Original Article

Analysis of lymph node metastasis in 200 patients with non-small cell lung cancer

Taobo Luo[1,2,3], Qixun Chen[1,2,3], Jian Zeng[1,2,3]

[1]Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Hangzhou 310022, China; [2]Cancer Hospital of University of Chinese Academy of Sciences, Hangzhou 310022, China; [3]Zhejiang Cancer Hospital, Department of Thoracic Surgery, Hangzhou 310022, China

Contributions: (I) Conception and design: J Zeng; (II) Administrative support: Q Chen; (III) Provision of study materials or patients: J Zeng; (IV) Collection and assembly of data: T Luo; (V) Data analysis and interpretation: T Luo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jian Zeng. Zhejiang Cancer Hospital, 1# East Banshan Road, Hangzhou 310022, China. Email: 68640770@qq.com.

Background: Lymph node metastasis occurs although clinical stage IA is a relatively early stage for patients with non-small cell lung cancer (NSCLC). This study aimed to explore the influencing factors of lymph node metastasis.

Methods: A total of 200 patients diagnosed with clinical stage IA NSCLC preoperatively from July 2014 to July 2016 were examined. Every patient underwent lobectomy and systematic lymph node dissection. Their clinicopathological characteristics and status of lymph node metastasis are analyzed.

Results: The rates of both N1 and N2 lymph node metastasis increase with the increase in the tumor diameter. The N1 lymph node metastasis rate is 0%, 2.82%, and 9.52%, while the N2 lymph node metastasis rate is 0%, 4.23%, and 25.40% for pure ground-glass nodules, mixed ground-glass nodules (solid component <50%), and mixed ground-glass nodules (solid component >50%), respectively. The difference is statistically significant (P=0.000). Patients with squamous cell carcinoma have a relatively higher N1 lymph node metastasis rate comparing with patients with adenocarcinoma (P<0.05). Tumors locate in the inner half lobe (close to hilus) are prone to metastasize to lymph nodes (P=0.018). Multiple regression analysis shows that tumor diameter, solid component rate, and tumor location are relevant factors for lymph node metastasis.

Conclusions: In patients with NSCLC, who have tumors smaller than 1 cm, pure ground-glass nodules, or tumors locate in the lateral half lobe, lymph node metastasis is rare and selective lymphadenectomy is considerable.

Keywords: Clinical pathology; lymph node metastasis; non-small cell lung cancer (NSCLC)

Submitted Oct 06, 2019. Accepted for publication Jan 07, 2020.
doi: 10.21037/tcr.2020.01.67
View this article at: http://dx.doi.org/10.21037/tcr.2020.01.67

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common malignant tumors worldwide (1,2). Surgical resection is the first choice for patients with NSCLC. The number of patients with clinical stage I has increased with early diagnosis. The scope of lymph node resection is a serious concern for these patients. Systematic lymph node dissection (SLND) is regarded as the standard procedure because it is conducive to a radical cure and accurate N staging, thus providing sound evidence for adjuvant treatment (3-5). Some previous studies indicate that cells of stage I NSCLC are stable, metastasis is rare, and the biological characteristics are distinct from those of advanced-stage NSCLC. Therefore, a narrower scope of lymph node dissection, which could reduce surgical trauma, is suggested (6-9). Previous studies use patients with stage I–IIIA NSCLC as targets. No clinical study investigates whether patients with clinical stage IA NSCLC benefit from SLND. In this prospective one-arm study, SLND is

performed on 200 patients with clinical stage IA NSCLC. Also, a correlation analysis between lymph node metastasis status and clinicopathological characteristics is conducted, providing evidence for selecting an appropriate way of lymph node dissection.

