



The prognostic impact of lymph node metastasis in patients with non-small cell lung cancer and distant organ metastasis

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Abstract

This study aimed to identify the prognostic value of lymph node metastasis in patients with non-small cell lung cancer (NSCLC) and distant organ metastasis. A total of 42,613 NSCLC patients with distant metastasis from the surveillance, epidemiology, and end results database between 2010 and 2013 were included for analysis. The proportion of N0 stage in M1a patients was significantly higher than that in M1b patients, 34.0% and 22.7% respectively ($P < 0.001$). Compared with N0 patients, patients had higher odds of experiencing multiorgan metastases (MOM) if they had higher N stage at diagnoses ($P < 0.001$). The Kaplan–Meier curves suggested both M1a and M1b groups patients at stage N0 had better survival than those at higher N stage ($P < 0.001$). Further analysis indicated that better survival was observed in N0 stage compared with N2 or N3 stage if patients had bone metastasis, brain metastasis, or MOM ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively), but there was no significant difference in survival among each N stage patients with liver metastasis only. Cox regression analysis showed that compared with N0 patients, higher hazard for disease-specific mortality was observed for patients with higher N stage. Among NSCLC patients with distant organ metastasis, lymph node metastasis was associated with higher odds of experiencing MOM and a worse prognosis in terms of longer survival except patients with liver metastasis. Better understandings of the role of lymphatic metastasis in M1 NSCLC could help clinicians with better management of the disease.

Keywords Non-small cell lung cancer · Lymph node metastasis · Distant metastasis · Prognosis · SEER

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Abbreviations

AD	Adenocarcinoma
AJCC	American Joint Committee on Cancer
HRs	Hazard ratios
IASLC	International Association for the Study of Lung Cancer
IQR	Interquartile range
MOM	Multiorgan metastases
NSCLC	Non-small cell lung cancer
ORs	Odds ratios
SEER	Surveillance, epidemiology and end results
SQCC	Squamous cell carcinoma
TNM	Tumor, node, and metastasis

Introduction

Lung cancer is the second most common cancer among both males and females. The American Cancer Society estimated that 116,990 men and 105,510 women developed new lung and bronchus cancers in 2017, with 84,590 men and 71,280 women dying from them [1]. The estimated numbers of new

cases and deaths were comparable to those in 2014 [2]. In addition, Bray et al. have reported that lung cancer was the leading cause of cancer mortality for women in 17 countries and for men in 94 countries [3]. Non-small cell lung cancer (NSCLC) and small cell lung cancer are the two major histological variants that account for 90% of lung cancers, with the major variants of NSCLC being adenocarcinoma (AD) and squamous cell carcinoma (SQCC). Lung cancer patients have a low 5-year survival rate [4] and approximately 40% of new NSCLC cases have distant metastases at diagnosis [5].

The eighth edition of the lung cancer staging system developed by the International Association for the Study of Lung Cancer (IASLC) has significant revisions regarding distant metastasis, while the lymph node (N) descriptors remained unchanged [6]. The 8th edition defines M1a as intrathoracic metastases, M1b as a single extra-thoracic metastasis, and M1c as multiple extra-thoracic metastases. For patients with distant metastasis, tumor, node, and metastasis (TNM) stage is determined only by M stage. IVA stage includes any T, any N, M1a and M1b; IVB stage includes any T, any N, and M1c. Previous studies have also demonstrated that multiorgan metastasis predict inferior survival in M1 NSCLC [7, 8]. It has been revealed that lymph node metastasis might have prognostic value in M1a NSCLC [9], and N2 disease is associated with poor survival in oligometastatic NSCLC [10], but the impact of N status on the outcome of NSCLC patients with specific organ metastasis, especially multiorgan metastases (MOM) remains to be determined. Identifying factors with prognostic value may contribute to management of disease [11], thus determining effective predictors of survival especially in late stage NSCLC is of great importance.

In the present study, we aimed to investigate the relationship between lymph node metastasis and distant organ metastasis and how N stage affects the outcome of M1 disease in NSCLC patients using surveillance, epidemiology, and end results (SEER) database.

Methods

Patients and clinicopathologic data

This retrospective study assessed (1) the association of N stage with distant metastases and (2) the prognostic value of N stage among patients with M1 NSCLC. Data for a large number of NSCLC patients were obtained from the SEER database, which was launched in 1973 by the National Cancer Institute and consists of 18 population-based cancer registries, covering approximately 28% of the total population of the United States.

The present study included NSCLC patients with M1 disease who were diagnosed between 2010 and 2013 and had

complete information. We initially identified 90,817 cases of lung cancer, 20,576 cases with two or more primary sites, 6918 with incomplete information on organs metastases, 55 cases with no information on survival, 17,845 cases with small cell lung cancer, and 2810 patients with incomplete N stage and histological information. Thus, a total of 42,613 NSCLC patients were eligible analyses, with 26,457 AD cases and 8637 SQCC cases. All patients had distant metastasis at diagnosis and complete information regarding N stage. TNM stage information in the present SEER database was based on the 7th TNM staging system. N stage is defined as follows: N0 stage as no regional lymph node metastasis, N1 stage as metastasis in the ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension, N2 stage as metastasis in the ipsilateral mediastinal and/or subcarinal lymph node(s), and N3 stage as metastasis in the contralateral mediastinal, contralateral hilar, ipsilateral, contralateral scalene, or supraclavicular lymph node(s). M1 is classified as two stages, M1a: presence of a malignant pleural or pericardial effusion, pleural dissemination, or pericardial disease, and metastasis in opposite lung; M1b: extrathoracic metastases. Multiorgan metastases refers to patients with two or more metastatic organs among lung, liver, brain and bone as previously described [7]. The endpoint of the present study was lung cancer specific survival, which was defined as the interval from diagnosis until death due to lung cancer or until the last follow-up.

