Original Article

Predictive risk factors for lymph node metastasis in patients with small size non-small cell lung cancer

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Background: Accurate clinical staging of non-small cell lung cancer (NSCLC) is essential for developing an optimal treatment strategy. This study aimed to determine the predictive risk factors for lymph node metastasis, including both N1 and N2 metastases, in clinical T1aN0 NSCLC patients.

Methods: We retrospectively evaluated clinical T1aN0M0 NSCLC patients who showed no radiologic evidence of lymph node metastasis, and who had undergone surgical pulmonary resection with systematic mediastinal node dissection or sampling at the First Affiliated Hospital of Zhejiang University between January 2011 and June 2013. Univariate and multivariate logistic regression analyses were performed to identify predictive factors for node metastasis.

Results: Pathologically positive lymph nodes were found in 16.2% (51/315) of the patients. Positive N1 nodes were found in 12.4% (39/315) of the patients, and positive N2 nodes were identified in 13.0% (41/315) of the patients. Some 9.2% (29/315) of the patients had both positive N1 and N2 nodes, and 3.8% (12/315) of the patients had nodal skip metastasis. Variables of preoperative radiographic tumor size, non-upper lobe located tumors, high carcinoembryonic antigen (CEA) levels and micropapillary predominant adenocarcinoma (AC) were identified as predictors for positive N1 or N2 node multivariate analysis.

Conclusions: Pathologically positive lymph nodes were common in small size NSCLC patients with clinical negative lymph nodes. Therefore, preoperative staging should be performed more thoroughly to increase accuracy, especially for patients who have the larger size, non-upper lobe located, high CEA level or micropapillary predominant ACs.

Keywords: Non-small cell lung cancer (NSCLC); lymph node metastasis; sublobar resections

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with a 5-year survival rate of 16% (1). With the widespread use of low-dose computed tomography, more small size (2 cm or less) non-small cell lung cancers (NSCLC) are being discovered (2). It is important to accurately stage NSCLC before treatment, as the treatment varies by stages. As for pT1aN0 NSCLC patients, lobectomies are recommended, as suggested by a randomized control trial performed by the Lung Cancer Study Group in 1995 (3). However, recent studies have indicated that for T1aN0M0 NSCLC patients, segmentectomy is as effective as lobectomy (4). For patients with T1aN1 NSCLC, the choice of treatment is controversial, as a recent multicenter phase III study favored neoadjuvant chemotherapy rather than surgery alone (5). However, for patients with T1aN2 NSCLC, it is clearly beneficial to take neoadjuvant chemotherapy (6).

Many sophisticated examination methods are being used for the accurate nodal staging of lung cancer patients. These methods include both non-invasive and invasive examination procedures such as integrated fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT), endobronchial

ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and mediastinoscopy (7). As for small size NSCLC patients, the frequencies for positive N1 and N2 are 5% and 4-10%, respectively, which are quite low (8-11). Therefore, this study aimed to determine the predictive risk factors for lymph node metastasis (including both N1 and N2 metastases) in clinical T1aN0 NSCLC patients.

Patients and methods

Patients

We retrospectively evaluated cT1aN0M0 NSCLC patients who showed no radiologic evidence of lymph node metastasis, and who underwent surgical pulmonary resections with systematic mediastinal node dissections or sampling at the First Affiliated Hospital of Zhejiang University between January 2011 and June 2013. Patients who received preoperative chemotherapy and/or radiation therapy were excluded from this study.

All of the participating patients underwent preoperative staging with contrast-enhanced CT scans. Mediastinal lymph nodes were considered to be positive by CT-scan criteria if their short axis was 1 cm wide or more. Additional diagnostic examinations [including brain magnetic resonance imaging (MRI) or CT, pulmonary function analysis, abdominal ultrasonography, bronchoscopy and bone scanning] were performed before each surgery, as was routine. However, no invasive examinations for mediastinal staging such as mediastinoscopy, EBUS-TBNA or EUS-FNA were used preoperatively.

We reviewed the medical records of each patient for demographic and clinical data. These data included age, sex, smoking status, preoperative serum carcinoembryonic antigen (CEA) level (<5 or ≥5 ng/mL), tumor lobe distribution (upper, middle or lower lobes), tumor location (central or peripheral), tumor size on preoperative radiologic findings, tumor histology [adenocarcinoma (AC), squamous-cell carcinoma or other cell types], symptoms at presentation, and node staging according to pathologic reports. Tumor locations were assessed with bronchoscopy. If the bronchoscopy showed a visible lesion, the location was defined as central. If no visible lesion was found, the location was defined as peripheral. Tumor staging was based on AJCC 7th edition of TNM staging, and the subtype of AC was determined according to the IASLC/ATS/ERS classification (12).

