Original Article

Age at diagnosis is a heterogeneous factor for non-small cell lung cancer patients

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Background: The incidence of lung cancer is reported as age dependent. However, the link between survival and age at diagnosis remains controversial. To date, few studies have examined the relationship between age and the clinicopathologic characteristics of patients with non-small cell lung cancer (NSCLC).

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, we included in our analysis 151,919 patients diagnosed with NSCLC between 2004 and 2013. Logistic regression was used to evaluate the associations between age and clinicopathological characteristics. N and M stages were separately assessed in each T stage.

Results: Of the patients enrolled, 60,271 patients were diagnosed at the M1 stage, 147,263 patients had lymph node metastasis, and 49,862 patients underwent surgery. Younger age was inversely associated with high N stage and M stage (P<0.001, respectively). For each T stage, the inverse associations with M1 stage and lymph node metastasis were also presented (P<0.001, respectively). Age was an independent risk predictor for NSCLC patients by using univariate and multivariate analyses.

Conclusions: Age at diagnosis is a heterogeneous factor for NSCLC patients: younger patients have an increased risk of lymph node and distant metastases, yet have a better prognosis.

Keywords: Age at diagnosis; lymph node metastasis; distant metastasis; prognosis; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the second most common malignant cancer and the leading cause of death from malignancy in the United States (1). Moreover, the prevalence of lung cancer has paralleled our increased life expectancy, with the median age at diagnosis 63 years (2). Elderly patients exhibit higher rates of mortality than younger patients with various solid cancers, regardless of the clinical characteristics of the primary tumor, including patients with advanced or metastatic non-small cell lung cancer (NSCLC) (3-5). In retrospective studies, younger lung cancer patients exhibited a higher incidence of adenocarcinoma, female, and an advanced stage disease (3,6). In addition, these patients tended to present with a higher malignant potential (7,8). Therefore, age is regarded as a heterogeneous fact for lung cancer patients. Interestingly, elder patients typically exhibit a lower frequency of lymph node metastasis, compared to patients with early-stage rectal cancer (9). The impact of age at diagnosis on clinicopathologic characteristics is not

well known for lung cancer patients.

We hypothesize that the behavior of NSCLC will differ between patients diagnosed at different ages. In the present study, we sought to assess the association between age and lymph node metastasis, M stage, and overall survival (OS) by examining surveillance, epidemiology, and end results (SEER) Database.

Methods

SEER database and patient selection

Lung cancer patient records were obtained from the special SEER database from 2004 to 2013. The inclusion criteria were definitive NSCLC diagnosis by pathology; no radiotherapy prior to surgery; pathological TNM stage information; complete follow-up data after treatment. And the exclusion criteria are as follows: (I) patients with small cell lung cancer (ICD-0-3 histology code 8041–8045); (II) patients without pathologic diagnosis; (III) patients received neoadjuvant chemotherapy; (IV) patients without any TNM information; (V) patients with non-cancer specific death (cardiovascular related mortality, and other causes).

SEER*Stat Version 8.2.1 (2015; National Cancer Institute Cancer Statistics Branch, Bethesda, MD; www.seer.Cancer.gov/seerstat) was used to identify all patients with NSCLC based on the International Classification of Diseases for Oncology. Patients' demographics on each case, including gender, age at diagnosis, extent of disease, primary site, histology, vital status, number of lymph nodes examined and positive, T stage, N stage, and M stage, were included. Adjuvant chemotherapy and neoadjuvant chemotherapy were not evaluated as the SEER registry does not include this information. The proportion of NSCLC patients was classified by 5-year intervals (0–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and 85+). The primary endpoint of the study was calculated from the date of diagnosis to the date of cancer specific death or the last follow-up. The study was approved by institutional ethics committee of Shanghai Pulmonary Hospital (No. K16-264).

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Inc., Chicago, IL, USA) software, version 16.0 for Windows. The descriptive data were expressed as mean ± standard deviation. Baseline characteristics were analyzed by the chi-squared (χ^2) test or Student's *t*-test for continuous variables. The association between age at diagnosis and distant metastasis, and lymph node metastasis were evaluated by using Poisson regression. OS was displayed using Kaplan-Meier survival curves with 95% confidence intervals (CIs); the differences between curves were displayed using the log-rank test. All risk factors identified by univariate analysis were adopted in multivariate Cox proportional hazard analysis. A two-tailed test of a P value of ≤0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