Statistical analyses

Patient characteristics were statistically described. Pearson's Chi square test was used to detect differences for categorical variables. Differences in NSCLC-specific survival time were compared among patients of different N stage using Kaplan–Meier analysis and the log-rank test. Cox regression analysis was used to investigate the predictors of survival, and binary logistic regression analysis was performed to calculate the odds ratios (ORs) of experiencing various organ metastases. Differences were considered statistically significant at two-tailed p-values of less than 0.05. All analyses were performed using IBM SPSS software (version 18.0; IBM Corp., Armonk, NY).

Results

Patient characteristics

Table 1 shows the clinical characteristics of total populations and subtypes, respectively. A total of 42,613 NSCLC patients (23,642 male and 18,971 female) were analyzed. The histological type AD had 26,475 cases and SQCC had

Table 1 Characteristics of overall and NSCLC subtypes with distant metastasis (SEER database 2010–2013, n = 42,613)

Cancer type	NSCLC		AD		SQCC		<i>P</i> ^a
Sample size	42,613		26,475		8637		
Characteristics	N	%	N	%	N	%	
Age							
≤45	917	2.1	685	2.6	83	1.0	<0.001
46–54	5103	12.0	3497	13.2	695	8.0	
55–64	11,249	26.4	7170	27.1	2032	23.5	
65–74	13,450	31.6	8040	30.4	3020	35	
≥75	11,894	27.9	7083	26.7	2807	32.5	
Gender							
Male	23,642	55.5	13,654	51.6	5611	65.0	<0.001
Female	18,971	44.5	12,821	48.4	3026	35.0	
Race							
White	33,035	77.5	20,157	76.1	6937	80.3	<0.001
Black	5769	13.5	3524	13.3	1199	13.9	
Others	3728	8.8	2736	10.3	489	5.7	
Unknown	81	0.2	58	0.2	12	0.1	
Tumor size							
≤1 cm	658	1.5	471	1.8	90	1.0	<0.001
> 1 cm, ≤2 cm	3491	8.2	2531	9.6	398	4.6	
> 2 cm, ≤3 cm	5494	12.9	3780	14.3	784	9.1	
> 3 cm, ≤4 cm	5392	12.7	3513	13.3	957	11.1	
> 4 cm, ≤5 cm	4760	11.2	2872	10.8	1043	12.1	
> 5 cm, ≤7 cm	6736	15.8	3748	14.2	1755	20.3	
> 7 cm	5925	13.9	2759	10.4	1940	22.5	
Unknown	10,157	23.8	6801	25.7	1670	19.3	
N stage							
N0	11,057	25.9	7111	26.9	2081	24.1	<0.001
N1	3443	8.1	2040	7.7	772	8.9	
N2	19,609	46.0	11,944	45.1	4118	47.7	
N3	8504	20.0	5380	20.3	1666	19.3	
Metastatic site							
Bone	7087	16.6	4479	16.9	1416	16.4	<0.001
Brain	5285	12.4	3380	12.7	768	8.9	
Liver	1859	4.4	922	3.5	527	6.1	
Lungs	6228	14.6	3706	14.0	1670	19.3	
MOM	11,523	27.1	7704	29.1	1756	20.3	
Others	10,631	24.9	6284	23.7	2500	28.9	

NSCLC non-small cell lung cancer, AD adenocarcinoma, SQCC squamous cell carcinoma, MOM multiorgan metastases, Others other organ metastasis but without bone, brain, liver and lung metastasis

^aComparison among AD and SQCC

8637 cases. The median age for the overall population was 67 years [interquartile range (IQR): 59–76 years] and the median follow-up time was 4 months (IQR 1–10 months). There were 25.9% (11,057 cases) patients diagnosed at N0 stage, 8.1% (3443 cases) at N1 stage, 46.0% for N2 stage

(19,609 cases), and 20.0% for N3 stage (8504 cases). The primary tumors were more common on the right side (54.9% overall, with 28.4% on the right upper lobe) and less common on the left side (39.1% overall) (Table 2).

Table 2 The location of NSCLC and its common subtypes (SEER database 2010–2013, n = 42,613)

Location	NSCLC		AD		SQCC	
	N	%	N	%	N	%
Right						
RUL	12,102	28.4	7542	28.5	2355	27.3
RML	1841	4.3	1192	4.5	322	3.7
RLL	6080	14.3	3633	13.7	1409	16.3
Overlapping	337	0.8	203	0.8	65	0.8
NOS	3041	7.1	2077	7.8	431	5.0
Overall	23,401	54.9	14,647	55.3	4582	53.1
Left						
LUL	9622	22.6	5765	21.8	2204	25.5
LLL	4963	11.6	2972	11.2	1152	13.3
Overlapping	151	0.4	91	0.3	35	0.4
NOS	1925	4.5	1283	4.8	281	3.3
Overall	16,661	39.1	10,111	38.2	3672	42.5
Bilateral, single primary	993	2.3	667	2.5	166	1.9
Paired site, but no information concerning laterality	1388	3.3	937	3.5	185	2.1
Only one side—side unspecified	170	0.4	113	0.4	32	0.4

