T1aN0-2M0 nonsmall cell lung cancer (NSCLC). Logistic regression analysis of clinical characteristics was used to estimate independent predictors of lymph node metastasis. The prediction model was validated by another group.

**Results:** Eighty-two patients were diagnosed with positive lymph nodes (17.3%), and four independent predictors of lymph node disease were identified: larger consolidation size (odds ratio [OR] = 2.356, 95% confidence interval [CI]: 1.517–3.658,  $P < 0.001$ ), central tumor location (OR = 2.810, 95% CI: 1.545–5.109,  $P = 0.001$ ), abnormal status of tumor marker (OR = 3.190, 95% CI: 1.797–5.661,  $P < 0.001$ ), and clinical N1–N2 stage (OR = 6.518, 95% CI: 3.242–11.697,  $P < 0.001$ ). The model showed good calibration (Hosmer–Lemeshow goodness-of-fit,  $P < 0.766$ ) with an area under the receiver operating characteristics curve (AUC) of 0.842 (95% [CI]: 0.797–0.886). For the validation group, the AUC was 0.810 (95% CI: 0.731–0.889).

**Conclusions:** The model can assess the lymph node status of patients with clinical stage T1aN0-2M0 NSCLC, enable surgeons perform an individualized prediction preoperatively, and assist the clinical decision-making procedure.

**Key words:** Carcinoma; Diagnosis; Lymph Nodes; Nonsmall Cell Lung Cancer; Predictive Models

## INTRODUCTION

With the prevalent use of low-dose computed tomography (CT), we can detect much smaller lung nodules than before. For patients with early-stage nonsmall cell lung cancer (NSCLC), surgical resection is the primary choice. According to previous studies, segmentectomy performed for pathological N0 stage NSCLC patients could work as an alternative of lobectomy.<sup>[1-5]</sup> To study the relationship between preoperative clinical variables and lymph node involvement and to help surgeons make decisions more reasonably, we built a model for predicting lymph node status.

In our study, all the evaluated clinical information could be obtained preoperatively by noninvasive test, which enhanced the utility. In addition, a separate cohort was used for validation. To our knowledge, it is the first model using preoperative clinical data to predict hilum and

mediastinum lymph node metastasis together for selecting sublobar resection candidates in patients with clinical stage T1aN0-2M0 NSCLC.

## METHODS

### Patients

The Institutional Review Board of Cancer Hospital, Chinese Academy of Medical Sciences, approved the study. As it was a retrospective study, the necessity to obtain written

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informed consent from each patient was waived. Clinical and dissected lymph node information of patients underwent surgical treatment from January 2010 to December 2015 at our institution was collected. The following patients were excluded from the study: patients with a history of malignant tumor and patients who had received chemotherapy or radiation therapy preoperatively. Totally 474 consecutive patients were enrolled as Group 1. According to the inclusion criteria, 135 patients who were surgically treated from January 2016 to April 2016 were selected as Group 2 for validation. All the enrolled patients underwent preoperative examination including chest and whole abdomen contrast-enhanced CT, either contrast-enhanced CT or magnetic resonance imaging of brain, bone scintigraphy, and the serum status of five kinds of tumor marker (carcinoembryonic antigen, carbohydrate antigen 125, neuron-specific enolase, squamous cell carcinoma antigen, and cytokeratin 19 fragment [CYFRA21-1]) was tested together preoperatively. Preoperative lymph node status was assessed by contrast-enhanced CT scanning for all patients, while mediastinoscopy and the integrated positron emission tomography-CT (PET-CT) were not routinely performed.

The American Joint Committee on Cancer 7<sup>th</sup> edition of lung cancer staging guidelines were adopted.<sup>[6]</sup> Preoperative clinical variables on age, gender, family history of malignant tumor, smoking history, tumor location, component of tumor, consolidation size, tumor size, consolidation size/tumor size (C/T) ratio, serum status of tumor marker, clinical lymph node stage, and dissected lymph node information from pathologic reports were collected.