Methods

Patients with preoperative clinical stage IA NSCLC admitted to Zhejiang Cancer Hospital from July 2014 to July 2016, who underwent surgical treatment, were examined. The inclusion criteria were as follows: patients with NSCLC confirmed by pathological examination (pre- or postoperative); patients with preoperative clinical stage IA [according to the National Comprehensive Cancer Network (NCCN) seventh edition of TNM staging system]; and patients who underwent lobectomy plus SLND (both video-assisted thoracoscopic surgery and thoracotomy included). The exclusion criteria were as follows: pathological examination revealing small-cell lung cancer; recurrent NSCLC; NSCLC combined with other malignant diseases; multiple primary tumors; and no surgery. This study was approved by the hospital ethics committee.

A total of 200 patients who met the inclusion criteria were enrolled. Of these, 72 were male, and 128 were female. The average age was 59.82±6.47 [42–75] years. All patients underwent lobectomy plus SLND. The scope of lymph node dissection included groups 2, 4, 7, 8, 9, 10, 11, 12, and 13 for tumors located in the right lung, and groups 5, 6, 7, 8, 9, 10, 11, 12, and 13 for tumors located in the left lung. The lymph node metastasis status depended on the postoperative pathological examination.

SPSS v22.0 is used to perform data analysis. A P value less than 0.05 indicate statistically significant differences. The chi-square test is used to analyze the differences among groups of enumeration data, and the multiple regression analysis is used to analyze the relevant factors for lymph node metastasis.

Results

The postoperative pathological examination shows lymph node metastasis in 27 patients (13.5%). Of these, eight have N1 (six with group 11 metastasis and two with group 10 metastasis), 19 have N2 (10 with group 7 metastasis, five with group 2/4 metastasis, two with group 5 metastasis, one with group 6 metastasis, and one with group 8 metastasis); none has N3. The detailed clinical information and the lymph node metastasis status are shown in *Table 1*. The lymph node metastasis status shows no correlation with sex, age, and tumor location.

The N1 lymph node metastasis rate is 1.89%, 3.67%, and 7.89% for patients with tumors measuring <1 cm; ≥1 and <2 cm; ≥2 and <3 cm, respectively. The difference is statistically significant (P=0.006). The difference in the metastasis rate between every two groups is also statistically significant (P<0.05) (*Table 2*).

The N1 lymph node metastasis rate is 0%, 2.82%, and 9.52%, and the N2 lymph node metastasis rate is 0%, 4.23%, and 25.40% for patients whose tumor is pure ground-glass opacity (GGO) nodule, solid component <50%, and solid component ≥50%, respectively. The difference is statistically significant (P=0.000). The rates of both N1 and N2 lymph node metastases are obviously higher in patients whose tumor is solid component ≥50% compared with the other two groups of patients (P<0.05) (*Table 3*).

The pathological examination shows that 173 patients have adenocarcinoma and 25 have squamous cell carcinoma. The N1 lymph node metastasis rate is 1.73% and 20.00% (P<0.05), and the N2 lymph node metastasis rate is 9.83% and 8.00% (P>0.05) for adenocarcinoma and squamous cell carcinoma, respectively. Patients with squamous cell carcinoma have a higher N1 lymph node metastasis rate (P=0.025). The data are shown in *Table 4*.

The N1 lymph node metastasis rate is 6.59% and 1.83%, and the N2 lymph node metastasis rate is 13.19% and 6.42% for patients whose tumors are located in the medial half lobe (the center of the tumors is closer to the hilus of the lungs rather than to the visceral pleura) and whose tumor is located in the lateral half lobe (the center of tumors is closer to the visceral pleura rather than to the hilus of the lungs), respectively. Patients with tumors locate in the medial half lobe are more prone to undergo lymph node metastasis comparing with patients with tumors locate in the lateral half lobe (*Table 5*).

The multiple regression analysis shows that tumor diameter, solid component rate, and tumor location are relevant factors for lymph node metastasis (*Tables 6*,*7*).