NSCLC non-small cell lung cancer, AD adenocarcinoma, SQCC squamous cell carcinoma, RUL right upper level, RML right middle level, RLL right low level, LUL left upper level, LLL left low level, NOS no other information

Table 3 Association between N stage and M stage among M1 NSCLC and its subtypes (SEER database 2010–2013, n = 42,613)

	M1a		M1b		M1NOS		<i>P</i> ^a	<i>P</i> ^b
	N	%	N	%	N	%		
NSCLC	12,161		29,806		646		<0.001	<0.001
N0	4129	34.0	6756	22.7	172	26.6	<0.001	<0.001
N1	829	6.8	2527	8.5	87	13.5	<0.001	<0.001
N2	5274	43.4	14,038	47.1	297	46.0	<0.001	<0.001
N3	1929	15.9	6485	21.8	90	13.9	<0.001	<0.001
AD	7421		18,671		383		<0.001	<0.001
N0	2732	36.8	4276	22.9	103	26.9	<0.001	<0.001
N1	486	6.5	1507	8.1	47	12.3	<0.001	<0.001
N2	3079	41.5	8689	46.5	176	46.0	<0.001	<0.001
N3	1124	15.1	4199	22.5	57	14.9	<0.001	<0.001
SQCC	2974		5523		140		<0.001	<0.001
N0	839	28.2	1214	22.0	28	20.0	<0.001	<0.001
N1	232	7.8	518	9.4	22	15.7	0.001	0.014
N2	1381	46.4	2669	48.3	68	48.6	0.245	0.096
N3	522	17.6	1122	20.3	22	15.7	0.005	0.002

NSCLC non-small cell lung cancer, SEER surveillance, epidemiology, and end results, AD adenocarcinoma, SQCC squamous cell carcinoma, NOS no other information

^aComparison among M1a, M1b and M1NOS

^bComparison between M1a and M1b

Table 4 Association between N stage and MOM (SEER database years of 2010–2013)

Stage by cancer type	MOM N/N (%)	Unadjusted		Adjusted ^a	
		OR (95% CI)	P	OR (95% CI)	P
NSCLC					
N0	2069/11,057 (18.7)	Ref	Ref	Ref	Ref
N1	862/3443 (25.0)	1.45 (1.33–1.59)	<0.001	1.30 (1.17–1.44)	<0.001
N2	5738/19,609 (29.3)	1.80 (1.70–1.90)	<0.001	1.70 (1.59–1.81)	<0.001
N3	2854/8504 (33.6)	2.19 (2.06–2.34)	<0.001	1.96 (1.81–2.11)	<0.001
AD					
N0	1424/7111 (20.0)	Ref	Ref	Ref	Ref
N1	539/2040 (26.4)	1.43 (1.28–1.61)	<0.001	1.29 (1.13–1.47)	<0.001
N2	3765/11,944 (31.5)	1.84 (1.72–1.97)	<0.001	1.74 (1.61–1.89)	<0.001
N3	1976/5380 (36.7)	2.32 (2.14–2.51)	<0.001	2.04 (1.85–2.24)	<0.001
SQCC					
N0	281/2081 (13.5)	Ref	Ref	Ref	Ref
N1	141/772 (18.3)	1.43 (1.15–1.79)	0.002	1.22 (0.96–1.57)	0.108
N2	935/4118 (22.7)	1.88 (1.63–2.18)	<0.001	1.68 (1.44–1.98)	<0.001
N3	399/1666 (23.9)	2.02 (1.70–2.39)	<0.001	1.73(1.43–2.09)	<0.001

NSCLC non-small cell lung cancer, AD adenocarcinoma, SQCC squamous cell carcinoma, MOM multi-organ metastases, OR odds ratio, CI confidence intervals

^aAdjusted for age, gender and tumor size; n/N refers to rate of MOM in each group

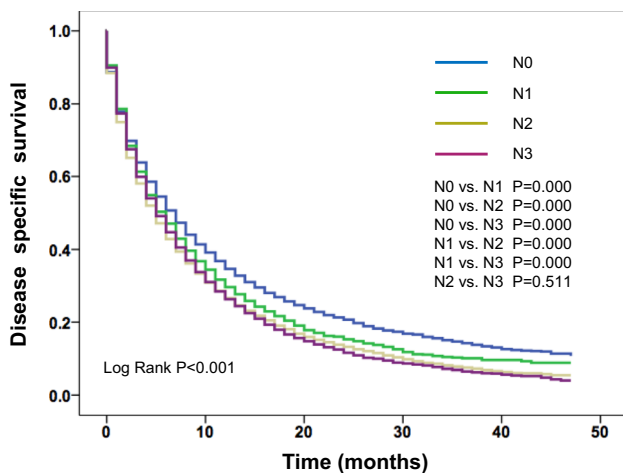


Fig. 1 Kaplan–Meier analysis of disease specific survival according to N stage in non-small cell lung cancer

Association between N stage and M stage in M1 NSCLC patients

Table 3 shows that in NSCLC patients, the proportion of N0 in M1a was significantly higher than that in M1b, 34.0% and 22.7% respectively ($P < 0.001$). Interestingly, the proportions of patients with N1, N2 and N3 were all lower in M1a NSCLC patients than that in M1b ($P < 0.001$). In the subgroup analysis, similar results were obtained in AD

patients, with N0 rate as high as 36.8% in M1a disease. While in SQCC patients, N0 rate was also higher in M1a group although the difference between M1a and M1b was relatively smaller compared with AD patients, and the N2 proportion between M1a and M1b group failed to reach statistical difference.