### Assessment of computed tomography scanning

All patients were grouped according to CT scanning: the pure ground-glass opacity (GGO) tumor group, the mixed tumor group, and the pure solid tumor group. Pure GGO tumors were defined as focal areas where the normal lung parenchymal structures and vascular markings were visually preserved. Pure solid tumors were abnormal areas which completely obscured the lung parenchymal structures and vascular markings. In the pure GGO tumor group, the diameter of solid component was 0 cm. In the pure solid tumor group, the consolidation size equals to total tumor size. In the mixed tumor group, both of the solid and GGO components could be found, the size of consolidation and total tumor were measured, respectively. Two experienced thoracic surgeons (Dr. Bin Qiu and Dr. Shu-Geng Gao) measured the size of consolidation, total tumor size, and the size of lymph node for each patient using a lung window level setting from CT scanning. 0.75 was set as the cutoff point of C/T ratio (consolidation/total tumor size ratio), and patients were grouped into two groups according to value of the ratio. Lung nodule located in the outer third of the lung was defined as peripheral tumor, while others were located centrally.

### Surgical technique

All patients had undergone pulmonary resection with systematic lymph node dissection by traditional open thoracotomy or video-assisted thoracic surgery. According

to the European Society of Thoracic Surgeons guidelines, three or more mediastinal nodal stations were excised, and the subcarinal station must be included.<sup>[7]</sup> The minimal number of dissected lymph nodes was 10. The hilar and the intrapulmonary lymph nodes were dissected as well. Resected specimens were separately labeled and examined histologically according to the World Health Organization classification.

### Statistical analysis

The statistical analysis was performed using the statistical software SPSS 22.0 (IBM, Armonk, NY, USA) and R 3.3.1 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org). The categorical data were compared using Pearson's Chi-square test, and independent sample *t*-test was used for continuous variables. Variables that were significant at the 0.05 level were entered into a backward stepwise logistic regression analysis. Only these factors that were significant at the 0.05 level remained in the final prediction model. Calibration of the predictive model, defined as concordance between predicted and observed probabilities, was determined by Hosmer–Lemeshow goodness-of-fit test ( $P > 0.05$ ). Area under the curve (AUC) of the receiver operating characteristic curve was used to assess the discriminative ability of the model. The value of AUC ranged from 0.5 to 1.0, with a value of 0.5 indicating that the model is of no discriminative ability, and a value of 1.0 indicating perfect discrimination. All presented *P* values were two sided.

## RESULTS

### Clinicopathological characteristics of patients

As shown in Table 1, in Group 1, the median age was  $58.4 \pm 8.7$  years, and 82 patients (17.3%) were diagnosed with lymph node involvement. In the pure GGO group, no patient was found with positive lymph nodes. There was one patient (1.3%) in the mixed tumor group, and the remaining 81 patients (98.7%) were all in the pure solid tumor group. In the central tumor group, the incidence of positive nodes was 37.2% (38/102); in the peripheral tumor group, the incidence of positive nodes was 11.8% (44/372). Other details are described in Table 1.

Patients with positive lymph nodes were more likely to be with longer size of consolidation, higher value of C/T ratio, pure solid tumor, centrally located tumor, abnormal status of tumor marker, and N1–N2 stage (all with  $P < 0.001$ ). When categorized by gender, male patients encountered more lymph node metastasis than female patients ( $P = 0.005$ ). Age, tumor size, family malignant tumor history, smoking history, and tumor location (except the central and peripheral location) were not associated with positive lymph nodes.

### Multivariate analysis

By multivariate logistic regression, four factors could be used in the model: longer consolidation size (odds ratio [OR] = 2.356, 95% confidence interval [CI]: 1.517–3.658,  $P < 0.001$ ), the clinical stage N1–N2 (OR = 6.518, 95% CI: 3.242–11.697,  $P < 0.001$ ), the central tumor

**Table 1: Patient characteristics in accordance to the lymph nodes status of Group I**

Characteristics	All patients (n = 474)	Patients without positive LNs (n = 392)	Patients with positive LNs (n = 82)	Statistic values	P
Age (years)	58.4 ± 8.7	58.4 ± 8.7	58.6 ± 9.0	-0.171 <sup>†</sup>	0.865
Gender, n				8.446*	0.005
Male	243	189	54		
Female	231	203	28		
Consolidation size (cm)	1.03 ± 0.80	0.90 ± 0.82	1.52 ± 0.48	-8.814 <sup>†</sup>	<0.001
Tumor size (cm)	1.55 ± 0.39	1.56 ± 0.37	1.53 ± 0.47	0.523 <sup>†</sup>	0.602
≤1.0 (n)	61	47	14	1.563*	0.275
>1.0 and ≤2.0 (n)	413	345	68		
C/T ratio, n				58.477*	<0.001
≤0.75	183	182	1		
>0.75	291	210	81		
Family malignant tumor history, n				0.815*	0.421
Yes	135	115	20		
No	339	277	62		
Smoking history, n				0.680*	0.438
Yes	155	125	30		
No	319	267	52		
Component of tumor, n				58.657*	<0.001
Pure GGO tumor	151	151	0		
Mixed tumor	32	31	1		
Pure solid tumor	291	210	81		
Location, n					
Central	102	64	38	36.175*	<0.001
Peripheral	372	328	44		
Left	173	138	35	1.637*	0.209
Right	301	254	47		
Upper	290	240	50	1.569*	0.466
Middle	32	24	8		
Lower	152	128	24		
Level of tumor marker, n				36.847*	<0.001
Normal	296	269	27		
Abnormal	178	123	55		
N stage, n				80.521*	<0.001
N0	408	363	45		
N1-N2	66	29	37		