Discussion

Recurrence is the main cause of the death of patients with NSCLC, even for patients with clinical stage IA (10,11). Studies reveal that recurrence occurs mainly

Table 1 The clinical information and lymph node metastasis status of 200 cases of clinical stage I NSCLC

Clinical data	N	Lymph node metastasis	Metastatic rate (%)	P
Gender				0.364
Male	72	11	15.3	
Female	128	16	12.5	
Age (years)				
≤60	114	16	14.0	0.462
>60	86	11	12.8	
Primary lung lobe				–
Right up lobe	69	7	10.1	
Right middle lobe	12	2	16.7	
Right lower lobe	43	6	14.0	
Left up lobe	49	8	16.3	
Left lower lobe	27	4	14.8	
Tumor size (cm)				0.001
<1	53	1	1.89	
≥1 and <2	109	15	13.8	
≥2 and ≤3	38	11	28.9	
Imaging features				0.001
GGO	66	0	0	
Solid components <50%	71	5	7.0	
Solid components ≥50%	63	22	34.9	
Tumor location				0.015
Medial 1/2	91	18	19.8	
Lateral 1/2	109	9	8.3	
Pathology				0.068
Adenocarcinoma	173	20	11.6	
Squamous cell carcinoma	25	7	28.0	
Others	2	0	0	

NSCLC, non-small cell lung cancer; GGO, ground-glass opacity.

Table 2 The relationship between the tumor size and lymph node metastasis

Tumor diameter (cm)	N	Lymph node metastasis, n (%)			Total
		N0	N1	N2	
<1	53	52 (98.11)	1 (1.89)	0 (0.00)	1 (1.89)
≥1 and <2	109	94 (86.24)	4 (3.67)	11 (10.09)*	15 (13.76)*
≥2 and ≤3	38	27 (71.05)	3 (7.89)	8 (21.05)*	11 (28.95)*#
χ^2			14.352		13.893
P			0.006		0.001

*, compared with those whose tumor size was <1 cm, P<0.05; #, compared with those whose tumor size was ≥1 and <2 cm, P<0.05.

because NSCLC shows the features of "skip metastasis" and "micrometastasis" (12-14). The tumor cells in micrometastases are the source of postoperative recurrence. In terms of radical resection, the traditional concept insists that SLND is necessary for NSCLC. SLND not only can clear tumor cells, but also is necessary for detailed pathological staging and provide evidence for adjuvant treatment.

With economic and social development, people pay more attention to a health examination. Besides, thin-section computed tomography (CT) is clinically used on a wide scale. Therefore, the detection rate of early-stage NSCLC increases every year. In Zhejiang Cancer Hospital, 35% of all surgically resected NSCLC were stage IA in 2002; in 2012, this rate increased to 63%. The value of reducing surgical trauma gradually increases with the acceptance of rapid rehabilitation by thoracic surgeons. Studies show that reduced surgical trauma is beneficial to postoperative recovery, can improve the quality of life, and promote the therapeutic effect (15-17). Patients who underwent selective lymphadenectomy have shorter surgical times, less intraoperative bleeding, less volume of thoracic drainage, and less postoperative complications, including continued air leakage, lymphatic fistula, recurrent laryngeal nerve injury, and pneumonia or atelectasis. The overall survival (OS) and disease-free survival (DFS) show no statistically significant differences in some patients with NSCLC (6,7). Whether surgeons can narrow the scope of lymph node dissection to reduce trauma, while maintaining the therapeutic effect, is a hot spot.

The traditional view considered that SLND is meaningful even for patients with stage IA NSCLC. Lardinois *et al.* (18) advocate to perform SLND. They find that patients with NSCLC stage I who undergo SLND have a prolonged DFS comparing with patients who undergo only lymph node sampling (LNS). The present study finds that 13.5% patients with clinical stage IA have lymph node metastasis, indicating that SLND cannot be ignored even in patients with stage IA. In addition, "skip metastasis" is not

Table 3 The relationship between the imaging features and lymph node metastasis

Imaging features	N	Lymph node metastasis, n (%)			Total
		N0	N1	N2	
GGO	66	66 (100.00)	0	0	0
Solid component <50%	71	66 (92.96)	2 (2.82)	3 (4.23)*	5 (7.04)
Solid component ≥50%	63	41 (65.08)	6 (9.52)	16 (25.40)*#	22 (34.92)*#
χ^2			37.877		37.591
P			0.000		0.000

*, compared with those whose imaging features was GGO, P<0.05; #, compared with those whose imaging features was solid component ≥50%, P<0.05. GGO, ground-glass opacity.