This study was approved by the institutional review board of the First Affiliated Hospital of Zhejiang University. As this was a retrospective analysis, the need to obtain written informed consent from each patient was waived.

Statistical analysis

Univariate analyses and multivariate logistic regression analyses were performed to identify predictors for positive N1 and N2 nodes. Fisher's exact test and Pearson's chi-squared test were used for the univariate analyses. A stepwise selection method was used to build logistic regression models. In the multivariate analyses, categorical variables (sex, tumor location, lobe distribution of tumor, smoking history, symptoms of presentation and tumor histology) and continuous variables (age, preoperative serum CEA level and tumor size on preoperative radiologic findings) were assessed to identify independent predictors. A probability value less than 0.05 was considered statistically significant. All analyses were performed using IBM SPSS 20.0 (IBM Co., Chicago, IL, USA).

Results

Patient characteristics

This study included 315 patients who had clinical T1aN0 non-small lung cancer between January 2011 and June 2013. The patient characteristics are shown in *Table 1*. There were 148 men (47.0%) and 167 women (53.0%). The median age was 59.4 years (range from 32 to 82 years). Some 218 patients (69.2%) were never smokers, and 97 patients (30.8%) were current or former smokers. Centrally located tumors were found in 32 (10.2%) of the patients. The histology of tumors consisted of AC in 281 (89.2%), squamous cell carcinoma (SQC) in 30 (9.5%) and other cell types in four (1.3%) of the patients.

Pathologically positive lymph nodes were found in 16.2% (51/315) of the patients. Positive N1 nodes were found in 12.4% (39/315), and positive N2 nodes were identified in 13.0% (41/315) of the patients. Some 9.2% (29/315) of the patients had both positive N1 and N2 nodes, and 3.8% (12/315) had nodal skip metastasis. Pathological N1 stage was identified in 3.2% (10/315) of the patients, and pathological N2 stage was found in 13.0% (41/315).

Table 1 Patients characteristics

Characteristics	No. of patients	Percentage
Sex		
Male	148	47.0
Female	167	53.0
Age		
<59	153	48.6
≥59	162	51.4
Smoking status		0.0
Never	218	69.2
Current or former	97	30.8
Symptom		
Absent	225	71.4
Present	80	25.4
Tumor size		
≤1 cm	60	19.0
1-2 cm	255	81.0
Tumor location		
Central	32	10.2
Peripheral	283	89.8
Lobe distribution		
LLL	14	4.4
LUL	36	11.4
RLL	26	8.3
RML	18	5.7
RUL	63	20.0
Histology		
AC	281	89.2
SQC	30	9.5
Others	4	1.3

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobes; RML, right middle lobes; RUL, right upper lobes; AC, adenocarcinoma; SQC, squamous cell carcinoma.

Table 2 Univariate analysis of positive N1 nodes

Variables	Negative N1 node (%)	Positive N1 node (%)	P value
Sex			
Male	125 (84.5)	23 (15.5)	
Female	151 (90.4)	16 (9.6)	0.109
Age			
<59	142 (86.3)	21 (13.7)	
≥59	144 (88.9)	18 (11.1)	0.623
Smoking status			
Never	197 (90.4)	21 (9.6)	
Current or former	81 (81.4)	18 (18.6)	0.032
Symptom			
Absent	210 (89.4)	25 (10.6)	
Present	66 (82.5)	14 (17.5)	0.108
Tumor size			
≤1 cm	60 (100)	0 (0)	
1-2 cm	216 (84.7)	39 (15.3)	<0.001
Tumor location			
Central	20 (62.5)	12 (37.5)	
Peripheral	256 (90.5)	27 (9.5)	<0.001
Lobe distribution			
UL	186 (93.5)	13 (6.5)	
Non-UL	90 (77.6)	26 (22.4)	<0.001
Histology			
AC	252 (89.7)	29 (10.3)	
Non-AC	24 (70.6)	10 (29.4)	0.001
MPA	16 (66.7)	8 (33.3)	0.004
CEA			
<5	231 (80.9)	23 (9.1)	
≥5	46 (74.2)	16 (25.8)	<0.001

UL, upper lobes; AC, adenocarcinoma; MPA, micropapillary adenocarcinoma; CEA, carcinoembryonic antigen.

Univariate analysis of predictive factors for nodal metastasis

As shown in *Table 2*, the univariate analysis identified the following variables as significant predictive factors for positive N1 nodes: current or former smoker (P=0.032), centrally located tumor (P<0.001), non-AC (P=0.001), micropapillary adenocarcinoma (MPA) (P=0.004), tumor size (P<0.001), non-upper lobe located tumor (P<0.001) and preoperative serum CEA level of 5 ng/mL or more (P=0.001). Symptoms at presentation, age and sex were not identified as significant predictive factors. As for positive N2 nodes, tumor size (P=0.010), MPA (P<0.001), non-upper lobe located tumors (P=0.006) and a preoperative serum CEA level of 5 ng/mL or more (P<0.001) were identified as significant predictors (*Table 3*).