In this retrospective study, 151,919 patients met the eligibility criteria. There were 72455 female patients (47.7%) and 79,464 male patients (52.3%). A total of 121,970 (80.3%) patients identified as white race. The median age at diagnosis was 68 years (range, 4–104 years). Of these patients, the 65–69 years old patient was also the greatest proportion (26,310, 17.3%), and 0–44 years old patient was the smallest proportion (3,134, 2.1%). As for treatment, 60,611 (39.9%) patients received radiation, and 49,862 (32.8%) patients received surgery. At follow-up, 54,004 (35.5%) patients were still alive. The 1-, 3-, and 5-year survival rates were 47.8%, 20.3%, and 10.3%. The median time of OS was 16.0 (95% CI: 15.813–16.187) months. According to AJCC TNM stage classification, 81,501 patients (53.6%) had at least one lymph node metastasis, 60,271 patients (39.7%) had M1 stage (including M1a and M1b). The greatest proportion was T4 stage (35,226 patients, 23.2% for T1 stage; 50,759 patients, 33.4% for T2 stage; 9,946 patients, 6.5% for T3 stage; 55,988 patients, 36.9% for T4 stage). In our cohort, 29.6%, 52.4%, 61.8%, and 68.5% of patients had stage T1, T2, T3, and T4 patients respectively, with lymph node positive, and 19.3%, 32.2%, 38.6%, and 59.5% for T1, T2, T3, and T4 patients with M1 stage. The proportion of NSCLC patients is presented in *Table 1*.

Age increases risks of lymph node metastasis and distant metastasis

As illustrated in *Table 2*, younger patients tended to have more node-positive disease, distant disease, adenocarcinoma, and black patients (P<0.001, respectively). Individuals

Table 1 Clinicopathological features of patients

Factors	n=151,919	%
Sex		
Male	79,464	52.3
Female	72,455	47.7
Age		
0–44	3,134	2.1
45–49	5,553	3.7
50–54	10,918	7.2
55–59	16,530	10.9
60–64	22,006	14.5
65–69	26,310	17.3
70–74	24,761	16.3
75–79	21,451	14.1
80–84	14,354	9.4
85+	6,902	4.5
Race		
White	121,970	80.3
Black	17,778	11.7
Others	11,837	7.8
Unknown	334	0.2
Year of diagnosis		
2004	12,248	8.1
2005	12,177	8.0
2006	13,230	8.7
2007	13,891	9.1
2008	14,653	9.6
2009	15,645	10.3
2010	16,796	11.1
2011	17,386	11.4
2012	18,143	11.9
2013	17,750	11.7
Histology		
Adenocarcinoma	101,085	66.5
Squamous	50,834	33.5
Surgery		
No	102,057	67.2
Yes	49,862	32.8
Radiation		
Yes	60,611	39.9
No	89,054	58.6
Unknown	4,656	3.1
TNM stage		
Ia	21,962	14.5
Ib	18,781	12.4
IIa	2,069	1.4
Iib	7,099	4.7
IIIa	14,638	9.6
IIIb	25,028	16.5
IV	60,271	39.7
Unstaged	2,071	1.4
N stage		
N0	65,762	43.3
N1	14,460	9.5
N2	50,507	33.2
N3	16,534	10.9
Unstaged	4656	3.1
Tumor location		
Left	87,244	57.4
Right	61,530	40.5
Paired sites	2,843	1.9
Unknown	302	0.2
T stage		
T1	35,226	23.2
T2	50,759	33.4
T3	9,946	6.5
T4	55,988	36.9
M stage		
M0	90,035	59.3
M1	60,271	39.7
Unstaged	1,613	1.1

T stage, tumor stage; N stage, node stage; M stage, metastasis stage.