Association between N stage and MOM

The proportion of patients diagnosed at stage N0, N1, N2, and N3 who developed MOM was 18.7%, 25.0%, 29.3%, and 33.6%, respectively (Table 4). Compared with the N0 group, the odds of having MOM were higher for patients diagnosed at stage N1 (OR 1.45 [1.33–1.59], $P < 0.001$), N2 (OR 1.80 [1.70–1.90], $P < 0.001$), and N3 (OR 2.19 [2.06–2.34], $P < 0.001$). After adjusting for age, sex, and tumor size, the ORs remained significant in N1 group (OR 1.30 [1.17–1.44]), N2 group (OR 1.70 [1.59–1.81]), and N3 group (OR 1.96 [1.81–2.11]) (all $P < 0.001$). Similar results were observed in the AD and SQCC subgroups (Table 4).

Association between N stage and disease-specific survival

The effects of N stage on disease-specific survival among overall NSCLC patients and two histological subtypes are shown in Figs. 1, 2 and 3. Survival decreased with

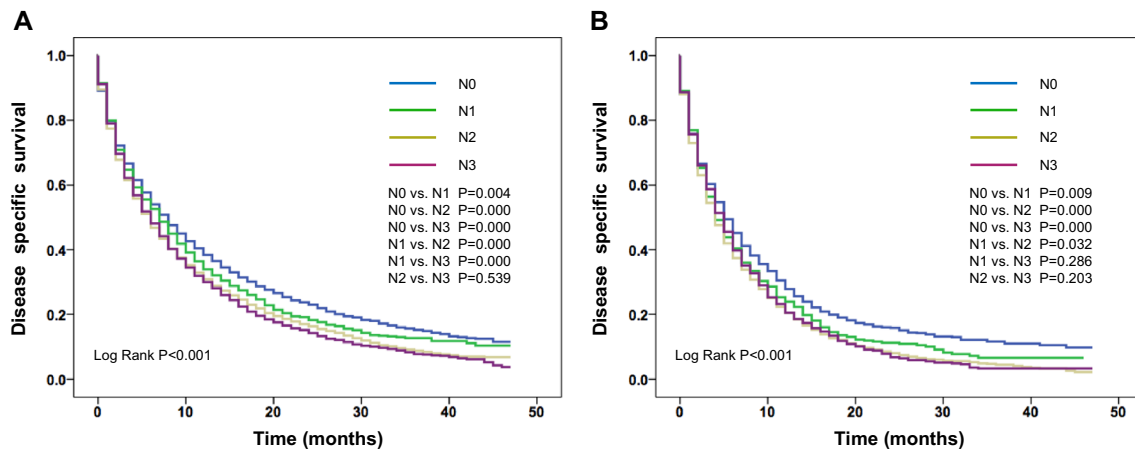


Fig. 2 Kaplan–Meier analysis of disease specific survival according to N stage in **a** adenocarcinoma and **b** squamous carcinoma

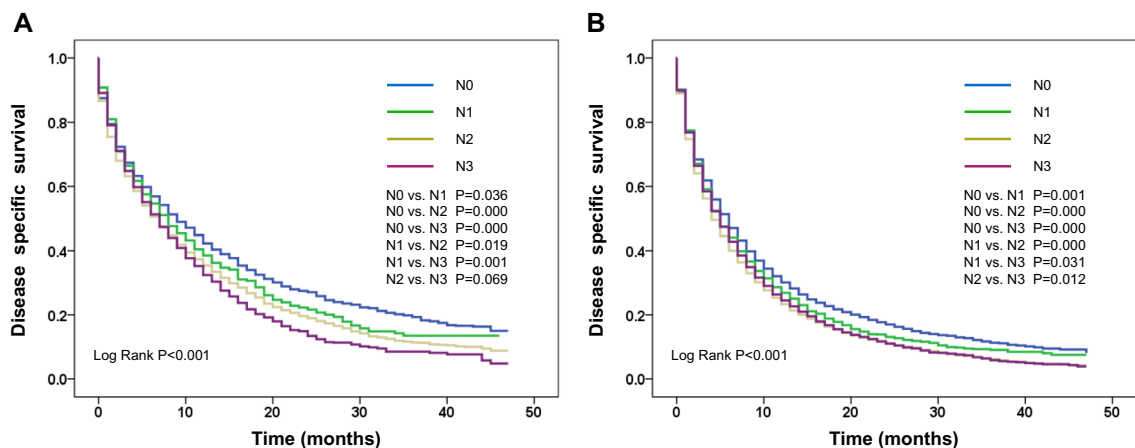


Fig. 3 Kaplan–Meier analysis of disease specific survival according to N stage in **a** M1a and **b** M1b non-small cell lung cancer

increasing N stage ($P < 0.001$), with the best survival observed in the N0 group, intermediate survival observed in N1 group, and similarly poor survival observed in both N2 and N3 groups (N3 vs. N2, $P = 0.511$) (Fig. 1). Similar results were observed when conducting analyses in AD and SQCC subgroups (Fig. 2).

Further analysis showed that in M1a patients, N0 stage was associated with better outcome compared with higher N stage, with 1- and 3-year survival rates as high as 42.3% and 19.3%, respectively ($P < 0.001$) (Table 5) (Fig. 3a). Similar results were obtained in M1b disease (Table 5) (Fig. 3b). M1a patients had better survival than M1b patients, but the difference between N3M1a and N0M1b was not significant ($P = 0.574$) (Table 5). In the subgroup analysis for the M1b group, better survival was observed in N0 stage compared with N2 or N3 stage if

patients had bone metastasis only, brain metastasis only, or MOM ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively), but there was no significant difference in survival among each N stage patients with liver metastasis only (Fig. 4).

