Oncology and Translational Medicine
DOI 10.1007/s10330-020-0421-1

August 2020, Vol. 6, No. 4, P165–P169

ORIGINAL ARTICLE

Correlation between clinicopathological parameters of lung adenocarcinoma and lymph node metastasis

Shixun Wang[1], **Gaoyang Lin**[2], **Nan Ge**[3], **Ronghua Yang**[3], **Mengjun Li**[1], **Donghua Zhao**[1], **Peng Li**[1], **Yongjie Wang**[3] (✉)

[1] Qingdao University, Qingdao 266000, China
[2] Department of Thoracic Surgery, The Affiliated Qingdao Hiser Medical Center of Qingdao University, Qingdao 266000, China
[3] Department of Thoracic Surgery, The Affiliated Hospital of Qingdao University, Qingdao 266000, China

Abstract

Objective The aim of the study was to study the correlation between the clinicopathological parameters of lung adenocarcinoma and lymph node metastasis and identify the risk factors of lymph node metastasis.
Methods The data of 258 patients with postoperative lung adenocarcinoma (mainly based on their pathological data) were collected and analyzed, and their basic information was counted.
Results Maximum tumor diameter was found to be an independent risk factor for lymph node metastasis. The larger the maximum diameter of the tumor in patients with lung adenocarcinoma, the higher the likelihood of lymph node metastasis. Solid predominant adenocarcinoma with mucin production is as an independent risk factor for superior mediastinal and subcarinal lymph node metastasis. Primary adenocarcinomas in the lower lobe of the lung may have a higher rate of lymph node metastasis than those in the upper lobe.
Conclusion The known pathological subtypes of lung adenocarcinoma can be used for the prediction of lymph node metastasis in various regions and guide the dissection of lymph nodes that would improve patients' prognosis.
Key words: lung adenocarcinoma; lymph node metastasis; pathological subtype; risk factors

Received: 19 April 2020
Revised: 14 May 2020
Accepted: 4 July 2020

Lung cancer is the most common malignancy, with the highest mortality rate, in China. High-resolution CT screening improves the detection of lung cancer, among which lung adenocarcinoma is the most common type [1]. In the 2015 WHO classification of lung tumors, lung adenocarcinoma was re-recognized [2], including adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), lepidic predominant adenocarcinoma (LPA), acinar predominant adenocarcinoma (ACI), and papillary predominant adenocarcinoma (PAP), solid predominant adenocarcinoma with mucin production (SPA), micropapillary predominant adenocarcinoma (MPA), and invasive mucinous adenocarcinoma (IMA). Subsequently, more studies have confirmed that the pathological subtype of adenocarcinoma is an independent predictor of disease-free survival, and lymph node metastasis is an important factor for long-term survival [3–4]. However, since there is no unified understanding of the adaptive scope and resection boundary in subpulmonary lobectomy and non-systematic lymph node dissection, more studies are needed to clarify the risk factors of the occurrence and development of tumors and of lymph node metastasis.

Therefore, it is necessary to analyze and summarize the rule of lymph node metastasis of lung adenocarcinoma and to clarify its risk factors to provide a reference for minimally invasive treatment of patients. This study aimed to investigate the correlation and risk factors between the clinicopathological parameters of adenocarcinoma and lymph node metastasis.

Materials and methods

Data of 258 patients with lung adenocarcinoma who met the inclusion criteria in the Department of Thoracic Surgery, Eastern District of the Affiliated Hospital of

✉ Correspondence to: Yongjie Wang. Email: wyjtgzy@163.com

Table 1 Analysis of lymph node metastasis at the different lobular stations in 258 patients with lung adenocarcinoma

Number of lymph node stations	RUL (*n* = 89, %)	RML (*n* = 16, %)	RLL (*n* = 55, %)	LUL (*n* = 56, %)	LLL (*n* =42, %)
2	2 (2.2)	0	3 (5.5)	0	0
3	0	0	1 (1.8)	0	0
4	3 (3.3)	0	1 (1.8)	1 (1.8)	0
5	0	0	0	2 (3.6)	0
6	0	0	0	1 (1.8)	0
7	0	2 (12.5)	5 (9.1)	0	3 (7.1)
8	0	0	0	0	0
9	2 (2.2)	0	0	0	1 (2.4)
10	3 (3.3)	0	3 (5.5)	1 (1.8)	3 (7.1)
11	4 (4.5)	0	5 (9.1)	2 (3.6)	2 (4.8)
12	4 (4.5)	0	6 (10.9)	3 (5.4)	3 (7.1)
13	0	0	0	0	0
Total	18 (20.2)	2 (12.5)	24 (43.6)	10 (17.9)	12 (28.6)