Table 2 The association of the clinicopathological characteristics

Factors (n)	0–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+	P
Sex											<0.01
Female	1,718	2,862	5,173	7,299	9,787	12,063	11,775	10,631	7,385	3,762	
Male	1,416	2,691	5,745	9,231	12,219	14,247	12,986	10,820	6,969	3,140	
Race											<0.01
White	2,235	4,072	8,051	12,536	17,337	21,382	20,465	17,907	12,208	5,777	
Black	465	957	1,962	2,706	3,006	3,039	2,372	1,840	953	478	
Others	419	508	877	1,246	1,618	1,840	1,863	1,668	1,164	634	
Unknown	15	16	28	42	45	49	61	36	29	13	
Histology											<0.01
Adenocarcinoma	2,633	4,363	8,180	11,743	14,841	16,955	15,505	13,276	9,041	4,548	
Squamous	501	1,190	2,738	4,787	7,165	9,355	9,256	8,175	5,313	2,354	
Surgery											<0.01
No	2,147	3,801	7,441	10,958	14,188	16,429	15,941	14,433	10,745	5,974	
Yes	987	1,752	3,477	5,572	7,818	9,881	8,820	7,018	3,609	928	
Radiation											<0.01
No	1,586	2,847	5,590	8,785	12,533	15,595	15,114	13,533	9,075	2,416	
Yes	1,490	2,624	5,168	7,483	9,159	10,301	9,252	7,648	5,070	4,396	
Unknown	58	82	160	262	314	414	395	270	209	90	
LNM stage											<0.01
Ia	282	555	1,265	2,082	3,279	4,272	4,088	3,330	820	820	
Ib	254	488	948	1,626	2,550	3,403	3,291	3,119	1,009	1,009	
IIa	44	81	130	245	304	391	364	283	48	48	
IIb	105	259	479	772	1,008	1,353	1,165	1,034	276	276	
IIIa	255	476	1,052	1,601	2,128	2,654	2,465	2,098	592	592	
IIIb	484	867	1,738	2,663	3,504	3,989	3,998	3,626	1,553	1,553	
IV	1,684	2,764	5,200	7,350	9,003	9,923	9,050	7,625	2,437	2,437	
Unknown	26	63	106	191	230	325	340	336	167	167	
N stage											<0.01
N0	1,009	1,924	3,873	6,123	9,082	11,685	11,466	10,271	6,941	3,388	
N1	289	584	1,050	1,685	2,192	2,605	2,284	1,980	1,264	527	
N2	1,172	2,012	4,045	6,023	7,514	8,608	7,946	6,708	4,388	2,091	
N3	546	888	1,649	2,251	2,657	2,714	2,366	1,789	1,164	510	
Unknown	118	145	301	448	561	698	699	703	597	386	

Table 2 (*continued*)

Table 2 (*continued*)

Factors (n)	0–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+	P
Lymph node metastasis											<0.01
No	1,009	1,924	3,873	6,123	9,082	11,685	11,466	10,271	6,941	3,388	
Yes	2,007	3,484	6,744	9,959	12,363	13,927	12,596	10,477	6,816	3,128	
Unknown	118	145	301	448	561	698	699	703	597	386	
Tumor location											<0.01
Left	1,854	3,216	6,457	9,601	12,652	15,123	14,116	12,236	8,148	3,841	
Right	1,150	2,175	4,204	6,562	8,935	10,694	10,222	8,829	5,901	2,858	
Paired sites	119	147	234	335	386	438	380	346	273	185	
Unknown	11	15	23	32	33	55	43	40	32	18	
T stage											<0.01
T1	587	1,112	2,312	3,641	5,187	6,620	6,270	5,117	3,122	1,258	
T2	862	1,663	3,421	5,308	7,216	9,032	8,370	7,564	5,007	2,316	
T3	201	368	766	1,197	1,454	1,769	1,606	1,338	872	375	
T4	1,484	2,410	4,419	6,384	8,149	8,889	8,515	7,432	5,353	2,953	
M stage											<0.01
M0	1,426	2,733	5,626	9,021	12,812	16,131	15,447	13,589	8,914	4,336	
M1	1,684	2,764	5,200	7,350	9,003	9,923	9,050	7,625	5,235	2,437	
Unknown	24	56	92	159	191	256	264	237	205	129	
Year of diagnosis											<0.01
2004	337	512	877	1,344	1,777	2,069	2,025	1,818	1,063	426	
2005	318	524	873	1,355	1,767	2,011	1,982	1,768	1,142	437	
2006	332	582	1,010	1,460	1,877	2,199	2,168	1,855	1,205	542	
2007	305	587	966	1,491	2,058	2,430	2,277	1,979	1,233	565	
2008	298	583	1,096	1,566	2,124	2,602	2,310	2,056	1,365	653	
2009	309	609	1,142	1,673	2,319	2,622	2,537	2,205	1,501	728	
2010	302	573	1,272	1,842	2,357	2,932	2,661	2,374	1,661	822	
2011	339	569	1,298	1,852	2,569	3,046	2,784	2,383	1,725	821	
2012	303	537	1,226	2,007	2,589	3,237	2,961	2,557	1,794	932	
2013	291	477	1,158	1,940	2,569	3,162	3,056	2,456	1,665	976	

younger than 45 years had a higher incidence of lymph node involvement (from 64.0% in patients 0–44 years old to 45.3% in patients 85 and over) and distant metastases (from 53.7% in patients 0–44 years old to 35.3% in patients 85 and over) (P<0.001, respectively) in each increasing age category (*Figure 1A*,*B*). And the percentage of population gradually increased by increasing age (*Table 2* and *Figure 1*).

