A prediction model for lymph node metastases using pathologic features in patients intraoperatively diagnosed as stage I non-small cell lung cancer

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Abstract

Background: There is little information on which pattern should be chosen to perform lymph node dissection for stage I non-small-cell lung cancer. This study aimed to develop a model for predicting lymph node metastasis using pathologic features of patients intraoperatively diagnosed as stage I non-small-cell lung cancer.

Methods: We collected pathology data from 284 patients intraoperatively diagnosed as stage I non-small-cell lung cancer who underwent lobectomy with complete lymph node dissection from 2013 through 2014, assessing various factors for an association with metastasis to lymph nodes (age, gender, pathology, tumour location, tumour differentiation, tumour size, pleural invasion, bronchus invasion, multicentric invasion and angiolymphatic invasion). After analysing these variables, we developed a multivariable logistic model to estimate risk of metastasis to lymph nodes.

Results: Univariate logistic regression identified tumour size >2.65 cm ($p < 0.001$), tumour differentiation ($p < 0.001$), pleural invasion ($p = 0.034$) and bronchus invasion ($p < 0.001$) to be risk factors significantly associated with the presence of metastatic lymph nodes. On multivariable analysis, only tumour size >2.65 cm ($p < 0.001$), tumour differentiation ($p = 0.006$) and bronchus invasion ($p = 0.017$) were independent predictors for lymph node metastasis. We developed a model based on these three pathologic factors that determined that the risk of metastasis ranged from 3% to 44% for patients intraoperatively diagnosed as stage I non-small-cell lung cancer. By applying the model, we found that the values $\hat{y} > 0.80$, $0.43 < \hat{y} \leq 0.80$, $\hat{y} \leq 0.43$ plus tumour size >2 cm and $\hat{y} \leq 0.43$ plus tumour size $\leq 2$ cm yielded positive lymph node metastasis predictive values of 44%, 18%, 14% and 0%, respectively.

Conclusions: A non-invasive prediction model including tumour size, tumour differentiation and bronchus invasion may be useful to give thoracic surgeons recommendations on lymph node dissection for patients intraoperatively diagnosed as Stage I non-small cell lung cancer.

Keywords: Non-small-cell lung cancer, Lymph node, Metastasis, Multivariable logistic model
Background
Lung cancer is the leading cause of cancer death worldwide [1] and metastasis to lymph nodes directly determines the stage and prognosis of this disease. Computed tomography (CT) remains the most widely used tool for assessment of the tumour and lymph node involvement in patients with early-stage non-small-cell lung cancer (NSCLC) [2–5]. In general, lymph nodes with short-axis diameters of >1 cm seen on CT scan are considered metastatic. Unfortunately, the accuracy of CT scan for preoperative lymph node stage is only 45%–79% [2–6]. In addition, studies have demonstrated that 12%–17% of patients histologically confirmed as N2 are preoperatively diagnosed as N0 because their CT scan results showed the involved lymph nodes to have short-axis diameters of <1 cm [4, 5, 7]. Many other methods of preoperative N-staging, e.g. positron emission tomography, mediastinoscopy and endoscopic ultrasound-guided fine-needle aspiration, are not routinely used for patients with clinical stage I disease. In addition, these methods yield a considerable number of false-negative results [8–10].

There is ample high-quality evidence on the advantages of lymph node dissection in lung cancer surgery, including the American College of Surgeons Oncology Group (ACOSOG) Z0030 trial [11], although the benefits of complete lymph node dissection for patients with stage I NSCLC are still controversial [12–14]. There is little information on which pattern should be chosen to perform lymph node dissection for patients intraoperatively diagnosed as stage I non-small-cell lung cancer. A non-invasive prediction model that is able to predict lymph node metastasis would allow surgeons to make appropriate decisions on the extent of the dissection, removing lymph nodes that are most likely to contain metastases, while avoiding unnecessary tissue damage in order to accelerate patients’ postoperative recovery.

The goal of this study was to identify risk factors that would predict differences in lymph node metastasis and to develop a scoring system to predict the presence of lymph node metastasis. The aim is to determine the appropriate pattern of lymph node dissection for various patients intraoperatively diagnosed as stage I NSCLC.