Note: RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe

Qingdao University (Qindao, China) from November 2018 to April 2019, were retrospectively analyzed. The inclusion criteria were as follows: patients with complete imaging data within 30 days before surgery; patients with single lung adenocarcinoma who were evaluated as stage N0–N2 for feasible surgical resection according to the eighth TNM staging; those who underwent R0 resection of lung tumor, including sublobectomy, lobectomy, or pneumonectomy with systematic lymph node dissection; all postoperative specimens that showed paraffin sectioning pathology. The exclusion criteria were as follows: pathologically confirmed non-lung adenocarcinoma; preoperative chemoradiotherapy or targeted therapy; incomplete medical history; multiple pulmonary nodules. Preoperative routine examination included tumor marker tests, electrocardiogram (ECG), echocardiography, and lung function test of all patients. All patients underwent a systematic physical examination before surgery. Imaging examinations of the brain, chest, and abdomen, such as computed tomography or (CT), magnetic resonance imaging (MRI), emission computerized tomography (ECT), and positron emission tomography (PET) were performed on some patients to determine that lung cancer is confined to one side of the chest without distant metastasis.

During the operation, at least three lymph nodes stations were dissected for each case, and the lymph node partitioning method was adopted: Group 2–6 was the superior mediastinal lymph region; Group 8–9 was the inferior mediastinal lymph region; Group 10–13 was the intrapulmonary lymph node (N1); and subcarinal lymph node was partitioned separately. The pathological report included tumor size (maximum tumor diameter as the evaluation index), site, histopathological type, total number of lymph nodes dissected, and positive number.

SPSS 18.0 software was used for data collation and analysis. Results were analyzed by using Pearson χ^2 test or calibration χ^2 test and logistic regression analysis. A P-value of less than 0.05 was considered statistically significant.

Results

There were 258 patients, including 88 males and 170 females, with a mean age of (59.3 ± 9.2) years. There were 89 cases of right upper lobe (34.5%), 16 cases of right middle lobe (6.2%), 55 cases of right lower lobe (21.3%), 56 cases of left upper lobe (21.7%), and 42 cases of left lower lobe (16.3%). The details are shown in Table 1. Among the pathological subtypes, there were 52 (20.2%) LPA, 128 (49.6%) ACI, 13 (5%) PAP, one (4.7%) MPA, 12 (4.7%) SPA, and nine (3.5%) IMA cases. A total of 1449 groups of 3499 lymph nodes were dissected. The mean number of lymph nodes dissected in each patient was 13.56 in 5.62 groups; 66 (4.6%) were positive, and 130 (3.7%) lymph nodes were metastatic, as shown in Table 2.

In tumors located in the right upper lobe, which included 89 cases, the lymph node metastasis rate was 20.2% (18/89). The frequency of lymph node metastasis from high to low in turn to were intrapulmonary lymph node (11–13) 9%, hilus pulmonis 3.3%, right lower paratracheal lymph node (4R) 3.3%, superior paratracheal lymph nodes (2R) 2.2%, inferior mediastinal lymph node (8–9) 2.2%. Among the 55 patients whose primary tumor was located in the right lower lobe, the total lymph node metastasis rate was 43.6% (24/55). The stations (11–13), subcarinal lymph node, and hilar lymph node were more prone to metastasis, and their metastasis rates were 20%, 9.1%, and 5.5%, respectively. There were 56 patients with a primary tumor in the left upper lobe, and the total lymph node metastasis rate was 17.9% (10/56), which was similar to that in the right upper lobe. The station lung

Table 2 Single factor analysis of the risk factors for regional lymph node metastasis