Cox regression analysis was performed to investigate the effect of N stage on disease-specific mortality risk of M1 NSCLC patients. Compared with patients diagnosed at N0 stage, patients diagnosed at N1 stage had higher hazard for crude mortality (HR 1.12 [1.07–1.17], $P < 0.001$) and for age, sex, M stage, and tumor size adjusted mortality (HR 1.13 [1.07–1.19], $P < 0.001$). For crude mortality, higher hazards were also observed for patients diagnosed at N2 stage (HR 1.23 [1.20–1.27], $P < 0.001$) and N3 stage (HR 1.23 [1.19–1.27], $P < 0.001$). Furthermore, for age, sex, M stage, and tumor size adjusted mortality, N2 group (HR 1.26 [1.22–1.30], $P < 0.001$) and N3 group (HR 1.29

Table 5 Kaplan–Meier analysis of the disease specific survival in M1 NSCLC patients (SEER database years of 2010–2013)

	N0			N1			N2			N3			P
	Survival rate		Median	Survival rate		Median	Survival rate		Median	Survival rate		Median	
	1-Year (%)	3-Year (%)	Months	1-Year (%)	3-Year (%)	Months	1-Year (%)	3-Year (%)	Months	1-Year (%)	3-Year (%)	Months	
M1a	42.3	19.3	9 (8.31–9.68)	38.5	13.5	8 (6.74–9.27)	35.4	11.3	7 (6.59–7.41)	32.4	8.5	7 (6.36–7.64)	< 0.001
M1b	30.1	11.3	6 (5.70–6.30)	26.9	9.0	5 (4.59–5.41)	23.3	6.2	4 (3.85–4.15)	24.5	5.8	5 (4.76–5.24)	< 0.001
Bone	30.3	12.3	6 (5.46–6.54)	27.7	8.6	5 (4.24–5.76)	25	6.1	5 (4.71–5.30)	26.2	6.5	6 (5.40–6.60)	< 0.001
Brain	34.4	13.8	7 (6.36–7.64)	33.7	12.3	7 (5.71–8.29)	26.4	6.7	5 (4.63–5.37)	25.4	8.6	5 (4.34–5.66)	< 0.001
Liver	22.2	7.7	4 (3.22–4.78)	20.6	6.4	3 (1.75–4.25)	20.0	4.8	4 (3.34–4.66)	22.7	3.6	5 (3.94–6.06)	0.340
MOM	24.6	5.9	4 (3.63–4.37)	19.9	6.0	4 (3.55–4.45)	19.8	4.4	3 (2.82–3.18)	19.9	3.7	4 (3.72–4.28)	0.002

NSCLC non-small cell lung cancer, MOM multi-organ metastases

[1.23–1.34], $P < 0.001$) had higher hazards compared to N0 group. Similar results were observed for the AD and SQCC subgroups (Table 6).

Discussion

In the newly developed 8th edition American Joint Committee on Cancer (AJCC) TNM staging manual for NSCLC, T descriptor and M descriptor were both revised, while N descriptors remained unchanged. Lymph node involvement is an important demarcation criterion for the staging of M0 patients, whereas stage IV is classified as IVA and IVB only based on the M stage, without concern of N status. It is well accepted that lymph node metastasis is a key predictor of outcome in M0 NSCLC [12], but few studies have focused on whether N status plays an important role in M1 patients [9, 10]. This study evaluated the relationships between lymph node metastasis and distant metastasis in NSCLC patients and further identified the prognostic value of N stage in M1 patients.

Our primary finding is that patients with M1a (intra-thoracic metastasis) NSCLC trends to have lower N stage compared with M1b (distant metastasis) patients, as N1, N2, and N3 rates in M1b were all significantly higher than those in M1a (Table 3). We observed that nearly 34% of M1a and 22.7% of M1b patients had no lymph node involvement in our study, which could be explained by that blood vessel dissemination is responsible for distant metastasis of cancer [13]. Nevertheless, we observed that lymph node metastasis is associated with higher risk of MOM in NSCLC patients. It has been a subject of considerable debate whether cancer cells in lymph nodes can seed distant organs. It is possible that primary tumors may remain noninvasive until somehow triggered to metastasize via both lymphatics and blood vessels simultaneously [14]. As lymph nodes are often the first site of metastasis, it is also possible that lymphatics serve as part of pathway contributing to the subsequent dissemination to distant organs [15]. Experimental evidence has demonstrated that inhibiting lymphatic dissemination could be a promising method for preventing distant metastases [16–18]. The exact mechanism of how lymphatic spread leads to systematic metastasis remains unclear, most likely through the left lymphatic duct (thoracic duct) or the right lymphatic duct and subsequently into the subclavian veins [14]. Recent studies revealed that lymph node metastases can disseminate by invading lymph node blood vessels rather than by transiting through efferent lymphatic vessels in a mouse model, but whether this form of tumor cell spreading occurs in cancer patients remains to be determined [19, 20]. Our findings also shed light on the important role of lymphatic route in distant metastasis.

