Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Risk factors of lymph node metastasis in patients with non-small cell lung cancer ≤ 2 cm in size: A monocentric population-based analysis

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Keywords
Lymph node dissection; lymph node metastasis; NSCLC ≤ 2 cm.

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Received: 11 April 2017;
Accepted: 17 July 2017.

doi: 10.1111/1759-7714.12490

Thoracic Cancer **9** (2018) 3–9

Abstract

Aim: This study was designed to determine the risk factors of lymph node metastasis in non-small cell lung cancer (NSCLC) patients with tumors ≤ 2 cm, using the Shanghai Chest Hospital Lung Cancer Database.

Methods: Five hundred and eighteen patients with NSCLC ≤ 2 cm were included in this study, and were classified into lymph node-positive and lymph node-negative groups. Univariate and multivariate logistic regression analyses were performed to select the independent risk factors for lymph node metastasis in NSCLC patients.

Results: No evidence of metastasis was found in tumors ≤ 1 cm, all positive results were in tumors sized 1–2 cm. Imaging characteristics, including solid and part-solid nodules, were strongly associated with lymph node metastasis (odds ratio [OR] 24.959, 95% confidence interval [CI] 5.999–103.835, $P < 0.001$; OR 12.559, 95% CI 3.564–44.259, $P < 0.001$) and subgroup logistic analysis (OR 21.384, 95% CI 5.058–90.407, $P < 0.001$; OR 11.632, 95% CI 3.290–41.126, $P < 0.001$). Greater lymph node metastasis was observed in non-adeno non-squamous carcinoma. The presence of pleural invasion and carcinoembryonic antigen levels indicated lymph node dissection. Similar results were revealed in subgroup analysis in tumors ≤ 2 to > 1 cm.

Conclusion: Size had a great impact on lymph node metastasis, especially tumors of 1–2 cm. Preoperative imaging, non-adeno non-squamous carcinoma, pleural invasion, and carcinoembryonic antigen all indicated lymph node dissection. There was no discrepancy between N1 and N2 positive lymph nodes.

Introduction

Lung cancer is the leading cause of death all over the world, but particularly in China.[1] Standard lobectomy with systemic lymph node dissection has become the recommended surgical treatment for clinical stage I non-small cell lung cancer (NSCLC) since a randomized controlled trial performed in 1995 recommended lobectomy as the best approach for stage I NSCLC patients.[2] The wide use of computed tomography (CT) has allowed for the detection of more small-sized nodules, especially greater quantities of small-sized ground grass opacities (GGOs)[3] thus, the use of classic and traditional anatomic resection (lobectomy) for lymph node dissection is being challenged.

It is well-known that lymph node evaluation of lung cancer can be classified into two groups, systemic lymph node dissection (SND) and lymph node sampling,[4,5] both of which play a significant role in evaluating lymph node metastasis and pathological N stage of lung cancer. It is difficult for surgeons to decide whether lymph node dissection is appropriate for patients with relatively good radiographic results but a poor general condition.

In this study, we retrospectively analyzed small-sized (≤ 2 cm) tumors in NSCLC patients who underwent lobectomy and lymph node dissection at the Shanghai Chest Hospital from 2012 to 2014 to determine the potential risk factors for lymph node metastasis in such patients.

Methods

Patients

We retrospectively collected the records of consecutive patients with NSCLC tumors ≤ 2 cm who had undergone lobectomy and lymph node dissection (including SND and lymph node sampling) at Shanghai Chest Hospital from 2012 to 2014. Inclusion criteria were: (i) single NSCLC, patient underwent anatomic resection and lymph node dissection, proven by final pathology; (ii) the tumor was ≤ 2cm; and (iii) lymph node dissection included SND and lymph node sampling. Patients were excluded for: (i) multiple lung cancer or small cell lung cancer, (ii) suspicious lymphadenectasis (hilum and /or mediastinum lymph node ≥ 1 cm in size) detected by CT scan or other techniques, and (iii) local or distant metastasis.

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from each patient to permit genetic analysis of biological samples.

The patients were divided into two groups: lymph node-positive and lymph node-negative. The baseline characteristics of these patients were gender, age, smoking history, family history, tumor location, imaging characteristics, pathology, size of tumor, pleural invasion (PI), the number of harvested lymph nodes, and serum tumor marker (carcinoembryonic antigen [CEA]) level, all of which were collected from the Shanghai Chest Hospital Lung Cancer database. Family history was defined whether there was the malignancy in a family member or not. Imaging characteristics included pure ground-grass nodules (pGGN), mixed ground-grass nodules (mGGN), and solid nodules. Pathology was classified into adenocarcinoma (ADC), squamous cell carcinoma (SCC), and other types of lung cancer according to final pathology. The size of tumor was divided into ≤ 1 and ≤ 2 cm in accordance with the 8th Tumor Node Metastasis (TNM) Classification for Lung Cancer. CEA level was tested before surgery and a normal level was considered < 5.0 μg/L.