Influence factor	Superior mediastinal region		Subcarinal region		Inferior mediastinal region		N1 region	
	Positive cases	*P*	Positive cases	*P*	Positive cases	*P*	Positive cases	*P*
Gender								
female	5	0.256	6	0.952	1	0.232	18	0.498
male	6		4		2		7	
Age (years)								
< 60	3	0.413	8	0.043	0	0.341	12	0.656
≥ 60	8		2		3		13	
Lung lobe								
RUL	3		0		2		5	
RML	0		2		0		0	
RLL	4	0.125	5	0.002	0	0.392	9	0.074
LUL	4		0		0		5	
LLL	0		3		1		6	
T								
Tis	0		0		0		0	
T1	3	0.002	5	0.140	1	0.460	14	0.006
T2	8		5		2		11	
T3	0		0		0		0	
Subtype								
LPA	0		1		0		1	
ACI	8		6		2		14	
PAP	0	0.007	0	0.046	0	0.445	1	0.000
MPA	0		0		0		1	
SPA	3		3		0		6	
IMA	0		0		1		1	

Note: RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LPA, lepidic predominant adenocarcinoma; ACI, acinar predominant adenocarcinoma; PAP, papillary predominant adenocarcinoma; MPA, micropapillary predominant adenocarcinoma; SPA, solid predominant adenocarcinoma with mucin production; IMA, invasive mucinous adenocarcinoma

lymph nodes with the highest lymph node metastasis rate were 8.9%, the main-pulmonary artery window lymph node (5) was 3.6%, and the lymph node region with the lowest metastasis rate was the inferior mediastinal lymph node (0%), which was similar to the right upper lobe. There were 42 patients with tumors in the left lower lobe, and the total metastasis rate was 28.6% (12/42). The most easily metastatic lymph node region was the N1 region 19.0% (8/42), followed by the subcarinal region 7.1% (3/42). There were 16 patients with a primary tumor in the right middle lobe, and only 12.5% (2/16) subcarinal lymph node metastasis was observed in this study.

In 258 patients, the N1 lymph node metastasis rate was 15.1% (39/258), N2 lymph node metastasis rate was 10.5% (27/258). Among them, the single N1 metastasis rate was 4.7% (12/258), only 30.8% of all N1 lymph nodes (12/39). The N2 division alone – hop lymph node metastasis, lymph node metastasis rate was 2.7% (7/258), while N1 and mediastinal lymph node metastasis occurred in 13 cases (5.0%). Among the primary pulmonary lobes, the N1 region had the highest metastasis rate, with the right lower lobe being the largest (25.5%). In the mediastinal lymphatic region, the subcarinal lymphatic region had the highest metastasis rate of 37.0% (10/27). In 89 patients with N2 lymphatic metastasis in the right upper lobe, the mediastinal lymphatic region above was dominant, accounting for 71.4% (5/7) of the N2 region. Only two patients had metastasis in the inferior mediastinal region. The same characteristics were observed in the left upper lobe in 56 cases as in the right upper lobe. Unlike the primary upper lobe pattern, the probability of non-regional lymph nodes in patients with primary lower lobe is higher than that with upper lobe. Subcarinal lymph nodes were the most easily metastasized N2 lymph nodes in the right lower lobe, accounting for 50% (5/10). Lymph node metastasis in the left lower lobe was similar to that in the right lower lobe, and subcarinal lymph nodes accounted for 75% (3/4) of the N2 lymph nodes.

Single-factor analysis, subcranial lymph node metastasis is more likely to happen in patients older than 60 years with a significant difference of P = 0.043 and patients with right lower lobe compared to the rest of the lung to subcarinal lymph node metastasis rate higher statistically significant (P = 0.002). Compared to other subtypes of adenocarcinoma, subcarinal and N1 lymph node metastasis rates were higher with SPA (subcarinal

Table 3 Multivariate logistic analysis of the risk factors for regional lymph node metastasis

Risk factors	Superior mediastinal region (*P*)	Subcarinal region (*P*)	Inferior mediastinal region (*P*)	N1 region (*P*)
≥ 60 years old	0.354	0.024	0.996	0.550
The maximum diameter	0.000	0.013	0.038	0.001
Lower lobe	0.721	0.025	0.760	0.049
SPA	0.021	0.015	0.999	0.002

Note: SPA, solid predominant adenocarcinoma with mucin production

area P = 0.046, N1 area P = 0.000). T2 in the superior mediastinal region and N1 region showed statistical differences compared to T1 (superior mediastinal region P = 0.002, N1 region P = 0.006; Table 2).

