ORIGINAL ARTICLE

Lymph node metastasis in Chinese patients with clinical T1 non-small cell lung cancer: A multicenter real-world observational study

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Abstract

Background: Approximately 8.3–15.9% of patients with clinical stage I non-small cell lung cancer are subsequently shown to have lymph node metastasis. However, the clinical characteristics of patients with lymph node metastasis in China are not fully understood.

Methods: This is a multicenter retrospective analysis of pathological T1 non-small cell lung cancer patients who underwent surgical resection from 2 January 2014 to 27 December 2017. Clinical and pathological information was collected with the assistance of the Large-scale Data Analysis Center of Cancer Precision Medicine-LinkDoc database. The clinical and pathological factors associated with lymph node metastasis were analyzed by univariate and multivariate logistic regression.

Results: A total of 10 885 participants (51.6% women; 15.3% squamous cell carcinoma) were included in the analysis. The median age was 60.0 years (range 12.9–86.6 years). A total of 1159 patients (10.6%) had metastases in mediastinal nodes (N2), and 640 patients (5.9%) had metastasis in pulmonary lymph nodes (N1). Most patients had T1b lung cancer (4766, 43.8%). Of the patients, 3260 (29.9%) were current or former smokers. The univariate and multivariate analyses showed that younger age, squamous cell carcinoma, poor differentiation, larger tumor size, carcinoembryonic antigen level ≥5 ng/mL, and vascular invasion (+) were significantly associated with higher percentages of lymph node metastases ($P < 0.001$ for all).

Conclusion: This real-world study showed the significant association of lymph node metastasis with age, tumor size, histology and differentiation, carcinoembryonic antigen levels, and status of vascular invasion. Female patients with T1a adenocarcinoma in the right upper lobe barely had lymph node metastasis.

Introduction

Lung cancer, particularly non-small cell lung cancer (NSCLC), is the most commonly diagnosed cancer and is the leading cause of cancer-related death all over the world, especially in China.[1,2] Increased adoption of radiographic screening methods, such as low-dose helical computed tomography (CT), high-resolution computed tomography (HRCT), and positron-emission tomography/computed tomography (PET-CT), have resulted in the increased number of early-stage lung cancers diagnosed.[3] The International Association for the Study of Lung Cancer has defined T1 NSCLC by tumor size ≤3 cm in the greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus.[4] The percentage of nodal or extrathoracic metastases has been reported to be >20% in T1 NSCLC patients.[5–7] Surgery is still the standard treatment for T1 NSCLC, of which lobectomy with the dissection of hilar (N1) and mediastinal (N2) lymph nodes is usually the common method.[8] However, dissection of lymph nodes without metastasis might be futile, and might also increase perioperative complications or prolong surgery time.[9,10] Selective lymph node dissection was therefore argued to be more suitable than the systematic procedure in elderly patients with early-stage disease.[11–16] Understanding of patient demographic and tumor biological characteristics is critical for matching appropriate patients with individualized surgical procedures and forecasting patient prognoses.

The aim of this observational study is to collect real-world data on the clinical characteristics of the Chinese T1 NSCLC patients with lymph node metastases and explore potential factors that predict lymph node metastases in the target population, which might help with individualized surgical plans.

Methods

Patient population

This multicenter real-world observational study in China included pathologically established T1 NSCLC patients from 10 participating hospitals. The clinical and pathological information of patients was collected with the assistance of the Large-scale Data Analysis Center of Cancer Precision Medicine-LinkDoc database. All patients underwent segmentectomy or lobectomy with lymph nodes resection during a period from 2 January 2014 to 27 December 2017. Patients receiving chemotherapies, radiotherapies, biotherapies, or intervention therapies before surgery were excluded, as well as those who underwent lung wedge resection.

Data evaluation

Clinical and pathological information, including age, sex, pathological type, lymph node metastases, tumor size, location, differentiation, smoking history, preoperative serum carcinoembryonic antigen (CEA) levels, and vascular invasion, were retrospectively collected from 10 thoracic surgery centers. The study data were retrospectively reviewed and collected for: (i) the risk factors associated with lymph node metastases; and (ii) comparison of the percentages of patients with lymph node metastases. Patient diagnosis was according to the classifications of the International Association for the Study of Lung Cancer and surgical approaches at the surgeons' discretion. The study protocol was reviewed and approved by the ethics committee at all 10 sites, and was registered at www.clinicaltrials.gov before the study was initiated (NCT03413956).

Statistical analysis

Continuous variables are presented as mean ± standard. Categorical variables are presented as the frequency and percentage. Univariate and multivariate logistic regression analyses were carried out to examine the risk factors associated with lymph node metastases. Results are summarized as odds ratios (ORs) and two-side 95% confidential intervals (CIs). All variables with significant associations ($P < 0.05$) in univariate analysis were entered into the multivariate model. In addition, in view of the significant association of age with N2 lymph node metastasis in NSCLC or T1 NSCLC reported previously, it was also included into the multivariate analysis.[17,18] All variables with $P \leq 0.2$ were retained in the final model. All statistical analyses were two-sided, and were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as $P < 0.05$.