Table 4 The relationship between the pathology and lymph node metastasis

Pathology	N	Lymph node metastasis (%)			Total
		N0	N1	N2	
Adenocarcinoma	173	153 (88.44)	3 (1.73)	17 (9.83)	20 (11.56)
Squamous cell carcinoma	25	18 (72.00)	5 (20.00)	2 (8.00)	7 (28.00)
χ^2			18.797		5.013
P			0.000		0.025

Table 5 The relationship between the tumor location and lymph node metastasis

Tumor location	N	Lymph node metastasis (%)			Total
		N0	N1	N2	
Medial 1/2	91	73 (80.22)	6 (6.59)	12 (13.19)	18 (19.78)
Lateral 1/2	109	100 (91.74)	2 (1.83)	7 (6.42)	9 (8.26)
χ^2			5.958		5.640
P			0.051		0.018

rare in this study. "Skip metastasis" means that NSCLC can skip adjacent lymph nodes and directly metastasize to lymph nodes at other sites (19), which usually occurs in 20–38% of patients with NSCLC (20). Hence, N1 lymph nodes found negative on LNS do not mean that N2 lymph nodes are clean. SLND is still necessary.

Nevertheless, whether SLND is indispensable for every patient with stage IA NSCLC is not confirmed yet. Cells of clinical stage IA NSCLC are relatively stable comparing with advanced-stage NSCLC cells. Their biological behaviors are different. The present study indicates that SLND is not necessary for some patients with clinical stage IA NSCLC, after carefully checking their preoperative clinical and imaging data.

In this study, the rates of both N1 and N2 lymph node metastases increase with the increase in tumor diameter. This is consistent with the result of Oda *et al.* (21). They retrospectively analyse the prognosis of 524 patients with clinical stage I NSCLC who undergo lobectomy and SLND. The postoperative pathological examination reveals that 409 patients have N0, 44 have N1, 67 have N2, and 4 have N3. The tumor diameter and pathological type are correlate with lymph node metastasis. Invasive growth and distant metastasis are the features of NSCLC. Larger diameter suggests longer growth time or worse biological behavior, leading to a higher lymph node metastasis rate.

Table 6 Factors related to N1 lymph metastasis by multiple regression analysis

Factors	OR (95% CI)	P	aOR (95% CI)	P
Tumor size (cm)				
<1	1	0.019	1	0.016
≥1	2.366 (1.149–4.869)		2.616 (1.192–5.742)	
Imaging features				
GGO	1	0.000	1	0.000
Containing solid component	6.296 (2.281–17.378)		6.546 (2.376–18.036)	
Tumor location				
Medial 1/2	1	0.038	1	0.066
Lateral 1/2	0.300 (0.096–0.937)		0.383 (0.138–1.067)	

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; GGO, ground-glass opacity.

Table 7 Factors related to N2 lymph metastasis by multiple regression analysis

Factors	OR (95% CI)	P	aOR (95% CI)	P
Tumor size (cm)				
<1	1	0.016	1	0.008
≥1	2.681 (1.203–5.974)		2.896 (1.326–6.324)	
Imaging features				
GGO	1	0.000	1	0.000
Containing solid component	16.912 (4.655–61.440)		9.536 (2.978–30.538)	
Tumor location				
Medial 1/2	1	0.019	1	0.111
Lateral 1/2	0.216 (0.060–0.776)		0.452 (0.170–1.201)	

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; GGO, ground-glass opacity.