In multiple factors analysis, tumor diameter was found to be an independent risk factor for lymph node metastasis. SPA in the mediastinal area (P = 0.021), subcarinal area (P = 0.015), and N1 area (P = 0.002) can be used as independent risk factors for lymph node metastasis. Tumors in the lower lobe occurring in the subcarinal area and N1 area are independent risk factors for lymph node metastasis (Table 3).

Discussion

For patients with lung adenocarcinoma, an accurate N stage is better for guiding the treatment and evaluating the prognosis. There is still a debate on how the preoperative N stage can be assessed accurately, and most doctors do not routinely use mediastinoscopy [5]. Although some researchers have tried to predict mediastinal lymph node metastasis [6], most of these researchers focused on only a particular histological type. The predictive value of the new classification of lung adenocarcinoma for patient survival and recurrence rate has been extensively studied. However, there is no evidence of correlation between subtypes and lymph node metastasis. Zhang *et al*[7] found that the lymph node metastasis rate of adenocarcinoma dominated by MPA and SPA was significantly higher than that of other subtypes, and the pathological subtypes were also analyzed as independent predictors of N0 metastasis (P = 0.008). Qin *et al*[8] found that MPA and SPA were independent risk factors for the upregulation of the N stage in clinical stage Ia adenocarcinoma. Studies have found that selective lymphadenectomy can be considered for better-differentiated subtypes (such as AIS, MIA, and LPA) [9–11], which will have greater benefits. This study also found that SPA was a risk factor for regional lymph node metastasis. However, there was no significant difference in the number of micropapillary cases.

There are some prospective studies [12] that continue to think that systemic cleaning of lymph nodes should be performed to improve the postoperative survival rate of patients with lung cancer following surgical treatment. The reason is that there can be a more accurate N stage to guide postoperative treatment [13] and can reduce the postoperative recurrence and metastasis; therefore, lobectomy and systemic lymph node cleaning techniques are still suggested as a standard procedure. However, more and more studies show that some patients with early lung cancer do not benefit from systematic cleaning [14], increasing the difficulty of surgery, surgical trauma, and some postoperative complications. Some patients had preoperative biopsy pathology, but few had lymph node biopsy results. Pathologic puncture results are helpful in guiding the surgical approach. Based on the correlation between clinicopathological parameters of adenocarcinoma and the lymph node regions in this study, lymph node dissection or lymph node sampling can be specifically selected during the operation without affecting the N stage to reduce surgical trauma. Combined with intraoperative rapid freezing pathology [15], intraoperative selective cleaning or sampling is feasible for early differentiation typing, which can increase the benefit in patients. Therefore, it is suggested that puncture pathology or freeze pathology should be accurate for the pathological subtypes. If conditions permit, accurate molecular typing can better analyze the patient's condition and allow more favorable conditions for long-term survival.

Based on the regional study of lymph nodes conducted in this study, the relationship between different pulmonary lobes and different pathological subtypes for lymph node metastasis is different. Lobe-specific lymph node dissection (L-SLD) determines the range of lymph node dissection according to the location of the tumor in the lung [16–17]. It is primarily applicable to patients in clinical stages I–II, and particularly for patients with a diameter < 2 cm; further, only when the main lymph node drainage area is frozen and pathologically negative can the lymph nodes in the non-drainage area not be dissected. However, the existence of skip transfer makes L-SLD controversial, and prospective research [18] is underway. This study is a retrospective analysis, and the data can be used as reference for future studies.

This study has limitations. For instance, there are errors and losses in the collection of medical history data and thus the findings need to be further proved using a prospective multicenter randomized controlled study. The number of cases included in this study is small, and the positive sample size is less than five in the subgroup analysis, which may produce false-negative results. The single-center study lacks the calibration of different reference indexes. Hence, the research conclusions should be extended carefully. The correlation between lymph node metastasis and lung adenocarcinoma typing remains to be further studied.