Results

Demographic characteristics and lymph node metastases of the patients

This study included a total of 10 885 patients who had pathological T1 (tumor size between 0 and 3 cm) NSCLC between 2014 and 2017 from 10 hospitals in China. The patient characteristics are shown in Table 1. Of the patients, 5265 were men (48.4%) with a median age of 60 years (range 12.9–86.6 years). A total of 458 patients were documented to have lymph node metastases preoperatively. On pathological diagnosis, 1808 patients (16.6%) were shown to have lymph node metastases. A total of 640 patients (5.9%) had metastasis in pulmonary lymph nodes (N1, 516 single N1 and 124 Multiple N1), and 1159

Table 1 Demographics and tumor characteristics of patients with T1 non-small cell lung cancer

	T1 non-small cell lung cancer			
Variable	Total (%)	pN0 (%)	pN+ (%)	*P*-value
All patients	10 885 (100%)	9077 (83.4%)	1808 (16.6%)	
Age				0.5646†
≤65 years	7797 (71.6%)	6512 (71.7%)	1285 (16.5%)	
>65 years	3088 (28.4%)	2565 (28.3%)	523 (16.9%)	
Sex				**<0.0001**
Male	5265 (48.4%)	4207 (46.3%)	1058 (20.1%)	
Female	5620 (51.6%)	4870 (53.7%)	750 (13.3%)	
Smoking history				**<0.0001**
Never smoke	7363 (67.6%)	6365 (71.8%)	998 (13.6%)	
Ever smoke	3260 (29.9%)	2497 (28.2%)	763 (23.4%)	
Unknown	262 (2.5%)	–	–	
Brinkman index‡				**<0.0001**
≤400	8309 (76.6%)	7098 (82.2%)	1211 (14.6%)	
>400	2039 (18.7%)	1533 (17.8%)	506 (24.6%)	
Unknown	537 (4.7%)	–	–	
Tumor histology				**<0.0001**
Adenocarcinoma	9216 (84.7%)	7916 (87.2%)	1300 (14.1%)	
Squamous cell carcinoma	1271 (11.7%)	885 (9.7%)	386 (30.4%)	
Others	398 (3.6%)	276 (3.0%)	122 (6.7%)	
Tumor grade				**<0.0001**
Poor differentiation	1765 (16.2%)	1126 (24.5%)	639 (36.2%)	
Moderate differentiation	3180 (29.2%)	2747 (59.7%)	433 (13.6%)	
Well differentiation	742 (6.8%)	727 (15.8%)	15 (2.0%)	
Tumor location[3]				**0.0099**
Upper lobe	6544 (60.1%)	5505 (60.6%)	1039 (15.9%)	
Middle lobe	820 (7.5%)	691 (7.6%)	129 (15.7%)	
Lower lobe	3521 (32.3%)	2881 (31.7%)	640 (18.2%)	
Tumor location[2]				**0.0008**
Left lobe	4508 (41.4%)	3695 (40.7%)	813 (18.0%)	
Right lobe	6377 (58.6%)	5382 (59.3%)	995 (15.6%)	
Tumor location[5]				**0.0003**
Left upper lobe	2887 (26.5%)	2378 (26.2%)	509 (17.6%)	
Left lower lobe	1621 (14.9%)	1317 (14.5%)	304 (18.8%)	
Right upper lobe	3657 (33.6%)	3127 (34.4%)	530 (14.5%)	
Right middle lobe	820 (7.5%)	691 (7.6%)	129 (15.7%)	
Right lower lobe	1900 (17.5%)	1564 (17.2%)	336 (17.7%)	
Tumor size (pathological)				**<0.0001**
>0 and ≤1 cm	2779 (25.5%)	2682 (29.5%)	97 (3.5%)	
>1 and ≤2 cm	4766 (43.8%)	4110 (45.3%)	656 (13.8%)	
>2 and ≤3 cm	3340 (30.7%)	2285 (25.2%)	1055 (31.6%)	
Preoperative serum CEA level				**<0.0001**
<5 ng/mL	5560 (51.1%)	4878 (88.9%)	682 (12.3%)	
≥5 ng/mL	1004 (9.2%)	606 (11.1%)	398 (39.6%)	
Unknown	4321 (39.7%)		-	
Vascular invasion				**<0.0001**
Positive	381 (3.5%)	8870 (97.9%)	188 (49.3%)	
Negative	10 488 (96.4%)	193 (2.1%)	1618 (15.4%)	
Unknown	16 (0.1%)	-	-	

