


ORIGINAL ARTICLE

Blind spot in lung cancer lymph node metastasis: Cross-lobe peripheral lymph node metastasis in early stage patients

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Abstract

Background: At present, it has not yet been determined whether metastasis can be transferred cross-lobe to peripheral lymph nodes (LNs) from other lobes in early stages of lung cancer, especially without any direct involvement to the pleura and parenchyma of the lobe. This study was conducted to investigate this issue.

Methods: A retrospective analysis was conducted at the Chinese Academy of Medical Sciences. Patients undergoing right middle and lower lobectomy with lymphadenectomy for preoperative clinical stage Ia–IIIa from 2014 to 2015 were identified. To avoid interference, cases were limited to tumors within the primary lobe. When a tumor is completely located in the lower lobe, no direct invasion occurs into the visceral pleura/bronchus/parenchyma of the middle lobe and tumor cell metastasis into the peripheral LNs (stations 12–14) in the middle lobe is defined as cross-lobe lymph node metastasis (CLM).

Results: A total of 68 patients were identified, of which nine (13.2%) had CLM. Seven had squamous cell carcinoma, one adenocarcinoma, and one small cell carcinoma. Seven cases (77.8%) had intermediate bronchus invasion, and seven cases (77.8%) intermediate bronchus adjacent lymph node involvement (station 11). Compared to non-CLM patients, tumor diameter (5.2 vs. 3.2; $P = 0.28$), N2 lymph node metastasis rate (66.7% vs. 28.8%; $P = 0.03$), late stage (IIIa 77.8% vs. 35.6%; $P = 0.04$), and invasion of intermediate bronchus (77.8% vs. 45.8%; $P = 0.07$) relatively increased.

Conclusion: Non-primary lobe peripheral LN metastasis exists in lung cancer and requires greater attention and further study.

Introduction

Lymph node (LN) metastasis is a common type of metastasis of the lung.¹ LN metastasis in lung cancer commonly follows a pattern: from solid tumor metastasis to the peripheral LNs (stations 12–14) in the primary lobe, then to the interlobar LNs (station 11), to the hilar LNs (station 10), and to the mediastinal LNs (stations 2–9).^{2–4} Although special circumstances, such as skip^{5,6} or micro⁷ metastasis may occur, the lymphatic drainage pattern is widely recognized. However, there have been no reports as to whether tumor cells could go beyond this pathway and metastasize to the non-primary lobe of the peripheral LN. In clinical

practice, we found lung cancer metastasis in the right middle lobe peripheral LN, while tumors located only in the right lower lobe did not directly invade the middle lobe. Therefore, we conducted this retrospective study to investigate this issue.

Methods

A retrospective analysis was conducted of lung cancer patients who underwent right middle and lower lobectomy with lymphadenectomy between November 2014 and November 2015 at the Cancer Institute and Hospital, Chinese Academy of Medical Sciences.

Surgical and pathology reports of each patient were carefully analyzed. To avoid interference, we only enrolled cases in which the tumor occurred within one lobe. Cases of tumors that directly invaded both lobes of the lung parenchyma or pleura, the presence of pulmonary metastasis, and tumors that originated in the intermediate bronchus of the right lung, as well as non-primary lung cancer cases, were excluded. Patients who received preoperative chemotherapy and radiotherapy, as well as those who underwent LN sampling, were also excluded.

Primary lung tumor location, size, histological type, degree of differentiation, LN metastasis, invasion of the intermediate bronchus, invasion between fissures, patient age, gender, and tumor node metastasis stage were recorded. Two cancer specialist pathologists conducted detailed anatomical examinations of resected lung specimens to determine LN metastasis. In particular, peripheral LN metastasis was evaluated, including segmental/sub-segmental LN (stations 13 and 14) and lobar LNs (station 12). Lobar LNs (station 12) refer to those located adjacent to the lobar bronchial lymph, while segmental/sub-segmental LNs (stations 13 and 14) refer to those located next to the segmental bronchi and the following parts of the LNs.^{1,8}

When a tumor is completely located in the lower lobe, no direct invasion occurs into the visceral pleura/bronchus/parenchyma of the middle lobe. Tumor cell metastasis into the peripheral LNs (stations 12–14) in the middle lobe is defined as cross-lobe lymph node metastasis (CLM).