Data are presented as mean ± standard deviation. \* $\chi^2$  values; <sup>†</sup>t values. LNs: Lymph nodes; C/T: Consolidation size/tumor size; GGO: Ground-glass opacity.

**Table 2: Independent predictors of lymph node metastasis in multivariate logistic regression analysis**

Variables	Regression coefficient	OR	95% CI	P
Consolidation size	0.857	2.356	1.517–3.658	<0.001
Central location	1.033	2.810	1.545–5.109	0.001
Clinical stage N1–N2	1.818	6.158	3.242–11.697	<0.001
Abnormal level of tumor marker	1.160	3.190	1.797–5.661	<0.001

OR: Odds ratio; CI: Confidence interval.

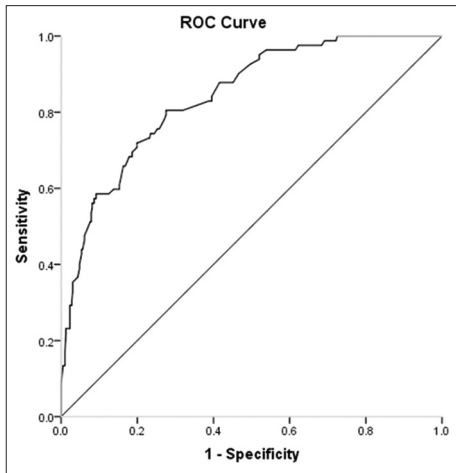
location (OR = 2.810, 95% CI: 1.545–5.109, P = 0.001), and the abnormal serum status of tumor marker (OR = 3.190, 95% CI: 1.797–5.661, P < 0.001). C/T ratio and gender were not identified as significant factors [Table 2].

### Predictive model and validation test

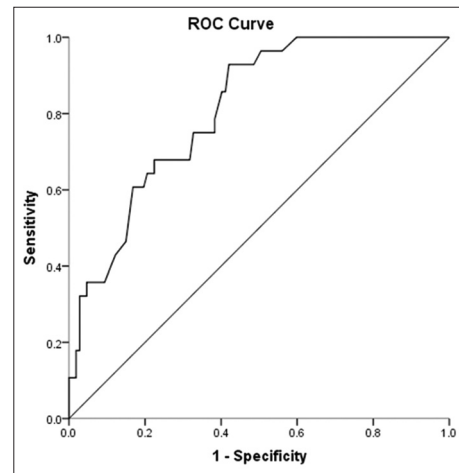
Based on the analytic results, we built a formula and a nomogram to assess the likelihood of positive lymph nodes. The consolidation size, location of the tumor, the clinical N stage, and the serum status of tumor marker were used to develop

the formula:  $e^x / (1 + e^x)$ ,  $x = -3.917 + 0.857 \times$  consolidation size +  $1.033 \times$  location +  $1.160 \times$  status of tumor marker +  $1.818 \times$  clinical N stage. The unit of consolidation size is centimeter. The corresponding value of each variable in the formula is listed in Table 3.

The result of Hosmer-Lemeshow goodness-of-fit test was not statistically significant (P < 0.766), indicating a high concordance between the predicted and observed probabilities. The AUC [Figure 1] was good at 0.842 (95%



**Figure 1:** The receiver operating characteristic curve of the Group 1. The area under the curve was 0.842 (95% confidence interval, 0.797–0.886).



**Figure 2:** The receiver operating characteristic curve of the Group 2. The area under the curve was 0.810 (95% confidence interval, 0.731–0.889).