Bold values (*P* < 0.05) indicate statistical significance. †χ²-test. ‡Scored as the number of cigarettes smoked per day multiplied by the number of years since smoking started. CEA, carcinoembryonic antigen.

patients (10.6%) had metastases in mediastinal nodes with or without pulmonary lymph nodes (N2, 618 single N2 and 541 multiple N2, 405 skip N2). Most patients (*n* = 9077, 83.4%), however, had no metastasis in lymph nodes (N0). Patients were divided into those who were aged ≥65 years and those who were aged <65 years. A total
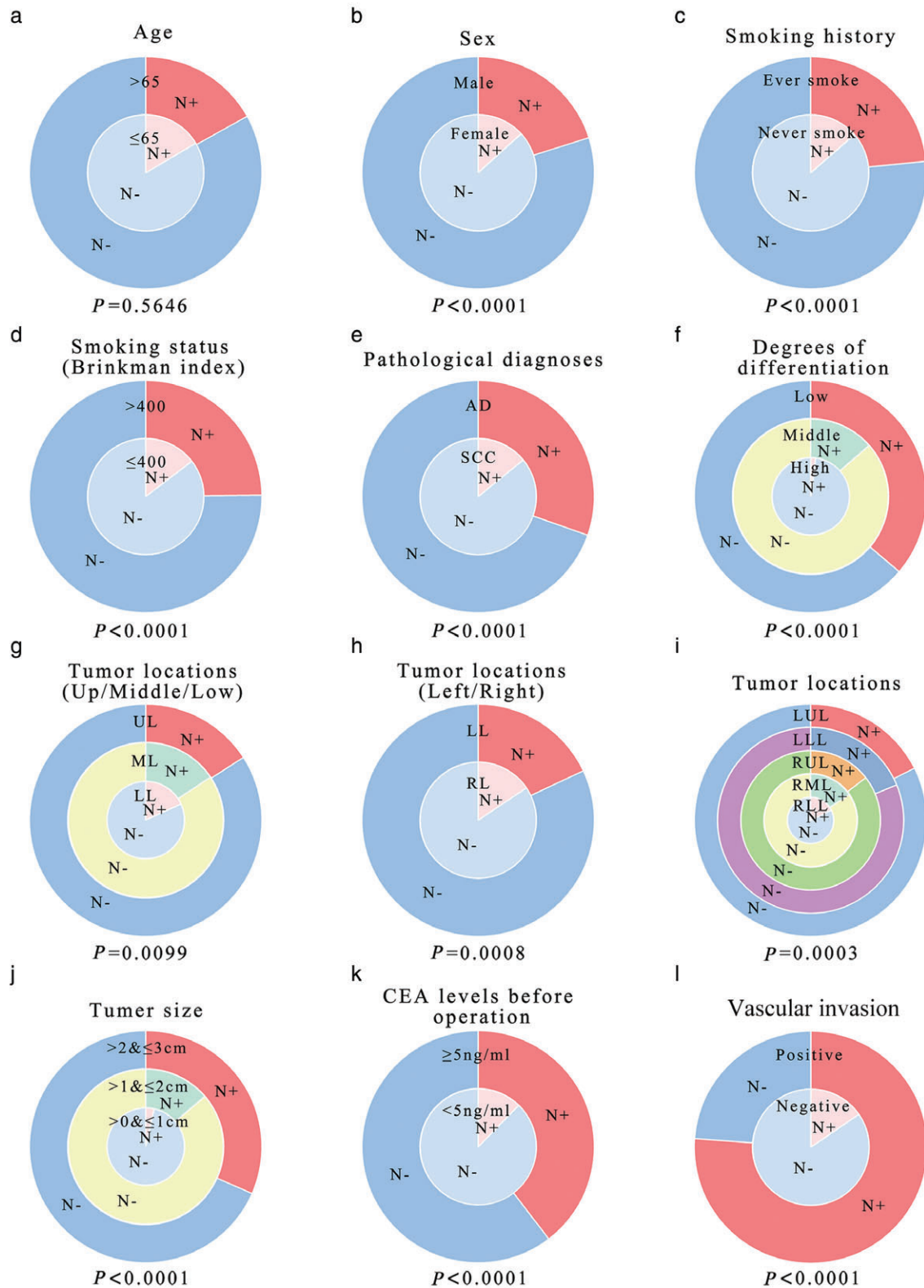
Figure 1 Probability of lymph node metastasis in T1 non-small cell lung cancer with different clinical and tumor characteristics. (**a**) Age, (**b**) sex, (**c**) smoking history, (**d**) smoking status, (**e**) pathological diagnosis, (**f**) degrees of differentiation, (**g**–**i**) tumor locations, (**j**) tumor size, (**k**) preoperative carcinoembryonic antigen level, and (**l**) vascular invasion are included.