Multivariate analysis of predictive factor for nodal metastasis

The multivariate analysis revealed the following four

Table 3 Univariate analysis of positive N2 nodes

Variables	Negative N2 node (%)	Positive N2 node (%)	P value
Sex			
Male	127 (85.8)	21 (14.2)	
Female	147 (88.0)	20 (12.0)	0.561
Age			
<59	128 (83.7)	25 (16.3)	
≥59	146 (91.0)	16 (9.0)	0.088
Smoking status			
Never	193 (88.5)	25 (11.5)	
Current or former	81 (83.5)	16 (16.5)	0.221
Symptom			
Absent	206 (77.7)	29 (12.3)	
Present	68 (85.0)	12 (15.0)	0.541
Tumor size			
≤1 cm	58 (96.7)	2 (3.3)	
1-2 cm	216 (84.7)	39 (15.3)	0.010
Tumor location			
Central	26 (81.2)	6 (18.8)	
Peripheral	248 (87.6)	35 (12.4)	0.459
Lobe distribution			
UL	181 (91.0)	18 (9.0)	
Non-UL	92 (80.0)	23 (20.0)	0.006
Histology			
AC	244 (86.8)	37 (13.2)	
Non-AC	30 (88.2)	4 (11.8)	0.818
MPA	14 (58.3)	10 (41.7)	<0.001
CEA			
<5	230 (80.9)	23 (9.1)	
≥5	44 (71.0)	18 (29.0)	<0.001

UL, upper lobes; AC, adenocarcinoma; MPA, micropapillary adenocarcinoma; CEA, carcinoembryonic antigen.

significant predictors for node metastasis: tumor size on preoperative radiologic findings [odds ratio (OR) =4.597; 95% confidence interval (CI): 1.427-14.815; P=0.011), non-upper lobe located tumors (OR =2.758; 95% CI: 1.345-5.656; P=0.006), preoperative serum CEA level (OR =1.195; 95% CI: 1.072-1.331; P=0.001) and MPA (OR =3.875; 95% CI: 1.374-10.933; P=0.010) (*Table 4*).

The predictive factors of positive N1 nodes by multivariate analysis were tumor size on preoperative radiologic findings (OR =7.524; 95% CI: 1.608-35.211; P=0.010), non-upper lobe located tumors (OR =3.343; 95% CI: 1.412-7.916; P=0.006), preoperative serum CEA level (OR =1.205; 95% CI: 1.076-1.349; P=0.001) and MPA (OR =3.955; 95% CI: 1.280-12.221; P=0.017) (*Table 4*).

The predictive factors of positive N2 nodes according to multivariate analysis were tumor size on preoperative radiologic findings (OR =4.284; 95% CI: 1.276-14.382; P=0.019), non-upper lobe located tumors (OR =2.577; 95% CI: 1.204-5.516; P=0.015), preoperative serum CEA level (OR =1.099; 95% CI: 1.030-1.173; P=0.004) and MPA (OR =4.038; 95% CI: 1.481-11.010; P=0.006) (*Table 4*).

Discussion

In this study, we identified tumor size (according to preoperative radiologic findings), non-upper lobe located tumors, preoperative serum CEA level and MPA as the four statistically significant predictors of both positive N1 and N2 nodes.

Precise assessment of lymph node metastasis is important for deciding the optimal treatment for patients with operable NSCLC. The survival rate is similar in patients with small NSCLC treated with segmentectomy and those treated with lobectomy (4,13). However, in theory, segmentectomy candidates should be node negative. Therefore, predicting pathological lymph node

Table 4 Multivariate analysis of positive node

Variables	Positive node		Positive N1 node		Positive N2 node	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Size	4.597 (1.427-14.815)	0.011	7.524 (1.608-35.211)	0.010	4.284 (1.276-14.382)	0.019
Non-UL	2.758 (1.345-5.656)	0.006	3.343 (1.412-7.916)	0.006	2.577 (1.204-5.516)	0.015
CEA	1.195 (1.072-1.331)	0.001	1.205 (1.076-1.349)	0.001	1.099 (1.030-1.173)	0.004
MPA	3.875 (1.374-10.933)	0.010	3.955 (1.280-12.221)	0.017	4.038 (1.481-11.010)	0.006

UL, upper lobes; CEA, carcinoembryonic antigen; MPA, micropapillary adenocarcinoma; OR, odds ratio; CI, confidence interval.