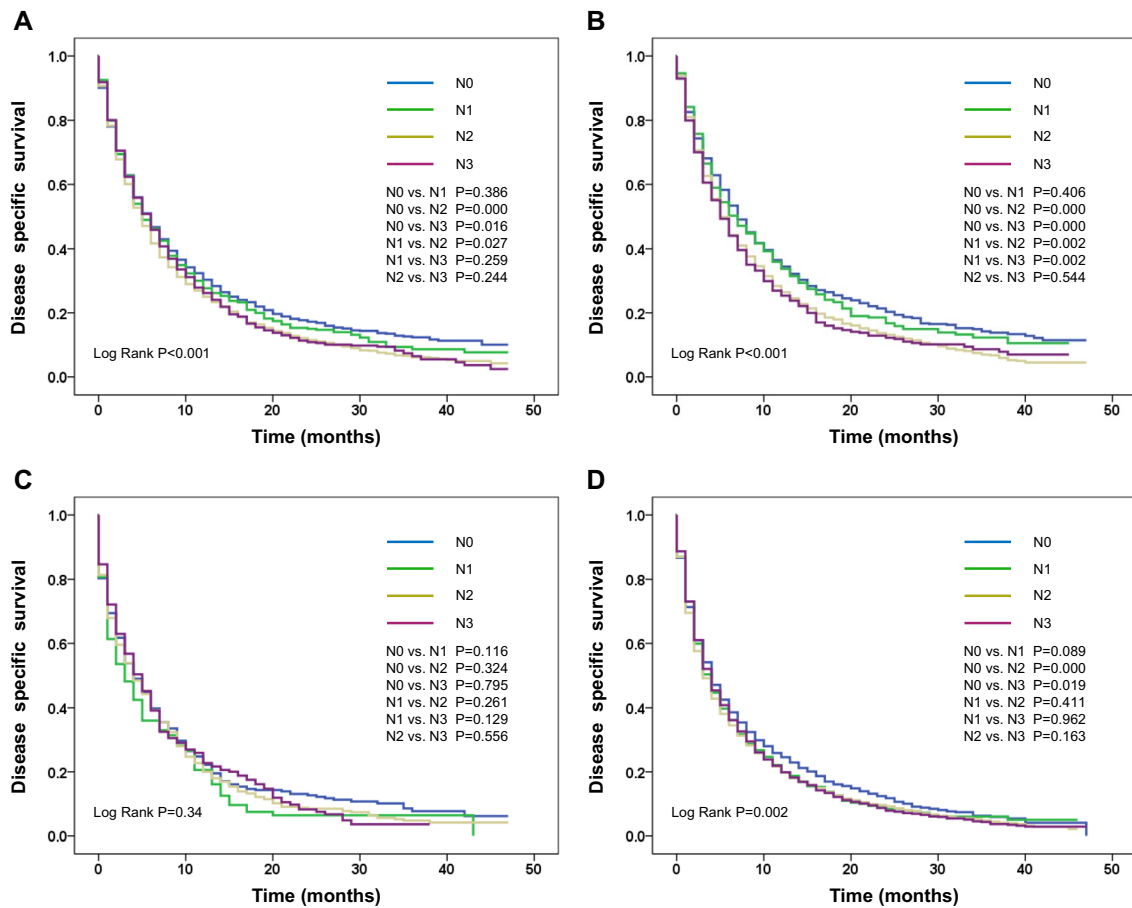


Fig. 4 Kaplan–Meier analysis of disease specific survival according to N stage in M1b non-small cell lung cancer with **a** bone metastasis, **b** brain metastasis, **c** liver metastasis, and **d** multiorgan metastases

Lymph node status is a powerful prognostic predictor as many studies have demonstrated that lymphatic metastasis is an independent prognostic factor for NSCLC [21, 22]. Lymphatic metastasis after surgical resection of NSCLC has been shown to be the most important determinant of long-term outcome [21], and even lymphatic micrometastasis could predict poor prognosis [23]. In the present study, earlier N stage was associated with better disease-specific survival, based on the result of Kaplan–Meier analysis that N0 patients had the best survival while N2 and N3 was associated with worse survival. Analyses of the current N descriptors at clinical and pathological staging in the IASLC database showed that they clearly separate lung cancers of significantly different prognosis [6]. In this cohort of patients, the 3-year survival rates were significantly lower than AJCC guidelines estimates due to the research design that our study only included patients with M1 disease at diagnosis. Despite the difference and limitation, our findings did highlight a similar trend to AJCC guidelines' estimates, that the survival was best for patients diagnosed at N0 stage and poorest at N2 or N3 stage. Similar trends were noticed in

the sub-group analysis of M1a and M1b disease. In addition, our results showed that although M1a disease was associated with better survival compared with M1b, N3M1a had equal survival as N0M1b. To exclude the impact of other prognostic factors, Cox regression analysis was employed to confirm the effect of N status in NSCLC and its two pathological subtypes AD and SQCC, showing that increasing N status was associated with higher risk of mortality after adjusted for age, sex, tumor size and M stage. These findings provide evidence for the prognostic value of lymph node metastasis in M1 NSCLC, and may be relevant for the next version of TNM staging system.