of 71.6% (n = 7797) of the patients were aged >65 years. Some 3260 patients (29.9%) were current or former smokers, 7363 patients (67.6%) were never smokers, and 262 (2.5%) patients did not provide this information. Of all the patients included, 8309 (76.6%) patients had a Brinkman Index ≤400, and 2039 (18.7%) >400. The index was scored as the number of cigarettes smoked per day multiplied by the number of years since smoking started. The tumor histology of patients consisted of adenocarcinoma (AD) in 9216 (84.7%), squamous cell carcinoma (SCC) in 1271 (11.7%), and other pathological types in 398 (3.6%) patients. The number of patients with poorly-, moderately-, and well-differentiated NSCLC were 6544 (60.1%), 820 (7.5%), and 3521 (32.3), respectively. A total of 6544 (60.1%) tumors were located in the upper lobe, 820 (7.5%) in the middle lobe, and the remaining 3521 (32.3%) were in the lower lobe. The details of tumor location are shown in Table 1. Pathological tumor size was divided into three groups according to T1 staging of lung cancer (T1a, T1b, T1c), and the number of patients in each group was 2779 (25.5%), 4766 (43.8%), and 3340(30.7%), respectively. Preoperative plasma CEA level was measured in 6564 of the patients. A total of 5560 patients (51.1%) showed <5 ng/mL, and the other 1004 (9.2%) patients showed >5 ng/mL. The patients with or without vascular invasion were 381 (3.5%) and 10 488 (96.4%), respectively.

Table 1 and Figure 1 also show the percentage of patients with lymph node metastasis under different variables. Some variables were found as significant predictors for lymph nodal metastasis after univariate analysis. Male smokers with a Brinkman Index >400 were more likely to develop lymph nodal metastasis. In addition, lung SCC (P < 0.0001), larger tumor size (>2 and ≤3 cm vs. >0 and ≤1 cm; >1 and ≤2 cm vs. >0 and ≤1 cm, P < 0.0001), poor tumor differentiation (P < 0.0001), and preoperative serum CEA level of ≥5 ng/mL (P < 0.0001) were identified as significant predictors.

Independent risk factors for lymph nodal metastasis

After eliminating cases with missing data to further optimize the study population, multivariate analysis of the remaining 3130 patients revealed the following variables as independent risk factors for lymph nodal metastasis: (i) age >65 years (OR 0.65, 95% CI 0.526–0.805, P < 0.0001); (ii) tumor histology of AD (*vs.* SCC, OR 0.58, 95% CI 0.451–0.735, P < 0.0001); (iii) moderate or poor tumor differentiation (vs. well differentiated, OR 0.42, 0.10, 95% CI 0.341–0.511, 0.053–0.178, P < 0.0001); (vi) larger (>2 and ≤3 cm, and >1 and ≤2 cm) pathological tumor size (vs. >0 and ≤1 cm, OR 1.74, 3.24, 95% CI 1.205–2.510, 2.250–4.673, P = 0.0031 and P < 0.0001); (v) preoperative

serum CEA level ≥5 ng/mL (vs. <5 ng/mL, OR 2.39, 95% CI 1.900–3.007, P < 0.0001); and (vi) vascular invasion (OR 3.88, 95% CI 2.377–6.349, P < 0.0001; Fig 2). Of note, the age of the patient was identified as an independent risk factor according to multivariate analysis, although there was no significant difference in univariate analysis (Fig 2; Table 1).

Subgroup analysis of lymph node metastasis

Regarding different pathological types, the lymph node metastasis rate was of great difference between men and women. A total of 16.1% of male patients (610/3784) with lung AD were observed with lymph node metastasis, significantly larger than that of their female counterparts (12.7%, 690/5432, P = 0.0007). In patients with lung SCC, however, the lymph node metastasis rate was similar regardless of sex, 30.4% and 30.6% of patients (367/1209, 19/62) had lymph node metastasis in male and female patients, respectively (Table 2; Fig 3a).

When grouping patients by pathological tumor size, the probability of lymph node metastasis varied with tumor location. As the size increased, the probability of lymph node metastasis increased irrespective of lobe location of tumors. In T1a-T1b NSCLC patients, tumors in the left lower lobe had the highest probability of lymph node metastasis (5.7%, 16.1%). Tumors in the right upper lobe were almost the least prone to have lymph node metastasis in each size subgroup (2.8%, 12.2%, 28.1%). The metastasis rate exceeded one-third when the tumor size was >2 cm (T1c; Fig 3b).

Different tumor sizes were also compared under different pathological types. There was a significant difference in lymph node metastasis rates between all sizes in both pathological types. For all tumor sizes, lymph node metastasis of SCC was more common than that of AD. The probability of lymph node metastasis in AD was <3% when the tumor size was ≤1 cm (Fig 3c). The details can be seen in Table 3.