Subgroup analysis according to different T stages (T1, T2, T3, and T4 stage) showed that the risk of lymph node metastasis (*Figure 2A*,*B*,*C*,*D*) and M1 stage (*Figure 3A*,*B*,*C*,*D*) were also decreased regardless of T stage. The incidence of distant metastasis and lymph node metastasis gradually

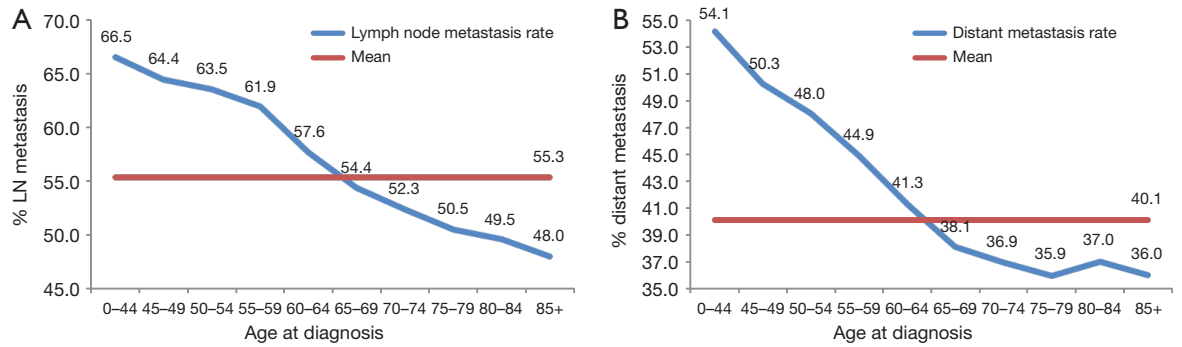

Figure 1 Young age was inversely associated with lymph node metastasis (A, P<0.001) and M stage (B, P<0.001).