Interestingly, in the subgroup analysis we found that the effect of lymph node metastasis was significantly attenuated in liver metastasis only group, which might be related to the strong negative effect of liver metastasis as previous studies have reported [8, 24, 25]. The exact mechanism why liver metastasis is associated with poorer survival is still not clear. More research will be necessary to study the molecular mechanisms of liver metastasis in lung cancer in order to devise effective treatment strategies. In the bone

Table 6 Association between N stage and cancer-specific mortality among M1 NSCLC and its subtypes (SEER database 2010–2013, n=42,613)

Stage by cancer type	Mortality N/N (%)	Unadjusted		Adjusted ^a	
		HR (95% CI)	P	HR (95% CI)	P
NSCLC					
N0	7470/11,057 (67.6)	Ref	Ref	Ref	Ref
N1	2469/3443 (71.7)	1.12 (1.07–1.17)	<0.001	1.13 (1.07–1.19)	<0.001
N2	14,477/19,609 (73.8)	1.23 (1.20–1.27)	<0.001	1.26 (1.22–1.30)	<0.001
N3	6286/8504 (73.9)	1.23 (1.19–1.27)	<0.001	1.29 (1.23–1.34)	<0.001
Overall	30,702/42,613 (72.0)				
AD					
N0	4642/7111 (65.3)	Ref	Ref	Ref	Ref
N1	1391/2040 (68.2)	1.09 (1.03–1.16)	0.006	1.12 (1.04–1.20)	0.003
N2	8428/11,944 (70.6)	1.21 (1.17–1.25)	<0.001	1.25 (1.20–1.31)	<0.001
N3	3837/5380 (71.3)	1.23 (1.17–1.28)	<0.001	1.31 (1.24–1.38)	<0.001
Overall	18,298/26,475 (69.1)				
SQCC					
N0	1485/2081 (71.4)	Ref	Ref	Ref	Ref
N1	586/772 (75.9)	1.13 (1.03–1.24)	0.013	1.14 (1.02–1.27)	0.016
N2	3200/4118 (77.7)	1.24 (1.17–1.32)	<0.001	1.27 (1.18–1.36)	<0.001
N3	1281/1666 (76.9)	1.19 (1.11–1.28)	<0.001	1.22 (1.12–1.34)	<0.001
Overall	6552/8637 (75.9)				

NSCLC non-small cell lung cancer, SEER surveillance, epidemiology, and end results, HR hazard ratio, CI confidence intervals, AD adenocarcinoma, SQCC squamous cell carcinoma

^aAdjusted for age, gender and tumor size and M stage; n/N refers to rate of mortality in each group

metastasis only group, brain metastasis only group, and MOM group, the best survival was observed in N0 patients, and N2–3 was associated with worse survival, while the difference between N0 and N1 group did not reach statistical significance. Although bone metastasis, brain metastasis, and MOM were associated with poor survival, our results showed that lymph node metastasis still had prognostic value and should be considered in the management of disease.

This study has several limitations. Firstly, metastases were identified based on the 7th edition of the AJCC guidelines, which did not provide information on the number of metastasis in the metastatic organ. Secondly, metastasis information was only available for the four common metastatic organs (lung, bone, brain, and liver) starting from 2010. This limited the data and population that could be included and omitted the influence of patients with metastases to other organs. In addition, the SEER database did not provide details regarding the methods used to determine N stage, and information such as comorbidities, treatment details, and gene mutations were also not available, which prevented us from further stratification analysis. Therefore, more research will be needed to confirm our findings.

Conclusion

In conclusion, these results reveal lymph node metastasis is associated with higher risk of MOM in M1 NSCLC. Our study also provides evidence that lymph node status has important prognostic value in patients with M1 NSCLC and may help guide the next TNM staging system. Knowledge of these findings may be helpful when making precise prognostic evaluation and treatment decisions for NSCLC patients.

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Compliance with ethical standards

Conflicts of interest The authors disclose no potential conflicts of interest related to this study.

Ethical approval Our study was approved by the ethical committee board of Shanghai Pulmonary Hospital and complied with 1964

Helsinki declaration and its later amendments or comparable ethical standards.