Based on this study, the following conclusions are drawn: primary adenocarcinomas located in different pulmonary lobes have different metastasis patterns corresponding to the lymph node regions, and the lower lobe of the subcarinal lymph node region has a higher metastasis rate, which is an important area for dissection. Patients with lung adenocarcinoma are more likely to have lymph node metastasis as the maximum tumor diameter (T stage) increases. Based on the risk factors identified in this study, it can be concluded that the greater the transition probability of lung adenocarcinoma to the regional lymph nodes, the greater the reference line; further mediastinal lymph node stage, the lower the risk factors for prediction of smaller patients, under the condition of no surgery taboo still suggest the complete resection of the tumor and systemic lymph node cleaning to help improve the postoperative survival rate.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin, 2017, 67: 7–30.
2. Travis WD, Brambilla E, Burke AP, *et al*. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. J Thorac Oncol, 2015, 10: 1240–1242.
3. Yoshizawa A, Motoi N, Riely GJ, *et al*. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol, 2011, 24: 653–664.
4. Izbicki JR, Passlick B, Pantel K, *et al*. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. Ann Surg, 1998, 227: 138–144.
5. Toloza EM, Harpole L, Detterbeck F, *et al*. Invasive staging of non-small cell lung cancer: a review of the current evidence. Chest, 2003, 123 (1 Suppl): 157S–166S.
6. Park SY, Yoon JK, Park KJ, *et al*. Prediction of occult lymph node metastasis using volume-based PET parameters in small-sized peripheral non-small cell lung cancer. Cancer Imaging, 2015, 15: 21.
7. Zhang Y, Sun Y, Shen L, *et al*. Predictive factors of lymph node status in small peripheral non-small cell lung cancers: tumor histology is more reliable. Ann Surg Oncol, 2013, 20: 1949–1954.
8. Qin Y, Qiu T, Xuan YP, *et al*. Risk factors of nodal upstaging in clinical Ia lung adenocarcinoma. Chin J Lung Cancer (Chinese), 2018, 21: 463–469.
9. Woo T, Okudela K, Mitsui H, *et al*. Prognostic value of the IASLC/ATS/ERS classification of lung adenocarcinoma in stage I disease of Japanese cases. Pathol Int, 2012, 62: 785–791.
10. Fan XH, Xu XC, Liu XY, *et al*. Analysis of risk factors for lymph node metastasis in clinical stage T1 lung adenocarcinomas. Chin J Thorac Cardiovasc Surg (Chinese), 2019, 35: 420–424.
11. Russell PA, Barnett SA, Walkiewicz M, *et al*. Correlation of mutation status and survival with predominant histologic subtype according to the new IASLC/ATS/ERS lung adenocarcinoma classification in stage III (N2) patients. J Thorac Oncol, 2013, 8: 461–468.
12. Wu YL, Wang SY, Huang ZF, *et al*. Extent of lymphadenectomy in stage I–IIIA non-small cell lung cancer: a randonmized clinical trial. Chin J Oncol (Chinese), 2001, 23: 43–45.
13. Liu ZZ, Xie XD. Whole process control and precision therapy in lung cancer. Oncol Transl Med, 2017, 3: 91–92.
14. Darling GE, Allen MS, Decker PA, *et al*. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg, 2011, 141: 662–670.
15. He P, Yao G, Guan Y, *et al*. Diagnosis of lung adenocarcinoma *in situ* and minimally invasive adenocarcinoma from intraoperative frozen sections: an analysis of 136 cases. J Clin Pathol, 2016, 69: 1076–1080.
16. Watanabe S, Asamura H, Suzuki K, *et al*. The new strategy of selective nodal dissection for lung cancer based on segment-specific patterns of nodal spread. Interact Cardiovasc Thorac Surg, 2005, 4: 106–109.
17. Okada M, Tsubota N, Yoshimura M, *et al*. Proposal for reasonable mediastinal lymphadenectomy in bronchogenic carcinomas: role of subcarinal nodes in selective dissection. J Thorac Cardiovasc Surg, 1998, 116: 949–953.
18. Hishida T, Saji H, Watanabe SI, *et al*. A randomized Phase III trial of lobe-specific vs. systematic nodal dissection for clinical Stage I–II non-small cell lung cancer (JCOG1413). Jpn J Clin Oncol, 2018, 48: 190–194.

DOI 10.1007/s10330-020-0421-1
Cite this article as: Wang SX, Lin GY, Ge N, *et al*. Correlation between clinicopathological parameters of lung adenocarcinoma and lymph node metastasis. Oncol Transl Med, 2020, 6: 165–169.