Methods
Patient selection
A total of 284 consecutive patients who underwent surgical resection for primary lung cancer at our hospital from January 2013 to December 2014 were reviewed retrospectively. The records of patients intraoperatively diagnosed as stage I NSCLC who underwent lobectomy with complete lymph node dissection according to the lymph node nomenclature were selected for this study. All patients met the criteria for stage I NSCLC based on the new International Staging System for NSCLC (National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2014: Staging Non-Small Cell Lung Cancer) [15]. We excluded patients from this study who met any one of the following conditions: 1) tumour size > 4 cm and lymph node > 1 cm at the largest diameter on CT imaging or evidence of distant metastasis; 2) preoperative chemotherapy or radiotherapy; 3) previous or coexistent tuberculosis or malignant disease; 4) complete lymph node dissection that did not meet the current standards (i.e. all lymph node stations, including right-hand stations 2–4 and 7–9 and left-hand stations 2–9); 5) pure ground-glass opacity on CT imaging; 6) synchronous lung cancers, 7) sublobar resection, segmentectomy or partial resection or 8) Intraoperative frozen rapid pathological results showed tumour size > 4 cm in the largest diameter.

Patients were preoperatively assessed with chest x-ray, chest and upper abdominal CT scan, brain magnetic resonance imaging and bone scintigraphy. CT scan was used for preoperative N-staging. The surgical approach for primary lung cancer resection was via video-assisted thoracic surgery.

Statistical analysis
The baseline patient characteristics were summarized in percentages for categorical variables and as mean ± SD (Standard Deviation) for continuous variables. The chi-square test and Fisher’s exact tests were used to analyse differences in these percentages between the groups. Differences between the groups were analysed using the Kruskal–Wallis test. Significance of associations with the outcome of nodal metastases was first evaluated using a univariate logistic analysis. Those significant variables were analysed by multivariable analysis as independent predictors for lymph node metastasis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Clinically relevant variables obtained by multivariable analysis were included in the multivariable model. The resulting model coefficients were applied to the cohort to calculate predicted values from the logistic equation: \( \hat{y} = 1/[1 + \exp. (-x\beta)] \). All confidence intervals, significance tests and resulting P values were two-sided, with an alpha level of 0.05. Statistical analyses were performed using STATA software, release 13.

Results
Patient characteristics and prevalence of lymph node metastasis
A total of 284 patients intraoperatively diagnosed as stage I NSCLC were included in this study. Table 1 shows the patients’ demographics and clinical characteristics. The mean age was 60.78 years (range 31–83). Histologically, the tumours in 248 patients (87%) were identified as adenocarcinoma and in 36 (13%) as squamous cell carcinoma. The tumour originated in the right upper lobe in 82 patients (29%), right middle lobe in 16...
(6%), right lower lobe in 39 (14%), left upper lobe in 77 (27%), left lower lobe in 51 (18%) and in mixed lobes in 19 (6%). Mean tumour size was 2.44 cm (range from 0.4 to 4 cm). The tumour differentiation included I (86 patients, 30%), II (176 patients, 62%), III (22 patients, 8%). Pleural invasion was present in 64 patients (23%) and bronchus invasion in 37 (13%).

**Table 1** Patient Demographics and Clinical Characteristics

| Variables                | Value |
|--------------------------|-------|
| Number                   | 284   |
| Age (years)              |       |
| Mean ± SD (range)        | 60.78 ± 9.2 (31–83) |
| Gender (%)               |       |
| Male                     | 144 (51%) |
| Female                   | 140 (49%) |
| Pathology                |       |
| Squamous cell carcinoma  | 36 (13%) |
| Adenocarcinoma           | 248 (87%) |
| Tumor location (%)       |       |
| Right Upper Lobe         | 82 (29%) |
| Right Middle Lobe        | 16 (6%)  |
| Right Lower Lobe         | 39 (14%) |
| Left Upper Lobe          | 77 (27%) |
| Left Lower Lobe          | 51 (18%) |
| Mixed lobes              | 19 (6%)  |
| Differentiation (%)      |       |
| I                        | 86 (30%) |
| II                       | 176 (62%) |
| III                      | 22 (8%)  |
| Tumor size (cm)          |       |
| Mean ± SD (range)        | 2.44 ± 0.97 (0.4-4 cm) |
| Pleura invasion          |       |
| Absent                   | 220 (77%) |
| Present                  | 64 (23%) |
| Bronchus invasion        |       |
| Absent                   | 247 (87%) |
| Present                  | 37 (13%) |
| Multicentric invasion (%)|       |
| Absent                   | 264 (93%) |
| Present                  | 20 (7%)  |
| Angiolympathic invasion (%)| 274 (96%) |
| Absent                   | 10 (4%)  |
| Neural invasion          |       |
| Absent                   | 283 (100%) |
| Present                  | 1 (0%)   |