Statistical analysis

Pearson χ^2 and Fisher's exact tests and *t*-tests were conducted to analyze the categorical and continuous variables, respectively. Univariable and multivariable logistic regression analyses were performed to select the independent risk factors for lymph node metastasis in NSCLC. Subgroup analysis was also performed according to the size of tumor, and the univariate and multivariate logistic regressions were subsequently analyzed. Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 518 patients with NSCLC tumors ≤ 2 cm were included in this study: 53 patients with positive lymph nodes and 465 with negative lymph nodes, proven by final pathology. The positive rate of N2 was 2.12% (11/518), the

Table 1 Clinicopathological characteristics of lymph node positive and negative groups and univariate logistic regression analysis in clinical T1a NSCLC patients

Characteristic	LN(–)(%)	LN(+)(%)	Univariable logistic
Gender			
Male	184 (39.6)	23 (43.4)	0.590
Female	281 (60.4)	30 (56.6)	—
Age			
≤60	291 (62.6)	30 (56.6)	0.396
>60	174 (37.4)	23 (43.4)	—
Smoke history			
No	405 (87.1)	43 (81.1)	0.229
Yes	60 (12.9)	10 (18.9)	—
Family history			
No	453 (97.4)	51 (96.2)	0.612
Yes	12 (2.6)	2 (3.8)	—
Location			
RUL	172 (37.0)	17 (32.1)	0.477
RML	36 (7.7)	5 (9.4)	—
RLL	78(16.8)	7 (13.2)	—
LUL	112 (24.1)	16 (30.2)	—
Imaging			
LLL	67 (14.4)	8 (15.1)	<0.001
pGGN	255 (54.8)	3 (5.7)	—
mGGN	57 (12.3)	9 (17.0)	—
Solid	153 (32.9)	41 (77.3)	—
Pathology			
ADC	440 (94.6)	46 (86.8)	0.008
SCC	12 (2.6)	1 (1.9)	—
Others	13 (2.8)	6 (11.3)	—
Size			
≤1 cm	122 (26.2)	0 (0)	0.966
≤2 cm	343 (73.8)	53 (100.0)	—
PI			
No	431 (92.7)	24 (45.3)	<0.001
Yes	34 (7.3)	29 (54.7)	—
HLN			
Average	6.85	7.13	0.589
CEA			
Normal	424 (91.2)	41 (77.4)	<0.001
Abnormal	41 (8.8)	15 (22.6)	—

ADC, adenocarcinoma; HLN, harvested lymph node; LLL, left lower lobe; LN, lymph node; LUL, left upper lobe; mGGN, mixed ground-grass nodules; NSCLC, non-small cell lung cancer; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma.

Table 2 Multivariate logistic regression analysis in clinical T1a NSCLC patients

	Multivariate logistic analysis					
	B	SE	Wald	*P*	OR	95% CI
Imaging						
pGGN	—	—	20.451	<0.001	—	—
mGGN	3.217	0.727	19.565	<0.001	24.959	5.999–103.835
Solid	2.530	0.643	15.504	<0.001	12.559	3.564–44.259
Pathology						
ADC	—	—	5.271	0.072	Reference	—
SCC	–0.826	1.124	0.540	0.463	0.438	0.048–3.963
Others	1.320	0.635	4.317	0.038	3.745	1.078–13.010
PI	2.696	0.416	42.076	<0.001	14.827	6.565–33.490
CEA	1.310	0.455	8.283	0.004	3.704	1.518–9.037
Constant	–5.255	0.638	67.085	<0.001	0.005	—

ADC, adenocarcinoma; CEA, carcinoembryonic antigen; CI, confidence interval; mGGN, mixed ground-grass nodules; NSCLC, non-small cell lung cancer; OR, odds ratio; pGGN, pure ground-grass nodules; PI, pleural invasion; SCC, squamous cell carcinoma; SE, standard error.

positive rate of N1 was 2.90% (15/518), and positive rate of N1 and N2 was 5.21% (27/518). In total, 3565 lymph nodes were harvested, including 2176 for N2 and 1389 for N1. The average number of harvested lymph nodes was 6.88, with averages of 4.20 for N2 and 2.88 for N1. The clinicopathological characteristics of the groups are listed in Table 1. A surprising result was that there were no lymph node metastases < 1 cm.