Lung SCC and AD in each lung lobe were also compared. Lung cancer was most common in the right upper lobe, but the probability of lymph node metastasis was one of the lowest (12.0%, 28.5%). Lymph node metastasis was most likely to occur in the left lower lobe of lung AD, and the trend of lymph node metastasis in different lobes of SCC was: LUL > LLL > RUL > RLL > RML (Table 4; Fig 3d). For two pathological types, the information of lymph node transferred to each station can be seen in Figure 3e, and the tumors in each lobe are shown separately. Patients with SCC were more prone to have N1 lymph node metastasis, whereas AD patients had more N2 lymph node metastasis.

Variables	OR (95% CI)	*P*-value
Age (yrs) (> 65 vs ⩽ 65)	0.65 (0.526,0.805)	**< 0.0001**
Smoking status (Ever vs Never)	0.85 (0.682,1.054)	0.1373
Tumor histology		**< 0.0001**
SCC vs Others	1.43 (0.828,2.478)	0.1987
AD vs Others	0.83 (0.483,1.409)	0.4816
AD vs SCC	0.58 (0.451,0.735)	**< 0.0001**
Tumor location (3)		0.0823
Middle lobe vs Upper lobe	0.76 (0.499,1.164)	0.2085
Lower lobe vs Upper lobe	1.18 (0.961,1.453)	0.1133
Lower lobe vs Middle lobe	1.55 (1.002,2.398)	**0.0488**
Degrees of tumor differentiation		**< 0.0001**
Moderate vs Poor	0.42 (0.341,0.511)	**< 0.0001**
Well vs Poor	0.10 (0.053,0.178)	**< 0.0001**
Well vs Moderate	0.23 (0.127,0.424)	**< 0.0001**
Tumor size (pathological)		**< 0.0001**
> 1& ⩽ 2 cm vs > 0& ⩽ 1 cm	1.74 (1.205,2.510)	**0.0031**
> 2& ⩽ 3 cm vs > 0& ⩽ 1 cm	3.24 (2.250,4.673)	**< 0.0001**
> 2& ⩽ 3 cm vs > 1& ⩽ 2 cm	1.86 (1.517,2.291)	**< 0.0001**
CEA level (⩾ 5 ng/ml vs <5 ng/ml)	2.39 (1.900,3.007)	**< 0.0001**
Vascular invasion (Positive vs Negative)	3.88 (2.377,6.349)	**< 0.0001**

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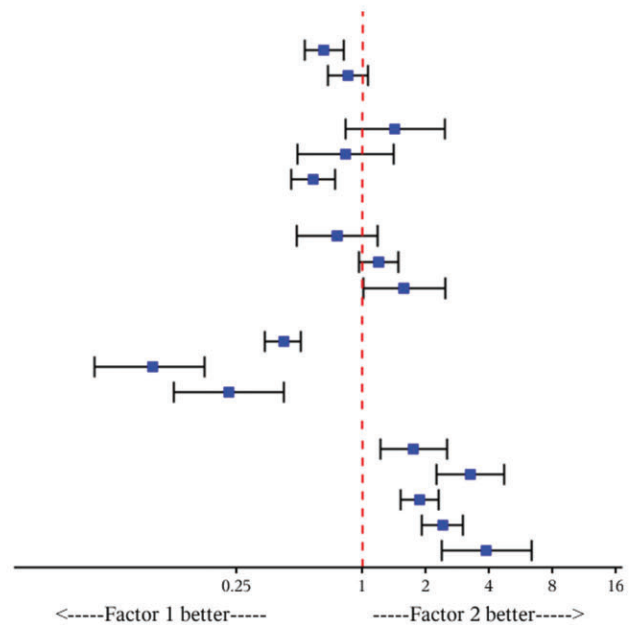
Figure 2 Multivariate analyses of risk factors of N2 lymph node metastases.

Table 2 Lymph node metastasis in male and female patients with adenocarcinoma and squamous cell carcinoma

	Male (5265)	Female (5620)	*P*-value
Adenocarcinoma			
No. patients	3784	5432	**0.0007**
Lymph node metastasis (%)	610 (16.1%)	690 (12.7%)	
Lymph node negative (%)	3174 (83.9%)	4742 (87.3%)	
Squamous cell carcinoma			
No. patients	1209	62	0.9128
Lymph node metastasis (%)	367 (30.4%)	19 (30.6%)	
Lymph node negative (%)	842 (69.6%)	43 (69.4%)	

Bold values (*P* < 0.05) indicate statistical significance.