The institutional review board approved the study. All analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). In univariate analysis, differences between the CLM and control groups were analyzed using X^2 or Fisher's exact tests. A P value of < 0.05 was considered statistically significant.

Results

One hundred and thirty-seven patients were admitted and underwent right lung middle and lower lobe resection at the Cancer Hospital between 2014 and 2015. Among these patients, 48 with tumor invasion of two lobes of lung parenchyma, 6 with pulmonary metastasis, 12 with tumors that originated from the intermediate bronchus, and 3 with benign lesions were excluded from the study. A total of 68 patients that underwent routine middle and lower lobectomy were included. Basic patient information including gender, age, tumor size, histological type, differentiation of cancer cells, pathological stage, and LN metastasis is shown in Table 1.

Nine patients had CLM, with tumors located in the right lower lobe, and cancer cells metastasized to the

Table 1 Clinicopathologic features of patients ($n = 68$)

Variables	No.	%
Gender		
Male	58	85.3%
Female	10	14.7%
Age		
Range	27–82	
< 59	37	54.4%
> 60	31	45.6%
Tumor size		
Range	0.6–11	
< 3 cm	26	38.2%
> 3 cm	42	61.8%
Histology type		
SCC	47	69.1%
AD	10	14.7%
SCLC	4	5.9%
LCLC	1	1.5%
Mucinous adenocarcinoma	3	4.4%
Adenoid cystic carcinoma	1	1.5%
Carcinoid	2	2.9%
Differentiation		
Poor	23	39.0%
Moderate	33	55.9%
Well	3	5.1%
Lesion location		
Middle lobe	4	5.9%
Lower lobe	64	94.1%
Intermediate bronchus invasion		
Yes	34	50.0%
No	34	50.0%
Pulmonary vascular invasion		
Yes	9	13.2%
No	59	86.8%
Visceral pleura invasion		
Yes	17	25.0%
No	51	75.0%
Stage		
I	16	23.5%
II	24	35.3%
IIIa	28	41.2%
N2 metastasis		
Yes	23	33.8%
No	45	66.2%

AD, adenocarcinoma; LCLC, large cell lung cancer; SCC, squamous cell cancer; SCLC, small cell lung cancer.

peripheral LNs (stations 12–14) of the right middle lobe, while parenchyma and pleura of the right middle lobe were cancer free.

All patients were male, the maximum tumor diameter was 1.8–7.5 cm, and pathological types comprised squamous cell carcinoma (7), adenocarcinoma (1), and small cell carcinoma (1). Seven cases had intermediate bronchus invasion and one had invasion of the hilar blood vessels. Furthermore, seven cases were positive in the intermediate bronchus adjacent LN (station 11), and six were positive

for peripheral LN metastasis in the right lower lobe (stations 12–14). Patients had 2–12 metastatic LNs and the pathological stages were IIB (2 patients), and IIIA (7 patients) (Table 2).

Patients were divided into two groups according to LN metastasis: CLM and non-CLM. After comparing the clinical characteristics of the patients, we found that in the CLM group, tumors were all located in the lower lobe (100% vs. 91.5%; $P = 0.42$); and tumor diameter (5.2 vs. 3.2; $P = 0.28$), N2 LN metastasis rate (66.7% vs. 28.8%; $P = 0.03$), late stage (IIIA 77.8% vs. 35.6%; $P = 0.04$), and invasion of the intermediate bronchus (77.8% vs. 45.8%; $P = 0.07$) relatively increased (Table 3). Furthermore, the difference in histological type ($P = 0.58$), invasion of the visceral pleura (33.3% vs. 23.7%; $P = 0.53$), or invasion of hilar vessels (11.1% vs. 13.6%; $P = 0.84$) was not statistically significant.

Among N positive patients, the proportion of invasion of the intermediate bronchus was significantly higher in the CLM than in the non-CLM group (77.8% vs. 47.5%; $P = 0.10$), and the N2 LN metastasis rate was also higher (66.7% vs. 42.5%; $P = 0.19$) (Table 4).