metastasis in patients with clinical T1aN0 lung cancer is of clinical significance for selecting optimal segmentectomy candidates. The prevalence of lymph node metastasis in patients with tumors of 2 cm is approximately 4-10%, which is quite low (8-10). In this study, the incidence of pathological N1 and N2 stages were 3.2% and 13%, respectively, which was consistent with previous studies (8-10). Radiological tumor size is a risk factor for nodal metastasis in clinical node-negative NSCLC patients (8,14-16). However, for tumors of 2 cm or less, the role of tumor size in predicting nodal metastasis remains controversial. Zhang and colleagues reported that the incidence of N1 and N2 metastasis for tumors of 1 cm or less and of 1 to 2 cm were 3.8% (2/51) and 7.4% (14/190), respectively. Large tumor size is commonly associated with aggressive node stage, but no statistical significance for this association was found in this study (9). However, Farjah (17) recently reported that for tumors of 1 cm or less and of 1 to 2 cm, with clinical node negative disease measured by the mean of positron emission tomography (PET), the frequencies of N2 metastases were 25% (8/32) and 4.3% (10/232), respectively. This result indicated that tumors of smaller size with clinical node-negative disease had a high prevalence of pathological N2 metastasis. In our study, large radiographic tumor size was one of the significant predictive factors for node metastasis.

According to our results, lobe distribution of tumors was not a significant predictor for nodal involvement. However, the distributions did suggest that non-upper lobe located tumors had a tendency toward higher incidence of lymph node metastasis (9,14,18). We speculate that a difference in nodal involvement exists between the upper lobe located tumors and the non-upper located tumors. Our data revealed that the incidences of positive N1 and N2 were different between the upper located group and non-upper located group. Both the univariate and multivariate logistic regression analyses identified tumor location as a significant predictor for nodal metastasis. According to present knowledge, the differential in nodal metastases between the upper located and non-upper located tumors may be caused by the different nodal spread patterns in the two types of locations (11).

Serum CEA level was associated with the post-operative pathological stage and prognosis (14,16,18,19). Inoue (19) reported that compared to patients with normal preoperative serum CEA levels and with NSCLC tumors of 2 cm or less in diameter, the 5-year mortality rate for patients with higher CEA levels (≥5 ng/mL) was significantly worse (92.1% *vs.* 77.6%; P<0.01). In addition, increased CEA level was associated with a much higher rate of lymph node metastasis with small size NSCLC (29.2% *vs.* 10.3%; P=0.02). Koike and colleagues reported that preoperative serum CEA level was a predictor for mediastinal nodal metastasis in clinical stage IA NSCLC patients (14). In our study, preoperative serum CEA level was determined to be a significant predictor of lymph node metastasis. This finding indicates that an elevated CEA level is associated with increased lymph node metastasis, might explain the worse prognoses of NSCLC patients with higher CEA levels. Care should thus be taken against lymph node metastasis in patients with high CEA levels.

In 2011, the IASLC/ATS/ERS added micropapillary predominant AC as a new subtype of lung AC (12). Micropapillary predominant AC is of great significance because of its poor prognosis and its higher likelihood of metastasis (20,21). Roh (20) reported that 62.5% (10/16) of patients with a micropapillary component and 21.1% (4/19) of patients with other subtypes of lung AC showed nodal micrometastasis (P=0.014). This finding suggested that a micropapillary component may be a manifestation of aggressive behavior, as shown by frequent nodal micrometastasis. Warth and colleagues (22) reported similar results, finding that 76% of micropapillary-predominant ACs were node positive. In addition, the overall survival rate was much worse for cases of micropapillary predominant AC than for cases of other subtypes. In our study, micropapillary predominant ACs had a much higher prevalence of both N1 and N2 nodes metastasis, and all of the patients with this condition had positive N1 nodes. This result might encourage surgeons to conduct more systematic lymph node dissections for patients with micropapillary predominant ACs. However, sublobar resections such as segmentectomies should be avoided.

We acknowledge that this study had some limitations. First, it was a retrospective study. Second, PET-CT was performed on only a small number of patients because of its unaffordable cost in China. Thus, a prospective, randomized trial needs to be conducted in which PET-CT is performed routinely.

In conclusion, we retrospectively analyzed 315 patients with clinical T1aN0M0 NSCLC who had undergone surgical pulmonary resection and systematic lymph node dissection or sampling at our center. Among these 315 patients, pathologically positive lymph nodes were found in 16.2% (51/315). The results indicate that preoperative staging should be performed more thoroughly to increase accuracy,

especially for patients who have larger size, non-upper lobe located, high CEA level and micropapillary predominant ACs. A prospective, randomized trial with routine PET-CT is warranted to validate our findings.

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