Univariate logistic analysis was performed to determine the potential risk factors for lymph node metastasis. Compared to the lymph node-negative group, the lymph node-positive group demonstrated significant differences in imaging characteristics ($P < 0.001$), pathological type ($P = 0.008$), PI ($P < 0.001$), and high CEA level ($P < 0.001$), while there were no discrepancies with other variables (Table 1). After univariate logistic regression analysis, the potential risk factors were entered into multivariable analysis using SPSS version 20.0. Specifically, the imaging containing solid or mGGN characteristics had a strong relationship to lymph node metastasis. In detail, mGGN and solid nodules definitely indicated local and mediastinal lymph node metastasis when compared to pGGN (odds ratio [OR] 24.959, 95% confidence interval [CI] 5.999–103.835, $P < 0.001$; OR 12.559, 95% CI 3.564–44.259, $P < 0.001$, respectively). Regarding the pathology subtype, SCC did not display any difference ($P = 0.463$), while other types demonstrated a discrepancy (OR 3.745, 95% CI 1.078–13.010, $P = 0.038$) compared to ADC. PI (OR 14.827, 95% CI 6.565–33.490, $P < 0.001$) and CEA (OR 3.704, 95% CI 1.518–9.037, $P = 0.004$) were also risk factors of lymph node metastasis according to the results of multivariate logistic analysis (Table 2).

We also conducted subgroup analysis of tumor size, because lymph node metastasis did not occur in tumors ≤ 1 cm in our study compared to tumors sized ≤ 2 to > 1 cm. Univariate and multivariate logistic analyses were successively performed in the subgroup of ≤ 2 to >1 cm. Similar to our previous results, mGGN and solid nodules played significant roles in indicating potential lymph node metastasis against pGGN (OR 21.384, 95% CI 5.058–90.407, $P < 0.001$; OR 11.632, 95% CI 3.290–41.126, $P < 0.001$, respectively). There was no statistical difference in lymph node metastasis between SCC and ADC ($P = 0.382$), but other types of lung cancer had a stronger tendency to metastasize compared to ADC (OR 3.712, 95% CI 1.035–13.319, $P = 0.044$). PI (OR 12.001, 95% CI 5.293–27.212, $P < 0.001$) and CEA (OR 3.218, 95% CI 1.321–7.843, $P = 0.010$) were associated with lymph node metastasis (Table 3).

In this study, we also compared the clinicopathological characteristics of N1-positive, N2-positive (mediastinal lymph node), and N1+2-positive groups according to the status of metastasis. It was surprising that there were no apparent differences in statistics, except for the N1+2-positive group in which a greater number of lymph nodes were harvested during dissection (Table 4). With respect to N1 and N2 subgroups, we sought to determine the potential risk factors using univariate and multivariate logistic analyses. Disappointingly, there seemed to be no discrepancy in statistics between N1-positive and N2-positive (including N1+2) groups (Table 5).

Discussion

Lymph node status in NSCLC, especially pathological status, is of great importance, not only for prognosis but also to guide postoperative therapeutic strategy.[6] Lymph node dissection is often indicated and is indeed essential, especially during surgery for cT1a-2bN0-1M0 NSCLC.[4]

Table 3 Univariate and multivariate logistic regression analyses in a subgroup of NSCLC tumors ≤ 2 to > 1 cm

Characteristic	Univariate	Multivariate					
	P	B	SE	Wald	*P*	OR	95% CI
Gender							
Male	0.973	—	—	—	—	—	—
Female	—	—	—	—	—	—	—
Age							
≤60	0.932	—	—	—	—	—	—
>60	—	—	—	—	—	—	—
Smoking history							
No	0.350	—	—	—	—	—	—
Yes	—	—	—	—	—	—	—
Family history							
No	0.635	—	—	—	—	—	—
Yes	—	—	—	—	—	—	—
Location							
RUL	0.462	—	—	—	—	—	—
RML	—	—	—	—	—	—	—
RLL	—	—	—	—	—	—	—
LUL	—	—	—	—	—	—	—
Imaging							
LLL	—	—	—	18.412	<0.001	Reference	—
pGGN	<0.001	3.063	0.736	17.335	<0.001	21.384	5.058–90.407
mGGN	—	2.454	0.644	14.053	<0.001	11.632	3.290–41.126
Solid	—	—	—	—	—	—	—
Pathology							
ADC	0.021	—	—	5.258	0.071	Reference	—
SCC	—	–0.976	1.117	0.764	0.382	0.377	0.042–3.365
Others	—	1.312	0.652	4.049	0.044	3.712	1.035–13.319
PI							
No	<0.001	2.485	0.418	35.395	<0.001	12.001	5.293–27.212
Yes	—	—	—	—	—	—	—
HLN							
Average	0.864	—	—	—	—	—	—
CEA							
Normal	<0.001	1.169	0.454	6.615	0.010	3.218	1.321–7.843
Abnormal	—	—	—	—	—	—	—
Constant	—	–4.874	0.645	57.075	<0.001	0.008	—