Discussion

Lymph node metastasis from lung cancer has been widely recognized for a long time. Tumor cells metastasize sequentially to occupy one lobe or skip to the same lobe of the peripheral and/or hilar and mediastinal LNs, but do not transfer to other LNs within the lung. This is also the basic theoretical foundation of standard lung cancer lobectomy. However, in clinical practice, using resected specimens from the right middle and lower lobes (bilobectomy), LN metastasis was continually detected in scans in the peripheral zone of the middle lobe, even though the tumor did not invade the parenchyma of the right middle lung. In this study, among the 68 patients who underwent bilobectomy,

nine patients had CLM, accounting for 13.2%. Among these, seven patients had LN metastasis in the segmental/sub-segmental stations (stations 13–14), two had LN metastasis in the lobar station (station 12), and two had multiple CLM, indicating that CLM is a universal phenomenon.

There are no previous related reports because lobes without lesions are not resected during surgery. Therefore, there is a lack of observable research objects. Another reason may be that peripheral LNs (stations 12–14), as well as the hilar and interlobar zone LNs (stations 10/11), both belong to the N1 station.^{1,9} When LN metastasis in other N1 areas exists, whether LN metastasis occurs in station 12–14 does not affect staging and treatment, and thus, it does not attract sufficient research attention.

How tumor cells move from the lower lobe into LNs in the middle lobe is an interesting question. Because tumors do not directly invade the middle lobe parenchyma and visceral pleura, they are unlikely to transfer from middle lobe parenchyma to the peripheral LNs. All CLM patients in our study had LN metastasis in other stations, and 67% of patients had LN metastasis in the intermediate bronchus. Therefore, we believe that metastasis to the peripheral LN of the middle lobe occurs through the lymphatic pathway (Fig 1). The pathway may be from the tumor to the peripheral LN of the lower lobe, and to the intermediate bronchial LNs (middle and lower lobe lymphatic pathway convergence station), which then retrogrades to the middle LN. It is noteworthy that 67% of CLM patients had mediastinal LN metastasis in the N2 area, which was significantly higher than in the non-CLM group at 29%. This may be a result of the distant metastasis pathway, which needs to go through multiple LNs. Therefore, tumors in CLM patients were relatively large (5.2 cm vs. 3.2 cm), and patients were at relatively late stages of the disease (stage IIIa 78% vs. 36%). Compared to other cases of LN metastasis, invasion of the intermediate bronchus in the CLM group was significantly higher (78% vs. 48%; $P = 0.10$).

Table 2 Detailed information of lymph node metastasis in nine CLM patients

No	Gender	Age	Tumor size (cm)	Pathology	Differentiation	TNM stage	N of LNM	Intermediate bronchus invasion	Pulmonary vascular invasion	Intermediate bronchus LNM	RLL LNM	RML N12 metastasis	RML N13 metastasis
1	M	45	5.6	SCC	M	T2N1	3	Yes	No	Yes	Yes	No	Yes
2	M	57	5.2	SCC	M	T2N1	2	Yes	No	Yes	No	Yes	No
3	M	64	7	SCC	M	T2N2	12	No	No	Yes	Yes	No	Yes
4	M	64	7.5	AD	P	T3N2	6	No	No	Yes	Yes	No	Yes
5	M	69	5.9	SCC	M	T2N2	6	Yes	No	Yes	Yes	No	Yes
6	M	64	1.8	AD	M	T2N2	8	Yes	No	No	Yes	No	Yes
7	M	51	2.5	SCLC	P	T1N2	11	Yes	No	No	Yes	Yes	No
8	M	61	4	SCC	M	T2N2	3	Yes	Yes	Yes	No	No	Yes
9	M	62	7.5	SCC	M	T3N1	2	Yes	No	No	No	No	Yes

AD, adenocarcinoma; CLM, cross-lobe lymph node metastasis; LNM, lymph node metastasis; M, moderately differentiated; P, poorly differentiated; RLL, right lower lobe; RML, right middle lobe; SCC, squamous cell cancer; SCLC, small cell lung cancer.