Discussion

As is reported, lymph node status, especially pathological status, is of great significance, for prognosis as well as guiding postoperative therapeutic strategy in NSCLC.[19] Lymph node dissection is often indicated and is indeed essential, especially during surgery for cT1a-2bN0-1M0 NSCLC patients.[20] Although lobectomy with systematic lymph node dissection has been globally accepted as a standard procedure for resectable primary NSCLC,[21] arguments still came out that systematic dissection of lymph nodes without tumor cells might be futile and may also increase perioperative complications or prolong surgery time.[9,10] Selective lymph node dissection might be more suitable, but a better understanding of lymph node metastasis is indispensable. Unfortunately, there has not been a large retrospective study to explore the characteristics of lymph node metastasis in patients with early-stage lung cancer in China. Our study was designed to understand the clinical characteristics of the Chinese target population, so as to determine the risk factors for lymph node metastases in real-world practice. The findings of our study might help to guide clinical patient management as complementary evidence to the randomized clinical trials.

Approximately 8.3–15.9% of patients with clinical stage I NSCLC have been subsequently shown to have lymph node metastasis.[22–26] The metastasis rate of our experimental group was 16.6%, consistent with the reports in the literature. Within the 10 885 patients with T1 NSCLC from 10 different prestigious hospitals, most (71.6%) patients were aged <65 years. However, male patients with NSCLC were more likely to develop lymph node metastasis than women.

According to our results, patient demographic characteristics (sex, smoking history/status), and tumor biological characteristics (tumor histology, degrees of differentiation, tumor location, size, preoperative serum CEA levels, and status of vascular invasion) were shown to influence lymph node metastasis in the univariate analyses, whereas age, tumor histology, degrees of differentiation, size, CEA levels, and status of vascular invasion were presented as the independent risk factors by the multivariate analyses.

Previous studies showed age as an independent predictor of N2 lymph node metastasis in NSCLC or those with T1 disease.[17,18] In our study, it was not found to be a relevant factor for nodal involvement in univariate analysis (*P* = 0.56), which was also observed in the study by Fuwa
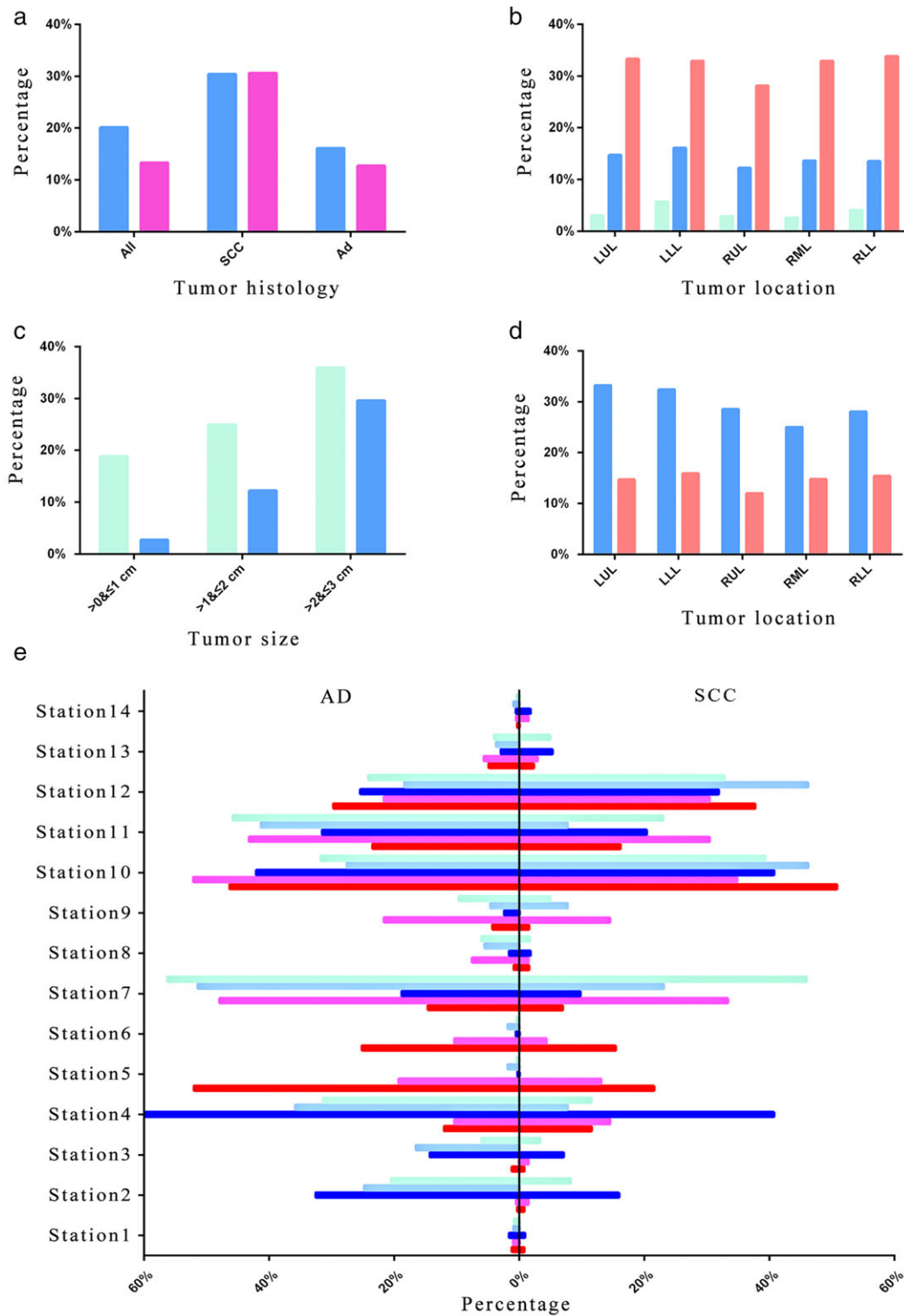
Figure 3 Subgroup analysis of lymph node metastasis. (**a**) Lymph node metastasis in patients with adenocarcinoma and squamous cell carcinoma of different sexes. ▮, Male; ▮, Female. (**b**) Lymph node metastasis of different stages of non-small cell lung cancer in different lung lobes. ▮, >0&≤1 cm; ▮, >1&≤2 cm; ▮, >2&≤3 cm. (**c**) Lymph node metastasis in patients with adenocarcinoma and squamous cell carcinoma of different stages. ▮, SCC; ▮, AD. (**d**) Different tumor histology of lymph node metastasis in different lung lobes. ▮, SCC; ▮, AD. (**e**) Lymph node metastasis to various stations of adenocarcinoma and squamous cell carcinoma in different lung lobes. ▮, LUL; ▮, LLL; ▮, RUL; ▮, RML; ▮, RLL. AD, adenocarcinoma; LUL, left upper lobe; LLL, left lower lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right lower lobe; SCC, squamous cell carcinoma.