**Table 2** Demographics of patients in the Negative lymph Node Metastases (LNM) and Positive LNM groups

| Variables                | Group               | P value |
|--------------------------|---------------------|---------|
| Number                   | 215                 | 69      |
| Age (years)              |                     |         |
| Mean ± SD                | 61.27 ± 9.38        | 59.28 ± 8.49 |
| Gender                   |                     |         |
| Male                     | 109                 | 35      |
| Female                   | 106                 | 34      |
| Pathology                |                     |         |
| Squamous cell carcinoma  | 24                  | 12      |
| Adenocarcinoma           | 191                 | 57      |
| Tumor location           |                     |         |
| Right Upper Lobe         | 62                  | 20      |
| Right Middle Lobe        | 14                  | 2       |
| Right Lower Lobe         | 28                  | 11      |
| Left Upper Lobe          | 63                  | 14      |
| Left Lower Lobe          | 34                  | 17      |
| Mixed lobes              | 14                  | 5       |
| Differentiation (%)      |                     | <0.001* |
| I                        | 80                  | 6       |
| II                       | 119                 | 57      |
| III                      | 16                  | 6       |
| Tumor size (cm)          |                     | <0.001  |
| Mean ± SD                | 2.28 ± 0.95         | 2.92 ± 0.87 |
| Pleura invasion          |                     | 0.033*  |
| Absent                   | 173                 | 47      |
| Present                  | 42                  | 22      |
| Bronchus invasion        |                     | <0.001  |
| Absent                   | 196                 | 51      |
| Present                  | 19                  | 18      |
| Multicentric invasion (%)|                     | 1 (Fish) |
| Absent                   | 200                 | 64      |
| Present                  | 15                  | 5       |
| Angiolympathic invasion (%)|                   | 0.263 (Fish) |
| Absent                   | 209                 | 65      |
| Present                  | 6                   | 4       |
| Neural invasion          |                     | 1.0 (Fish) |
| Absent                   | 214                 | 69      |
| Present                  | 1                   | 0       |

SD standard deviation

*P < 0.05
location, tumour differentiation, tumour size, pleural invasion, bronchus invasion, multicentric invasion, neural invasion and angiolymphatic invasion. Compared with group I, group II had a significantly larger tumour size than that in group I (2.92 ± 0.87 vs. 2.28 ± 0.95, \( P < 0.001 \)). There were significant statistical differences between the groups by the \( \chi^2 \) test in terms of tumour differentiation (I, II, III) (\( P < 0.001 \)), bronchus invasion (absent vs. present) (\( P < 0.001 \)) and pleural invasion (absent vs. present) (\( P = 0.033 \)).

To evaluate the predictive value of tumour size between the groups, we used Receiver Operating Characteristic (ROC) curve analysis. As shown in Fig. 1, the area under the ROC curve for tumour size between group I and group II was 0.691 (95% CI: 0.621–0.761; \( P < 0.001 \)); the optimal cut-off value was 2.650 cm (sensitivity: 67%; specificity: 70%; Youden’s index: 0.364).

### Association of Individual Pathologic Characteristics with Nodal Metastasis

Univariate analysis showed that tumour size greater than 2.650 cm (OR =4.62, 95% CI 2.59–8.24; \( P < 0.001 \)), tumour differentiation (I vs II + III, OR =6.22, 95% CI 2.58–15.03; \( P < 0.001 \)), pleural invasion (absent vs present, OR =1.93, 95% CI 1.05–3.54; \( P = 0.034 \)) and bronchus invasion (absent vs present, OR =3.64, 95% CI 1.78–7.44; \( P < 0.001 \)) were the four significant risk factors associated with the presence of metastatic lymph nodes (Table 3).

### Multivariable analysis of pathologic characteristics associated with nodal metastasis

Multivariate analysis of the four risk factors obtained on univariate analysis showed that only the tumour size (\( \leq 2.65 \text{ cm} \) vs. \( >2.65 \text{ cm} \), OR =3.23, 95% CI 1.75–5.93; \( P < 0.001 \)), tumour differentiation (I vs II + III, OR =3.64, 95% CI 1.44–9.16; \( P = 0.006 \)) and bronchus invasion (absent vs. present, OR =2.54, 95% CI 1.18–5.46; \( P = 0.017 \)) were independent predictors associated with the presence of metastatic lymph nodes. However, pleural invasion (absent vs. present, OR =1.64, 95% CI 0.84–3.21; \( P = 0.146 \)) was not a significant predictor of lymph node metastasis (Table 4).