Table 3 Clinicopathologic features of patients with or without CLM

Variables	Non-CLM (n = 59)		CLM (n = 9)		P
Age					
Median (Range)	59 (27–82)		62 (45–69)		
< 59	31	52.5%	3	33.3%	0.28
> 60	28	47.5%	6	66.7%	
Gender					
Male	49	83.1%	9	100.0%	0.18
Female	10	16.9%	0	0.0%	
Histology type					
SCC	41	69.5%	6	66.7%	0.58
AD	8	13.6%	2	22.2%	
SCLC	3	5.1%	1	11.1%	
Other type	7	11.9%	0	0.0%	
Size of tumor					
Median (range)	3.2 (0.6–11)		5.2 (1.8–7.5)		0.28
< 3	24	40.7%	2	22.2%	
> 3	35	59.3%	7	77.8%	
Differentiation					
Poor	21	35.6%	2	22.2%	0.33
Moderate	26	44.1%	7	77.8%	
Well	3	5.1%	0	0.0%	
Lesion location					
Middle L	4	6.8%	0	0.0%	0.42
Lower L	54	91.5%	9	100.0%	
Intermediate bronchus invasion					
Yes	27	45.8%	7	77.8%	0.07
No	32	54.2%	2	22.2%	
Pulmonary vascular invasion					
Yes	8	13.6%	1	11.1%	0.84
No	51	86.4%	8	88.9%	
Visceral pleura invasion					
Yes	14	23.7%	3	33.3%	0.53
No	45	76.3%	6	66.7%	
Intermediate bronchus LNM					
Yes	26	44.1%	6	66.7%	0.2
No	33	55.9%	3	33.3%	
Primary lobe N13 metastasis					
Yes	27	45.8%	6	66.7%	0.24
No	32	54.2%	3	33.3%	
N2 lymph node metastasis					
Yes	17	28.8%	6	66.7%	0.03
No	42	71.2%	3	33.3%	
Stage					
I	16	27.1%	0	0.0%	0.04
II	22	37.3%	2	22.2%	
IIla	21	35.6%	7	77.8%	

AD, adenocarcinoma; CLM, cross-lobe lymph node metastasis; LNM, lymph node metastasis; SCC, squamous cell cancer; SCLC, small cell lung cancer.

In order to retain greater respiratory function, when the tumor only invades the intermediate bronchus without invading the middle lobe bronchus and parenchyma, the

Table 4 Clinicopathologic features of N positive patients with or without CLM

Feature	Non-CLM (n = 40)		CLM (n = 9)		P
Size of tumor					
Median					
< 3	14	35.0%	2	22.2%	0.46
> 3	26	65.0%	7	77.8%	
Intermediate bronchus invasion					
Yes	19	47.5%	7	77.8%	0.1
No	21	52.5%	2	22.2%	
Intermediate bronchus LNM					
Yes	26	65.0%	6	66.7%	0.92
No	14	35.0%	3	33.3%	
Same lobe N13 metastasis					
Yes	27	67.5%	6	66.7%	0.96
No	13	32.5%	3	33.3%	
N2 LNM					
Yes	17	42.5%	6	66.7%	0.19
No	23	57.5%	3	33.3%	
Stage					
II	19	47.5%	2	22.2%	0.17
III	21	52.5%	7	77.8%	

LNM, lymph node metastasis.

surgeon can choose sleeve resection to retain the middle lobe.^{10,11} However, more than a quarter of patients in this study with LN metastasis, especially those with N2 LN metastasis, had metastatic tumor cells left in the middle lobe, thus radical resection cannot be achieved. Kim *et al.* reported that the local recurrence rate in patients who underwent sleeve resection was significantly higher than in patients who underwent lung resection (57% vs. 31%).¹² Furthermore, Schirren *et al.* reported that the local recurrence rate of sleeve resection is higher than in pneumonectomy (3.2% vs. 0%).¹³ As previously discussed, sleeve resection has a high local recurrence rate, mainly because of the insufficient cutting edge distance. However, the results of our study suggest that CLM caused non-radical surgery, which might be another important reason for recurrence.