Table 3 Lymph node metastasis in patients with adenocarcinoma and squamous cell carcinoma of different stages

	>0 and ≤1 cm (T1a)	>1 and ≤2 cm (T1b)	>2 and ≤3 cm (T1c)
Adenocarcinoma			
No. patients	2632	4143	2441
Lymph node metastasis (%)	71 (2.7%)	506 (12.2%)	723 (29.6%)
Lymph node negative (%)	2561 (97.3%)	3637 (87.8%)	1718 (70.4%)
OR, *P*-value			
vs. >0 and ≤ 1 cm		5.02, **<0.0001**	15.17, **<0.0001**
vs. >1 and ≤ 2 cm			3.02, **<0.0001**
Squamous-cell carcinoma			
No. patients	117	461	693
Lymph node metastasis (%)	22 (18.8%)	115 (24.9%)	249 (35.9%)
Lymph node negative (%)	95 (81.2%)	346 (75.1%)	444 (64.1%)
OR, *P*-value			
vs. >0 and ≤ 1 cm		1.44, 0.1645	2.42, **0.0004**
vs. >1 and ≤ 2 cm			1.69, **<0.0001**

Bold values (*P* < 0.05) indicate statistical significance.

et al.[27] According to multivariate analysis, however, age seemed to be an independent risk factor (OR 0.65, *P* < 0.0001), which means younger patients were more prone to having lymph node metastases. There was no statistical difference between AD and SCC in the light of the study by Yu *et al.*[28] However, in our study, we found that patients with tumor histology of SCC were much more likely to have lymph node metastases (30.4%) compared with AD patients.

Tumor size is considered one of the important risk factors for lymph node metastasis according to univariate and multivariate analysis, and can be detected by preoperative radiology.[29] Zhang *et al.* showed a prevalence of lymph node metastasis of 7.4% in tumors 1–2 cm, and 3.8% in tumors <1 cm.[30] In our study, 97 of 2779 patients (3.5%) had pathological lymph node metastases of tumors 0–1 cm, and 656 of 4766 patients (13.8%) had lymph node metastases of tumors 1–2 cm; whereas in the patients with tumor size 2–3 cm, the percentage of lymph node metastases increased to 31.6% (1055/3340). These findings indicated an increasing tendency of lymph node metastases with the increased tumor size. Our data support the work of Asamura *et al.*, which showed a significant association between increasing tumor size and higher incidences of lymph node metastasis.[31]

Serum CEA level has long been established to be associated with lymph node metastases in NSCLC patients.[32,33] According to Suzuki *et al.*, lymph node metastasis occurred significantly more frequently in cases with a high CEA value than those with a normal value.[34] The results of our study showed the same conclusion that preoperative serum CEA level is another significant risk factor. In patients with a normal CEA value, the rate of lymph node metastases was 12.3%, significantly lower than those with a high CEA value (39.6%), suggesting that serum CEA level might act as an indication to carry out more aggressive lymph node dissection.