Many studies show that the solid component of NSCLC correlate with the invasiveness and metastatic ability of NSCLC. More solid component suggests worse biological behavior, and pure GGO suggests that tumors are inert and did not metastasize easily, and the patient may have a better prognosis (22,23). None of the patients with pure GGO show lymph node metastasis. This suggests narrowing the scope of lymph node dissection or LNS for patients with pure GGO. On the contrary, patients whose tumors are solid component <50% and solid component ≥50% are likely to have lymph node metastasis; especially patients whose tumors are solid component ≥50% are more likely to have "skip metastasis". An SLND is definitely necessary for these patients.

NSCLC can be divided into central lung cancer and peripheral lung cancer. Most previous studies do not further segregate peripheral lung cancer according to its location. The present study find that most clinical stage IA NSCLC are peripheral, and the actual location is related to lymph node metastasis. Patients whose tumors are located in the medial half lobe have a higher lymph node metastasis rate for both N1 and N2 lymph nodes. This phenomenon is consistent with the regular pattern of tumor metastases, from distal to proximal. As the hilus and the mediastinum are the production sites of lymph node metastasis, tumors closer to the hilus and mediastinum are more likely to metastasize.

The present study shows that squamous cell carcinoma is more likely to have lymph node metastasis comparing with adenocarcinoma. However, patients with squamous cell

carcinoma account for only 12.5% of all patients, reducing the significance. In addition, 66 patients with pure GGO are adenocarcinoma, reducing the lymph node metastasis rate of adenocarcinoma. In the group with solid component ≥50%, the lymph node metastasis rate is 28% and 41.7% for squamous cell carcinoma and adenocarcinoma, respectively, with no significant differences (P=0.274). Hence, the pathological type should be combined with the imaging findings to evaluate the risk of lymph node metastasis.

For early-stage NSCLC, selective lymph node dissection is attempted. By reviewing patients with T1aN0M0 NSCLC, Ma *et al.* (6) reveal that SLND and selective lymph node dissection show no differences in determining N stage, DFS, and OS. Jiang *et al.* (7) believe that selective lymph node dissection can reduce surgical trauma for patients with clinical stage I NSCLC, especially old patients with underlying diseases; the OS rate shows no difference comparing with patients who underwent SLND.

This study finds that patients with clinical stage IA NSCLC, whose tumor diameter is larger, solid component rate is high, and tumor locates in the medial half lobe, have lymph node metastasis. Selective lymphadenectomy is considered for those with tumors smaller than 1 cm, pure GGOs, or tumors locate in the lateral half lobe. Preoperative clinical and imaging evaluation is important for patients with clinical stage IA NSCLC. SLND must not be ignored for patients with a high risk of lymph node metastasis; selective lymphadenectomy may benefit patients with a low risk of lymph node metastasis.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.01.67). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the study and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the hospital ethics committee {No. [2014]-05-51} and informed consent was taken from all individual participants.

References

1. Zhang J, Gold KA, Lin HY, et al. Relationship Between Tumor Size and Survival in Non–Small-Cell Lung Cancer (NSCLC): An Analysis of the Surveillance, Epidemiology, and End Results (SEER) Registry. J Thorac Oncol 2015;10:682-90.
2. Corrales-Rodriguez L, Juárez M, Ramos-Esquivel A, et al. P1.10: Follow-Up on Results of a Multidisciplinary Team in the Management of Non-Small Cell Lung Cancer in a Developing Country: Track: Prevention, Early Detection, Epidemiology and Tobacco Control. J Thorac Oncol 2016;11:S185-6.
3. Wang Y, Darling GE. Complete mediastinal lymph node dissection versus systematic lymph node sampling in surgical treatment of non-small cell lung cancer: do we have the answer? J Thorac Dis 2017;9:4169-70.
4. Zhong WZ, Liu SY, Wu YL. Numbers or Stations: From Systematic Sampling to Individualized Lymph Node Dissection in Non-Small-Cell Lung Cancer. J Clin Oncol 2017;35:1143-5.
5. Adachi H, Maehara T, Nakayama H, et al. Mediastinal lymph node dissection in surgical treatment for early stage non-small-cell lung cancer: lobe-specific or systematic? J Thorac Dis 2017;9:2728-31.
6. Ma W, Zhang ZJ, Li Y, et al. Comparison of lobe-specific mediastinal lymphadenectomy versus systematic mediastinal lymphadenectomy for clinical stage T_{1a} N_0 M_0 non-small cell lung cancer. J Cancer Res Ther 2013;9 Suppl 2:S101-5.
7. Jiang W, Chen X, Xi J, et al. Selective mediastinal lymphadenectomy without intraoperative frozen section examinations for clinical stage I non-small-cell lung cancer: retrospective study of 403 cases. World J Surg 2013;37:392-7.
8. Okada M, Sakamoto T, Yuki T, et al. Selective mediastinal