References

- Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. *CA Cancer J Clin* 67(1):7–30. <https://doi.org/10.3322/caac.21387>
- Siegel R, Desantis C, Jemal A (2014) Colorectal cancer statistics, 2014. *CA Cancer J Clin* 64(2):104–117. <https://doi.org/10.3322/caac.21220>
- Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012) Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol* 13(8):790–801. [https://doi.org/10.1016/S1470-2045\(12\)70211-5](https://doi.org/10.1016/S1470-2045(12)70211-5)
- Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT (2017) The eighth edition lung cancer stage classification. *Chest* 151(1):193–203. <https://doi.org/10.1016/j.chest.2016.10.010>
- Morgensztern D, Ng SH, Gao F, Govindan R (2010) Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. *J Thorac Oncol* 5(1):29–33. <https://doi.org/10.1097/JTO.0b013e3181c5920c>
- Rami-Porta R, Asamura H, Travis WD, Rusch VW (2017) Lung cancer—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 67(2):138–155. <https://doi.org/10.3322/caac.21390>
- Yang J, Zhang Y, Sun X, Gusdon AM, Song N, Chen L, Jiang G, Huang Y (2018) The prognostic value of multiorgan metastases in patients with non-small cell lung cancer and its variants: a SEER-based study. *J Cancer Res Clin Oncol* 144(9):1835–1842. <https://doi.org/10.1007/s00432-018-2702-9>
- Ren Y, Dai C, Zheng H, Zhou F, She Y, Jiang G, Fei K, Yang P, Xie D, Chen C (2016) Prognostic effect of liver metastasis in lung cancer patients with distant metastasis. *Oncotarget* 7(33):53245–53253. <https://doi.org/10.18632/oncotarget.10644>
- Dai C, Ren Y, Xie D, Zheng H, She Y, Fei K, Jiang G, Chen C (2016) Does lymph node metastasis have a negative prognostic impact in patients with NSCLC and M1a disease? *J Thorac Oncol* 11(10):1745–1754. <https://doi.org/10.1016/j.jtho.2016.06.030>
- Johnson KK, Rosen JE, Salazar MC, Boffa DJ (2016) Outcomes of a highly selective surgical approach to oligometastatic lung cancer. *Ann Thorac Surg* 102(4):1166–1171. <https://doi.org/10.1016/j.athoracsur.2016.04.086>
- Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, Cheney RT, Chirieac LR, D'Amico TA, Demmy TL, Dilling TJ, Dobelbower MC, Govindan R, Grannis FW Jr, Horn L, Jahan TM, Komaki R, Krug LM, Lackner RP, Lanuti M, Lilenbaum R, Lin J, Loo BW Jr, Martins R, Otterson GA, Patel JD, Pisters KM, Reckamp K, Riely GJ, Rohren E, Schild SE, Shapiro TA, Swanson SJ, Tauer K, Yang SC, Gregory K, Hughes M, National Comprehensive Cancer Network (2015) Non-small cell lung cancer, Version 6.2015. *J Natl Compr Cancer Netw* 13(5):515–524
- Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, Watanabe H, Wu YL, Zielinski M, Ball D, Rami-Porta R, International Association for the Study of Lung Cancer S, Prognostic Factors Committee ABM, Participating I (2015) The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 10(12):1675–1684. <https://doi.org/10.1097/jto.0000000000000678>
- Leung E, Xue A, Wang Y, Rougerie P, Sharma VP, Eddy R, Cox D, Condeelis J (2017) Blood vessel endothelium-directed tumor cell streaming in breast tumors requires the HGF/C-Met signaling pathway. *Oncogene* 36(19):2680–2692. <https://doi.org/10.1038/onc.2016.421>
- Wong SY, Hynes RO (2006) Lymphatic or hematogenous dissemination: how does a metastatic tumor cell decide? *Cell Cycle* 5(8):812–817. <https://doi.org/10.4161/cc.5.8.2646>
- Podgrabinska S, Skobe M (2014) Role of lymphatic vasculature in regional and distant metastases. *Microvasc Res* 95:46–52. <https://doi.org/10.1016/j.mvr.2014.07.004>
- Brakenhielm E, Burton JB, Johnson M, Chavarria N, Morizono K, Chen I, Alitalo K, Wu L (2007) Modulating metastasis by a lymphangiogenic switch in prostate cancer. *Int J Cancer* 121(10):2153–2161. <https://doi.org/10.1002/ijc.22900>
- Burton JB, Priceman SJ, Sung JL, Brakenhielm E, An DS, Pytowski B, Alitalo K, Wu L (2008) Suppression of prostate cancer nodal and systemic metastasis by blockade of the lymphangiogenic axis. *Cancer Res* 68(19):7828–7837. <https://doi.org/10.1158/0008-5472.CAN-08-1488>
- Roberts N, Kloos B, Cassella M, Podgrabinska S, Persaud K, Wu Y, Pytowski B, Skobe M (2006) Inhibition of VEGFR-3 activation with the antagonistic antibody more potently suppresses lymph node and distant metastases than inactivation of VEGFR-2. *Cancer Res* 66(5):2650–2657. <https://doi.org/10.1158/0008-5472.CAN-05-1843>
- Brown M, Assen FP, Leithner A, Abe J, Schachner H, Asfour G, Bago-Horvath Z, Stein JV, Uhrin P, Sixt M, Kerjaschki D (2018) Lymph node blood vessels provide exit routes for metastatic tumor cell dissemination in mice. *Science* 359(6382):1408–1411. <https://doi.org/10.1126/science.aal3662>
- Pereira ER, Kedrin D, Seano G, Gautier O, Meijer EFJ, Jones D, Chin SM, Kitahara S, Bouta EM, Chang J, Beech E, Jeong HS, Carroll MC, Taghian AG, Padera TP (2018) Lymph node metastases can invade local blood vessels, exit the node, and colonize distant organs in mice. *Science* 359(6382):1403–1407. <https://doi.org/10.1126/science.aal3622>
- Osarogiabon RU, Allen JW, Farooq A, Berry A, Spencer D, O'Brien T (2010) Outcome of surgical resection for pathologic N0 and Nx non-small cell lung cancer. *J Thorac Oncol* 5(2):191–196. <https://doi.org/10.1097/JTO.0b013e3181c8cc32>
- Osarogiabon RU, Allen JW, Farooq A, Berry A, O'Brien T (2011) Pathologic lymph node staging practice and stage-predicted survival after resection of lung cancer. *Ann Thorac Surg* 91(5):1486–1492. <https://doi.org/10.1016/j.athoracsur.2010.11.065>
- Ohta Y, Oda M, Wu J, Tsunozuka Y, Hiroshi M, Nonomura A, Watanabe G (2001) Can tumor size be a guide for limited surgical intervention in patients with peripheral non-small cell lung cancer? Assessment from the point of view of nodal micrometastasis. *J Thorac Cardiovasc Surg* 122(5):900–906. <https://doi.org/10.1067/mtc.2001.117626>
- Tamura T, Kurishima K, Nakazawa K, Kagohashi K, Ishikawa H, Satoh H, Hizawa N (2015) Specific organ metastases and survival in metastatic non-small-cell lung cancer. *Mol Clin Oncol* 3(1):217–221. <https://doi.org/10.3892/mco.2014.410>
- Riihimaki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J, Hemminki K (2014) Metastatic sites and survival in lung cancer. *Lung Cancer* 86(1):78–84. <https://doi.org/10.1016/j.lungcan.2014.07.020>

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