Our results also suggested that tumor differentiation and vascular invasion were the other two independent risk factors for lymph node metastasis in T1 NSCLC. Well-differentiated cases occupied the smallest proportion, with the lymph node metastases rate of just 2%. In contrast, in patients with moderately and poorly differentiated tumors, the lymph node metastasis rate reached 13.6% and 36.2%, respectively (*P* < 0.0001). The status of vascular invasion

Table 4 Different tumor histology of lymph node metastasis in different lung lobes

	LUL	LLL	RUL	RML	RLL
Adenocarcinoma					
No. patients	2380	1341	3148	735	1612
Lymph node metastasis (%)	350 (14.7%)	213 (15.9%)	379 (12.0%)	109 (14.8%)	249 (15.4%)
Lymph node negative (%)	2030 (85.3%)	1128 (84.1%)	2769 (88.0%)	626 (85.2%)	1363 (84.6%)
***P*-value**	**0.0013**				
OR, *P*-value					
vs. Left upper lobe		1.10, 0.3358	0.79, **0.0038**	1.01, 0.9339	1.06, 0.5202
vs. Left lower lobe			0.72, **0.0005**	0.92, 0.5259	0.97, 0.7447
vs. Right upper lobe				1.27, **0.0403**	1.33, **0.0010**
vs. Right middle lobe					1.05, 0.6999
Squamous cell carcinoma					
No. patients	391	213	397	52	218
Lymph node metastasis (%)	130 (33.2%)	69 (32.4%)	113 (28.5%)	13 (25.0%)	61 (28.0%)
Lymph node negative (%)	261 (66.8%)	144 (67.6%)	284 (71.5%)	39 (75.0%)	157 (72.0%)
***P*-value**	0.4178				

Bold values (*P* < 0.05) indicate statistical significance.

was associated with a greater tendency for lymph node metastases, with the highest ORs (3.88, $P < 0.0001$) in univariate and multivariate logistic analyses. The same conclusion was reached in the study of Sung *et al.*[35] Analysis of the reason might be that the worse the tumor differentiation is, the stronger the invasiveness would be, which leads to early metastasis. The status of vascular invasion suggests that tumor cells invade and migrate along surrounding tiny blood vessels or lymphatic vessels, which might cause early metastasis and poor prognosis. Although these two factors cannot be clearly defined before surgery, the detection of tumor differentiation and vascular invasion in the pathological results of postoperative disease might help to predict the prognosis of patients with early-stage NSCLC.

In our subgroup analysis, most female patients with AD had a smaller percentage of lymph node metastases compared with male AD patients ($P = 0.0007$). However, the rate of metastasis in patients with SCC was much greater, and there is no significant difference between men and women. Our results suggest that left lower lung cancer was more likely to have lymph node metastases in patients with tumor size of ≤2 cm. Patients with SCC had a much higher percentage of lymph node metastases irrespective of tumor size. Also, as the tumor size increased, the proportion of patients with lymph node metastases increased gradually in both lung SCC and AD.

Results from others' studies suggest that non-upper lobe-located tumors had a tendency toward a higher incidence of lymph node metastases.[18,30,32] According to multivariate analysis of our study, lobe distribution of tumors was not a significant predictor for lymph node metastases, but subgroup analysis showed that the incidences of lymph node metastases were significantly different between the right upper lobe and left lower lobe ($P = 0.0005$).

This study was limited by the constraints of a retrospective study with the inherent bias, such as patient selection, preoperative clinical and invasive staging modalities, and heterogeneity of treatment approaches. A prospectively collected database with predefined clinical parameters, investigation modalities, and treatment approaches might be helpful in clarifying the findings observed in this retrospective observational study.

In conclusion, the real-world clinical study data offered solid guidance on the assessments of clinical characteristics of the target patients and patient management in clinical practice: in the Chinese T1 NSCLC patients with lymph node metastases, the clinical characteristics were defined and similar patient profiles were observed, as compared with the other studies. The percentages of lymph node metastases were shown to be associated with sex, smoking history/status, tumor histology, degrees of differentiation, tumor location, size, preoperative serum CEA levels, and status of vascular invasion, whereas age, tumor histology, degrees of differentiation, size, CEA levels, and status of vascular invasion were presented as the independent risk factors. Female patients with T1a AD barely had lymph node metastasis, especially in the right upper lobe. However, whether omission of systematic lymph node dissection may be considered is still difficult to say. Further studies should be carried out to evaluate the need for lymph node sampling in this patient subgroup. Our study might offer some clues to preoperative assessment of lymph node metastasis in T1 NSCLC, which could help to provide optimal care for operable NSCLC patients.

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Disclosure

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