ADC, adenocarcinoma; CEA, carcinoembryonic antigen; CI, confidence interval; LLL, left lower lobe; HLN, harvested lymph node; LUL, left upper lobe; mGGN, mixed ground-grass nodules; NSCLC, non-small cell lung cancer; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma; SE, standard error.

Tumor size is considered an important risk factor for lymph node metastasis, and can be detected by preoperative radiology.[7] Zhang *et al.* demonstrated a prevalence of lymph node metastasis of 7.4% in tumors 1–2 cm, and 3.8% in tumors < 1 cm.[8] In this study, 53 patients had pathological lymph node metastasis of tumors 1–2 cm, while there was no evidence of metastasis in tumors < 1 cm. This finding could indicate a tendency of lymph node metastasis to increase with tumor size, especially in tumors ≤ 2 cm. These results were consistent with those determined by Asamura *et al.*[9]

In this study, preoperative imaging characteristics, pathology subtype, PI, and serum CEA level before surgery were considered independent risk factors indicating lymph node metastasis in NSCLC patients. Similar results were found in subgroup analysis of tumor size.

Regarding imaging characteristics, mGGN and solid nodules were correlated with a higher rate of local and mediastinal lymph node metastasis when compared to pure GGO, evident by the appearance of a solid component in the imaging scans, strongly indicating the existence of a much more invasive component or pathological subtype. Thus, the characteristics of preoperative CT scanning could represent a much more convenient and reliable strategy for deciding whether to perform lymph node dissection during surgery.

There was no statistical difference between ADC and SCC, but other types of pathology demonstrated statistic

Table 4 Clinicopathological characteristics of N1-positive, N2-positive, and N1+2-positive groups

Characteristics	N1(%) N = 15	N2(%) N = 11	N1 + 2(%) N = 27	*P*
Gender				
Male	6 (40.0)	5 (45.5)	12 (44.4)	0.951
Female	9 (60.0)	6 (54.5)	15 (55.6)	—
Age				
≤60	10 (66.7)	4 (36.4)	16 (59.3)	0.282
>60	5 (33.3)	7 (63.6)	11 (40.7)	—
Smoking history				
No	12 (80.0)	10 (90.9)	21 (77.8)	0.718
Yes	3 (20.0)	1 (9.1)	5 (22.2)	—
Family history				
No	15 (100)	11 (100)	25 (92.6)	0.368
Yes	0 (0)	0 (0)	2 (7.4)	—
Location				
RUL	5 (33.4)	2 (18.2)	10 (37.0)	0.986
RML	2 (13.3)	1 (9.1)	2 (7.4)	—
RLL	2 (13.3)	2 (18.2)	3 (11.1)	—
LUL	4 (26.7)	4 (36.3)	8 (29.7)	—
LLL	2 (13.3)	2 (18.2)	4 (14.8)	—
Imaging				
pGGN	2 (13.3)	1 (9.1)	0 (0)	0.117
mGGN	0 (0)	2 (18.2)	7 (25.9)	—
Solid	13 (86.7)	8 (72.7)	20 (74.1)	—
Pathology				
ADC	13 (86.6)	10 (90.9)	23 (85.2)	0.527
SCC	1 (6.7)	0 (0)	0 (0)	—
Others	1 (6.7)	1 (9.1)	4 (14.8)	—
PI				
No	6 (40.0)	5 (45.5)	13 (48.1)	0.879
Yes	9 (60.0)	6 (54.5)	14 (51.9)	—
HLN				
Average	6.27	5.18	8.41	0.038
CEA				
Normal	11 (73.3)	9 (81.8)	18 (66.7)	0.634
Abnormal	4 (26.7)	2 (18.2)	9 (33.3)	—

ADC, adenocarcinoma; CEA, carcinoembryonic antigen; HLN, harvested lymph node; LLL, left lower lobe; LUL, left upper lobe; mGGN, mixed ground-grass nodules; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma.