**Table 3: Value of the three variables in the formula\***

Variable	Value in the formula
Consolidation size (cm)	Numeric value of the size
Peripheral location tumor	0
Central location tumor	1
Clinical stage N0	0
Clinical stage N1–N2	1
Normal serum level of tumor marker	0
Abnormal serum level of tumor marker	1

\* $e^x/(1 + e^x)$ ,  $x = -3.917 + 0.857 \times \text{consolidation size} + 1.033 \times \text{location} + 1.160 \times \text{status of tumor marker} + 1.818 \times \text{clinical N stage}$ .

CI: 0.797–0.886). For Group 2, the accuracy of the prediction model was reasonable, and the AUC was 0.810 (95% CI: 0.731–0.889) [Figure 2].

## DISCUSSION

With the advanced CT, we can detect much more early-stage lung cancers sized 2 cm or less.<sup>[8]</sup> For patients with early-stage lung cancers, the 10-year survival rate has been estimated to be 88%,<sup>[9]</sup> so the incidence of the second primary lung cancer may be higher. As the larger extent of excision may reduce the chance of treatment for the second primary lung cancer, we cannot help thinking that it is uniformly required to perform the lobectomy for this population of early-stage NSCLC?

The diagnostic technologies used to assess lymph node status have developed into the invasive and noninvasive methods. As the gold standard for primary lymph node staging,<sup>[10,11]</sup> mediastinoscopy was not recommended in patients with peripheral tumors and negative mediastinal PET images, because it is not cost effective for patients with clinical stage N0 NSCLC,<sup>[12]</sup> and direct surgical resection with systematic nodal dissection is indicated for tumors  $\leq 3$  cm located in the outer third of the lung.<sup>[13]</sup> CT has been used to assess lymph node status and in the lung cancer screening program. Owing to its disadvantage of differentiating benign enlarged lymph nodes from normal-sized positive lymph nodes, the sensitivity and

specificity are 55% and 81%, respectively.<sup>[14]</sup> The PET had been proved significantly more accurately than CT in demonstrating and staging of nodal involvement.<sup>[15]</sup> Nevertheless, presurgical staging by PET-CT was more reliable with a 26% greater overall diagnostic accuracy compared with PET alone,<sup>[16,17]</sup> but its application may be limited by high expense.

There were some published models developed for the assessment of lymph node disease,<sup>[18–20]</sup> however, they did only focus on the outcome of N2 disease, and the pathology was included. However, the appropriate candidates for limited resection should be with negative lymph nodes, both in the hilar and mediastinal areas. On the other hand, the CT-guided transthoracic needle aspiration biopsy has been used with accuracy, the complications could still be as high as 26.5%.<sup>[21]</sup> The categorical variable was not analyzed in the study considering its utility, which made the model works for patients without pathological diagnosis either. Confirming that there was no positive lymph node both in mediastinum and hilum through presection sampling, the randomized trial ACOSOG Z0030 concluded that systematic mediastinal lymph node dissection could not improve survival in patients with early-stage NSCLC.<sup>[22]</sup> Moreover, for early-stage NSCLC patients treated with limited resection, the survival rate was similar in contrast with those treated with lobectomy.<sup>[23,24]</sup> Therefore, accurate integration of preoperative lymph node staging in patients with early-stage NSCLC is important in guiding the choices of surgical treatment.

For patients with lymph node disease, the diameter of consolidation was longer than those without positive lymph nodes significantly ( $1.52 \pm 0.48$  cm vs.  $0.90 \pm 0.82$  cm,  $P < 0.001$ ). Of note, overall tumor size was not a significant independent factor. We speculated that there was no patient with positive nodes in the pure GGO group; overall tumor size may unable to reflect the features of the three groups. The Union for International Cancer Control suggested that the invasive component of tumor should be measured as its T-stage, which could better predict prognosis than the

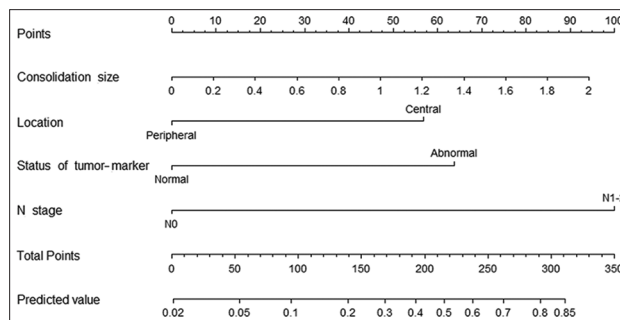
overall tumor size.<sup>[25]</sup> In addition, the impact of maximal tumor size should be applied exclusively to solid lung cancer without any component of GGO.<sup>[26]</sup> The statistical analysis demonstrated that the size of consolidation was an independent factor predicting the likelihood of lymph node disease, and Maeyashiki *et al.* had the comparable result.<sup>[27]</sup>