lymphadenectomy for clinico-surgical stage I non-small cell lung cancer. Ann Thorac Surg 2006;81:1028-32.
9. Muraoka M, Akamine S, Oka T, et al. Sentinel node sampling limits lymphadenectomy in stage I non-small cell lung cancer. Eur J Cardiothorac Surg 2007;32:356-61.
10. Frakulli R, Salvi F, Balestrini D, et al. Radiological differential diagnosis between fibrosis and recurrence after stereotactic body radiation therapy (SBRT) in early stage non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2017;6:S1-7.
11. Lee K, Kim HR, Kim DK, et al. Post-recurrence survival analysis of stage I non-small-cell lung cancer. Asian Cardiovasc Thorac Ann 2017;25:623-9.
12. Kong M, Jin J, Cai X, et al. Characteristics of lymph node metastasis in resected adenosquamous lung cancer. Medicine (Baltimore) 2017;96:e8870.
13. Lee DH, Yoon TM, Lee JK, et al. Supraclavicular Lymph Node Excision Biopsy in Patients with Suspected Supraclavicular Lymph Node Metastasis of Lung Cancer: Experience in a Tertiary Hospital. Chonnam Med J 2017;53:69-72.
14. Liu B, Wan Z, Sheng B, et al. Overexpression of EMMPRIN is associated with lymph node metastasis and advanced stage of non-small cell lung cancer: a retrospective study. BMC Pulm Med 2017;17:214.
15. Li TC, Li CI, Tseng CH, et al. Quality of life predicts survival in patients with non-small cell lung cancer. BMC Public Health 2012;12:790.
16. Kenny PM, King MT, Viney RC, et al. Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. J Clin Oncol 2008;26:233-41.
17. Efficace F, Bottomley A, Smit EF, et al. Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. Ann Oncol 2006;17:1698-704.
18. Lardinois D, Suter H, Hakki H, et al. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. Ann Thorac Surg 2005;80:268-74; discussion 274-5.
19. Kawano R, Hata E, Ikeda S, et al. Lobe-specific skip nodal metastasis in non-small cell lung cancer patients. Ann Thorac Cardiovasc Surg 2008;14:9-14.
20. Riquet M, Assouad J, Bagan P, et al. Skip mediastinal lymph node metastasis and lung cancer: a particular N2 subgroup with a better prognosis. Ann Thorac Surg 2005;79:225-33.
21. Oda M, Watanabe Y, Shimizu J, et al. Extent of mediastinal node metastasis in clinical stage I non-small-cell lung cancer: the role of systematic nodal dissection. Lung Cancer 1998;22:23-30.
22. Chang B, Hwang JH, Choi YH, et al. Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan. Chest 2013;143:172-8.
23. Yamaguchi M, Furuya A, Edagawa M, et al. How should we manage small focal pure ground-glass opacity nodules on high-resolution computed tomography? A single institute experience. Surg Oncol 2015;24:258-63.

Cite this article as: Luo T, Chen Q, Zeng J. Analysis of lymph node metastasis in 200 patients with non-small cell lung cancer. Transl Cancer Res 2020;9(3):1577-1583. doi: 10.21037/tcr.2020.01.67