How to detect peripheral LN metastasis before surgery is a difficult and unpopular question. Methods used to detect metastasis of the mediastinal LNs include mediastinoscopic lymph node biopsy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and positron emission tomography-computed tomography (PET-CT).^{14–16} Metastasized LNs in the peripheral zone are much smaller than in the mediastinal zone, and most are < 0.5 cm. Current PET-CT and EBUS-TBNA examinations have limitations for detecting and estimating metastatic LNs of sub-centimeter size.^{17,18}

This study has some limitations. First, our study was restricted to metastasis of right lower lobe tumors to the LN in the right middle lobe. We did not determine

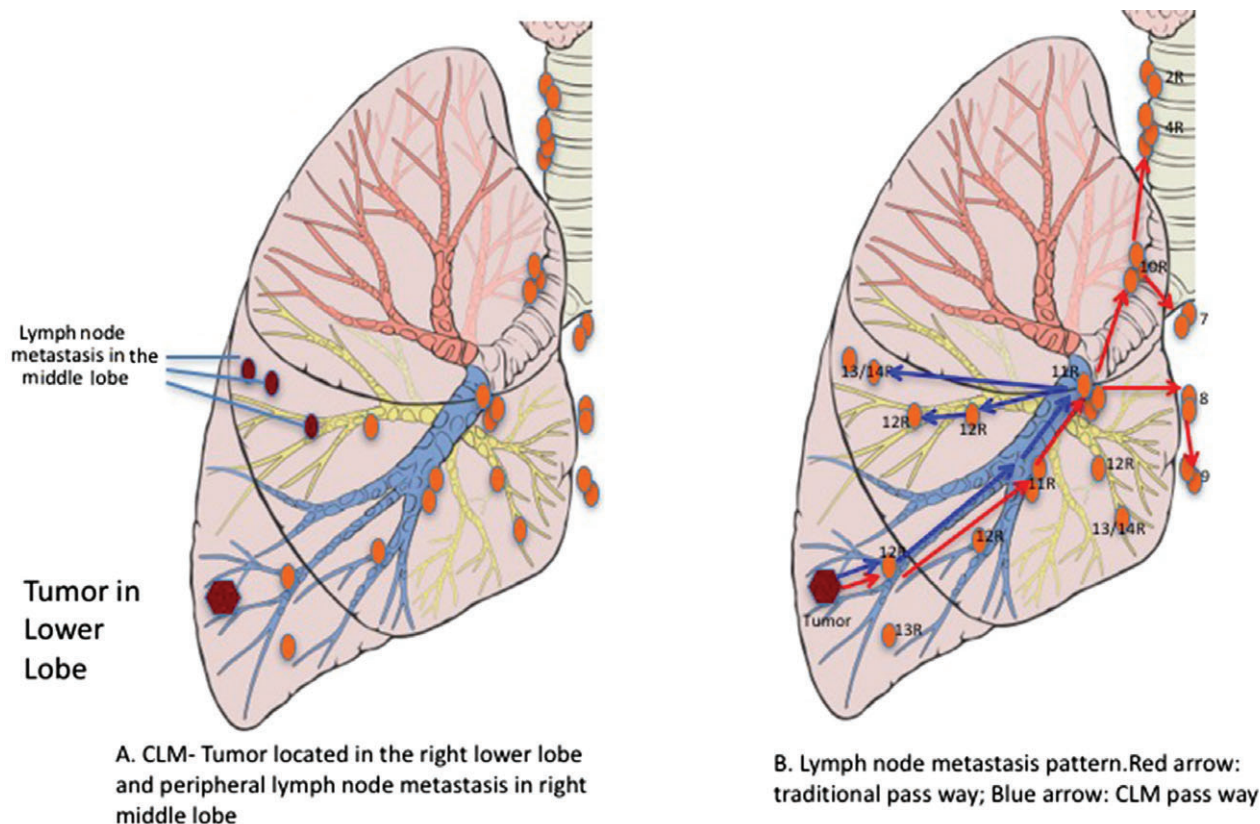


Figure 1 Cross-lobe lymph node metastasis (CLM). (a) CLM-tumor located in the right lower lobe and peripheral lymph node metastasis in the right middle lobe. (b) Lymph node metastasis pattern. Red arrow: traditional pathway; blue arrow: CLM pathway.

whether CLM exists in other lobes. Second, there were a limited number of samples in our study. Because this study was retrospective, surgical specimens needed to be carefully reviewed and we only enrolled patients with adequate specimens. Finally, whether this phenomenon directly affects staging and prognosis remains unclear. We will conduct long-term follow-up of this group of patients to seek relevant answers.

Whether metastasis exists in LNs within the non-primary lobe in early stage lung cancer patients has long been a blind spot of clinical studies. This study is the first to present the CLM phenomenon, and it is hoped this will attract further attention from surgeons and tumor experts.

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Disclosure

No authors report any conflict of interest.

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