Table 5 Univariate and multivariate logistic analyses of N1-positive and N2-positive groups

Characteristics	Univariate	Multivariate					
	P	B	SE	Wald	df	*P*	OR
Gender							
Male	0.696	—	—	—	—	—	—
Female	—	—	—	—	—	—	—
Age							
≤60	0.314	—	—	—	—	—	—
>60	—	—	—	—	—	—	—
Smoking history							
No	0.929	—	—	—	—	—	—
Yes	—	—	—	—	—	—	—
Family history							
No	0.358	—	—	—	—	—	—
Yes	—	—	—	—	—	—	—
Location							
RUL	0.732	—	—	—	—	—	—
RML	—	—	—	—	—	—	—
RLL	—	—	—	—	—	—	—
LUL	—	—	—	—	—	—	—
LLL	—	—	—	—	—	—	—
Imaging							
pGGN	0.983	—	—	—	—	—	—
mGGN	—	—	—	—	—	—	—
Solid	—	—	—	—	—	—	—
Pathology							
ADC	0.723	—	—	—	—	—	—
SCC	—	—	—	—	—	—	—
Others	—	—	—	—	—	—	—
PI							
No	0.696	—	—	—	—	—	—
Yes	—	—	—	—	—	—	—
HLN							
Average	0.273	—	—	—	—	—	—
CEA							
Normal	0.825	—	—	—	—	—	—
Abnormal	—	—	—	—	—	—	—

ADC, adenocarcinoma; CEA, carcinoembryonic antigen; HLN, harvested lymph node; LLL, left lower lobe; LUL, left upper lobe; mGGN, mixed ground-grass nodules; pGGN, pure ground-grass nodules; PI, pleural invasion; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma.

significance in subgroup analysis, with ORs of > 5 to > 6 indicating a close relationship with lymph node metastasis. With regard to ADC, although several types of ADC, such as adenocarcinoma in situ and minimally invasive adenocarcinoma, did not tend to spread to lymph nodes[10] and GGO-predominant tumors displayed a low incidence of mediastinal lymph node metastasis,[11] it is well-known that invasive adenocarcinoma possesses the metastatic ability to progress to regional lymph nodes and even occult lymph node metastasis.[12] Subtypes, such as micropapillary-predominant adenocarcinoma, are even related to a higher likelihood of metastasis and poor prognosis.[13]

Pleural invasion is another significant risk factor associated with a greater tendency for lymph node metastasis, with the highest ORs in univariate and multivariate logistic analyses. Not only were more lymph nodes involved, but PI also indicated a high risk of systemic metastasis because the tumor cells could be reabsorbed by the parietal pleura after desquamating from visceral pleura.[14,15]

It is well known that there is a relationship between the serum CEA level and mediastinal lymph node metastasis in patients with clinical stage IA NSCLC.[16,17] Inoue *et al.* reported that higher CEA levels corresponded with higher five-year mortality among patients with NSCLC tumors ≤

2 cm.[18] In this study, an abnormal preoperative CEA level also showed a significant correlation to lymph node metastasis, which could be an indication to conduct lymph node dissection, even systemic dissection, when lower-lobar clinical stage I adenocarcinoma occurs, suggesting that high CEA levels are associated with upper mediastinal lymph node metastasis.[11]

There are several techniques for lymph node dissection, including preoperative integrated fluorodeoxyglucose positron emission tomography/CT[19] and freezing sections of lymph nodes during surgery;[20] however, it is much more feasible and practical for surgeons to make a decision using preoperative clinicopathological characteristics.

Although part of our study objective was to determine any difference between N1 and N2 patients, univariate and multivariate logistic analysis revealed no obvious discrepancy between these groups. Fewer lymph nodes were harvested in the N1 and N2 groups compared to the N1+2 group.

There were several limitations to this study. First, it was a retrospective analysis with a relatively limited number of patients and parameters, which may restrict the wide usage of our indications in clinics. Second, our research did not take recurrence and survival outcomes into consideration, which means that we may have overlooked some indications for lymph node dissection. This requires further investigation.

In conclusion, preoperative imaging characteristics are essential for indicating lymph node metastasis. Tumor size is also a significant risk factor for lymph node metastasis, especially in tumors of 1–2 cm. Non-adeno and non-squamous subtypes of lung cancer (large cell lung cancer, carcinoid, etc.) demonstrate a higher risk of lymph node metastasis compared to ADC and SCC. PI and high preoperative CEA level are further risk factors for lymph node metastasis, indicating a need for dissection. There was no difference between N1 positive and N2 positive lymph nodes. Further research is required to determine whether there are any other potential risk factors for lymph node metastasis.

Disclosure

No authors report any conflict of interest.

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