Currently, the primary tumor location is not recognized as an important factor in TNM staging system, but it influences on the extent of resection for early-stage NSCLC. All the enrolled patients were grouped by the location of tumor: the peripheral and central groups. We have found that if the tumor was located in the outer third of the lung, the incidence of positive lymph nodes was lower than that of central tumor significantly ( $P < 0.001$ ). Owing to the higher potentiality of regional lymph node metastases in patients with central tumors,<sup>[28]</sup> we should carefully assess the preoperative lymph node status for patients with centrally located tumor.

Previous studies demonstrated that the increased serum level of tumor marker was associated with advanced pathological lymph node staging and poor prognosis,<sup>[29-31]</sup> and we also analyzed the predictive ability of serum tumor marker. We defined the serum status of tumor marker as abnormal if one or more kinds elevated abnormally. The statistical analysis showed that abnormal status of serum tumor marker, which was an independent predictive factor for lymph node metastasis ( $P < 0.001$ ), could be used in the final model.

Candidates for sublobar resection should be with pathology stage N0, and two experienced thoracic surgeons assessed the clinical stage of lymph nodes according to the CT scanning in our study. The mediastinoscopy or PET-CT was not routinely performed, so patients with lymph nodes larger than 1 cm were enrolled into the analysis. For the clinical stage N0 group, they have a lower incidence of positive lymph nodes ( $P < 0.001$ ). For the clinical stage N1–N2 patients, the possibility for lymph nodes involvement was ranged from 10.9% to 85.9% calculated by our model indicating that the advanced assessment of lymph node stage is of great importance.

Based on the four significant independent predictors obtained preoperatively mentioned above, we built the predictive formula and nomogram which could be calculated or applied directly in patients with clinical stage T1aN0-2M0 NSCLC as diagnostic tools pretesting the probability of lymph node metastasis, allowing clinicians to make reasonable options in decision-making process. For example, if one patient without enlarged lymph node (N0 stage) has a peripherally located pure GGO tumor, the preoperative serum status of tumor marker is normal, and we can calculate the likelihood of lymph node involvement which is only 1.9%. For this patient, there is no need for further advanced invasive or noninvasive diagnostic tests, and thoracic surgeons shall suggest the patient undergo limited resection as an alternative of lobectomy. Nevertheless, if one N1 or N2 lymph node stage patient was diagnosed with a central tumor (2cm in size) which was of pure consolidation, and the serum status of tumor-marker was abnormal, we can get the



**Figure 3:** Nomogram predicts the likelihood of lymph node disease in patients with clinical stage T1aN0-2M0 NSCLC. According to the location of value on the second to the fifth axis, we can get the vertically corresponding points on the first axis. Summing up the four points together, we can get the total points and the vertically corresponding predicted value on the last axis. NSCLC: Nonsmall cell lung cancer.

probability with nearly 85.9% from the formula or 0.86 in the nomogram [Figure 3], which indicates that the patient is not a candidate for sublobar resection and may need further staging procedures. The modality of multiple disciplinary treatments will be adopted for this patient to determine which is of the biggest necessity: the lobectomy, the neoadjuvant chemotherapy, or further assessment of lymph nodes by invasive staging or by PET-CT.

### Study limitations

Although we validated the model, it still needs to be validated by more patients with clinical stage T1aN0-2M0 NSCLC from comparative centers. The serum status of multiple tumor markers was a predictive factor in our model, but the kinds of tumor marker may not be the same at different hospitals. Moreover, the interval between blood test of tumor marker and surgery was not uniformly standardized, which may exert uncertain impact on the serum status. As we did not study the survival rate, the relationship between survival rate and predictive value is unknown. Attitude to the numerical probability of clinical outcome may vary among surgeons, thus the invasive and diagnostic staging cannot be waived when necessary. Our study is not the stand-alone assessment; the application should be controlled in a reasonable way considering the actual situation individually.

In conclusion, an accurate and easy-to-use predictive model for lymph node metastasis was built and validated. Based on preoperative clinical factors, the predictive model can be incorporated in the decision-making process of specific therapeutic strategies for patients with clinical stage T1aN0-2M0 NSCLC and identifying subgroup patients for sublobar resection.

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## Conflicts of interest

There are no conflicts of interest.

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