### Multivariable logistic regression model derivation and development

On multivariable analysis, only three covariates remained in the final model. Using these three variables (Table 5), a scoring system was developed to discriminate between patients with and without lymph node metastasis. The risk scores for individual patients were calculated using the following formula: \( \hat{\beta} = -2.947 + (1.368 \times \text{Differentiation (I vs. II + III, I} = 0, \text{ II + III} = 1)) + (1.188 \times \text{Tumour Size (2.65 cm vs. >2.65 cm, } \leq 2.65 \text{ cm} = 0, >2.65 \text{ cm} = 1)) + (0.876 \times \text{Bronchus Invasion (absent =0, present =1)}). \)

The probabilities of lymph node metastasis were calculated using the following formula (\( \hat{y} = 1/(1 + \exp(-\hat{\beta})) \)): \( \hat{y} = 1/(1 + \exp(-2.947 - (1.368 \times \text{Differentiation (I vs. II + III, I} = 0, \text{ II + III} = 1)) - (1.188 \times \text{Tumour Size (2.65 cm vs. >2.65 cm, } \leq 2.65 \text{ cm} = 0, >2.65 \text{ cm} = 1)) - (0.876 \times \text{Bronchus Invasion (absent =0, present =1)})) \).
As shown in Fig. 2, the area under the ROC curve of the selected model was 0.753 (95% CI 0.692–0.814, standard error 0.031) and the optimal cut-off value was 0.7997 ≈ 0.80 (sensitivity: 71%, specificity: 71%, Youden’s index: 0.417). In all patients, using a score threshold of ≤0.80, 20 (12%) of 172 patients with lymph node metastasis were correctly identified, whereas 152 (88%) of 172 without lymph node metastasis were correctly identified. Using a score threshold of >0.80, 49 (44%) of 112 patients with lymph node metastasis were correctly identified, whereas 63 (56%) of 112 without lymph node metastasis were correctly identified.

When all three covariates (tumour size, tumour differentiation, bronchus invasion) were equal to zero, we found that the cut-off value was 0.42685 ≈ 0.43. In all patients, using a score threshold of ≤0.43, 2 (3%) of 71 patients with lymph node metastasis were correctly identified, whereas 69 (97%) of 71 without lymph node metastasis were correctly identified. Using a score threshold of >0.43, 67 (31%) of 213 patients with lymph node metastasis were correctly identified, whereas 146 (69%) of 213 without lymph node metastasis were correctly identified.

Using a score threshold between 0.43 and 0.80, 18 (18%) of 101 patients with lymph node metastasis were correctly identified, whereas 83 (82%) of 101 without lymph node metastasis were correctly identified. So, we obtained three score thresholds, ŷ ≤ 0.43, 0.43 < ŷ ≤ 0.80 and ŷ > 0.80.

**Discussion**

A complete lymph node dissection, removing all ipsilateral lymph nodes which can be seen at operation [16], can provide more accurate pathologic staging and better clinical outcomes for some patients. It is considered a standard surgical treatment for patients diagnosed preoperatively with lymph node metastasis. However, complete lymph node dissection is not regarded as a routine surgical procedure for patients intraoperatively diagnosed as stage I NSCLC, as some studies have demonstrated a lack of significant differences in outcome between selective lymph node sampling and complete lymph node dissection in patients with early-stage lung cancer [13, 17].

However each patient exhibits different clinical characteristics that affect the risk of lymph node metastasis in early-stage lung cancer. In this study, we collected
pathology data from 284 patients intraoperatively diagnosed as stage I NSCLC who underwent lobectomy with complete lymph node dissection and investigated factors that might be associated with metastasis to lymph nodes (age, gender, pathology, tumour location, tumour differentiation, tumour size, pleural invasion, bronchus invasion, multicentric invasion and angiolymphatic invasion).

First, we used univariate analysis to find associations between pathologic factors and lymph node metastasis. The results showed that only the tumour size (>2.65 cm), tumour differentiation, pleural invasion and bronchus invasion were significant risk factors. The other factors tested, including age, gender, pathologic type, tumour location, multicentric invasion, angiolymphatic invasion and neural invasion were excluded as risk factors associated with lymph node metastasis.

Furthermore, multivariate analysis of the four risk factors identified on univariate analysis found that only tumour size (>2.65 cm), tumour differentiation and bronchus invasion were independent predictors of lymph node metastasis. Pleural invasion was excluded as an independent predictor in this analysis.

These three independent predictors were kept in the final model. After developing the multivariable logistic regression model, we finally obtained three score thresholds, \( \hat{y} \leq 0.43, 0.43 < \hat{y} \leq 0.80 \) and \( \hat{y} > 0.80 \) (Table 6). As shown

![Fig. 2 The ROC (Receiver Operating Characteristic) curve of the selected model](image)

| Variables | \( \hat{y} \leq 0.43 \) | | | 0.43 ~ 0.80 | | | \( \hat{y} > 0.80 \) |
|---|---|---|---|---|---|---|
| | Negative LNM | Positive LNM (%) | Total | Negative LNM | Positive LNM (%) | Total | Negative LNM | Positive LNM (%) | Total |
| Num | 69 | 2(3) | 71 | 83 | 18(18) | 101 | 63 | 49(44) | 112 |
| Differentiation | | | | | | | | | |
| I | 69 | 2(3) | 71 | 11 | 2(15) | 13 | 0 | 2(100) | 2 |
| II + III | – | – | – | 72 | 16(18) | 88 | 63 | 47(43) | 110 |
| Tumor size(cm) | | | | | | | | | |
| ≤ 2 | 57 | 0(0) | 57 | 50 | 13(20) | 64 | 4 | 4(50) | 8 |
| 2 ~ 2.65 | 12 | 2(14) | 14 | 22 | 4(15) | 26 | 5 | 0(0) | 5 |
| > 2.65 | – | – | – | 11 | 1(8) | 12 | 54 | 45(45) | 99 |
| Bronchus invasion | | | | | | | | | |
| Absent | 69 | 2(3) | 71 | 83 | 17(17) | 100 | 44 | 32(42) | 76 |
| Present | – | – | – | 0 | 1(100) | 1 | 19 | 17(47) | 36 |
in the table, we found that when $\hat{y}$ was $\leq 0.43$, patients with lymph node metastasis accounted for 3% of all patients, and when $\hat{y}$ was $> 0.43$ and tumour size was $\leq 2$ cm, no patients had lymph node metastasis. However, when $\hat{y}$ was $\leq 0.43$ and tumour size was $> 2$ cm, the percentage of patients identified with lymph node metastasis increased to 14%. With $0.43 < \hat{y} \leq 0.80$, patients with lymph node metastasis accounted for 18% of all patients. When $\hat{y}$ was $> 0.80$, the patients with lymph node metastasis accounted for 44% of all patients.

Thus we demonstrated that lymph node dissection is not necessary for those patients intraoperatively diagnosed as Stage I NSCLC whose $\hat{y}$ value obtained from the model is less than or equal to 0.43 and whose tumour size is $\leq 2$ cm. Complete lymph node dissection or lymph node sampling would be appropriate if the $\hat{y}$ value from the model is less than or equal to 0.43 but the tumour size is $> 2$ cm or if $\hat{y}$ is more than 0.43 and less than or equal to 0.80. Complete lymph node dissection must be performed for patients whose $\hat{y}$ value obtained from the model is more than 0.80.

However, our study has some limitations. This study was conducted at a single institution with retrospective methods and demonstrated the necessity of further prospective study. Further prospective study with multicenter trial should be performed to comprehensively evaluate this model for prediction of lymph node metastases in patients intraoperatively diagnosed as Stage I non-small cell lung cancer.

**Conclusions**

After a comprehensive analysis of our results concerning various clinical factors, we conclude that the incidence of lymph node metastasis would be lowest when we obtained a $\hat{y}$ value from the model less than or equal to 0.43 along with a tumour size $\leq 2$ cm. For other patients intraoperatively diagnosed as stage I NSCLC, the risk of lymph node lymph node metastasis was greater, so that complete lymph node dissection or lymph node sampling is necessary.

**Additional file**

Additional file 1: Support file containing the Age ranges, Pathology, location, Differentiation, Tumor size 2.65 cm, Pleura invasion, Bronchus Invasion, Multicentric invasion, Angiolymphatic invasion, Neural invasion and LNM (lymph node metastasis) described in categorical variables and Tumorsize, $x\beta$ and $\hat{y}$ described in continuous variables. (XLSX 32 kb)

**Abbreviations**

ACOSOG: American College of Surgeons Oncology Group; CT: Computed tomography; NSCLC: Non-small-cell lung cancer; ROC: Receiver Operating Characteristic; SD: Standard Deviation

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**Availability of data and materials**

We presented raw data within Additional file 1.

**Authors’ contributions**

ZF and ZY drafted the manuscript. GP, HC, YY, LJ, SY, MY, XJ, JT, ZZ, SJ participated in collecting clinical data and performed the statistical analysis. WW conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

This study was conducted in accordance with the amended Declaration of Helsinki. The approval of the Ethical Committee of Nanjing Medical University was obtained (project approval no. 2012-SRFA-161). The written informed consent from either the patients or their representatives was waived due to the retrospective nature of this study in accordance with the American Medical Association.

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