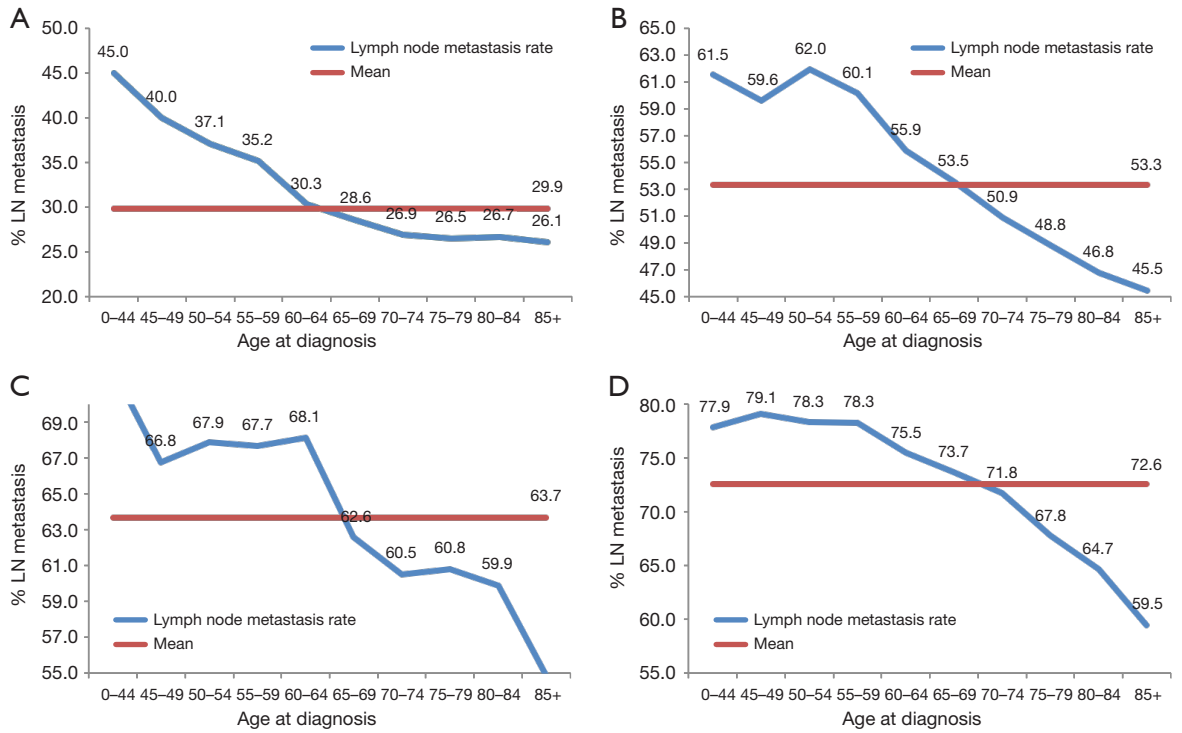

Figure 2 The associations between age and lymph node metastasis according to T stage (A: T_1; B: T_2; C: T_3; and D: T_4) (P<0.001, respectively).

decreased with increasing age in different stages (P<0.001, respectively) (*Figures 2* and *3*).

Age at diagnosis is an independent factor for predicting outcome

Age at diagnosis (*Figure 4A,B,C*), sex, race, year of diagnosis, histology, location of tumor, T stage, N stage, M stage, TNM, radiotherapy, and surgery (P<0.001, respectively) were statistically significant risk predictors for survival in the univariate analyses. In the multivariate analyses, age at diagnosis, sex, race, year of diagnosis, histology, location of tumor, T stage, N stage, M stage, TNM, radiotherapy, and surgery were analyzed as continuous or categorized variables and were significantly associated with an increased risk of death, independent of tumor location (*Table 3*).

Discussion

In recent decades, the cancer-associated death rate in

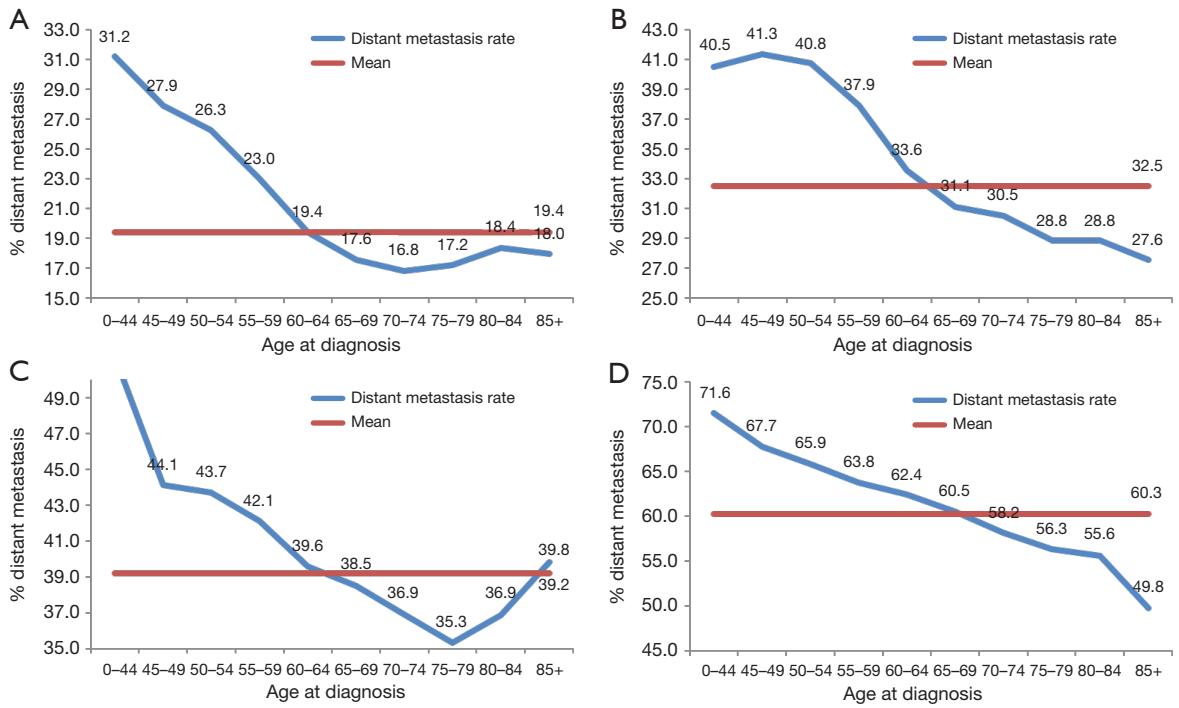

Figure 3 The associations between age and distant metastasis according to T stage (A: T_1; B: T_2; C: T_3; D: T_4) (P<0.001, respectively).

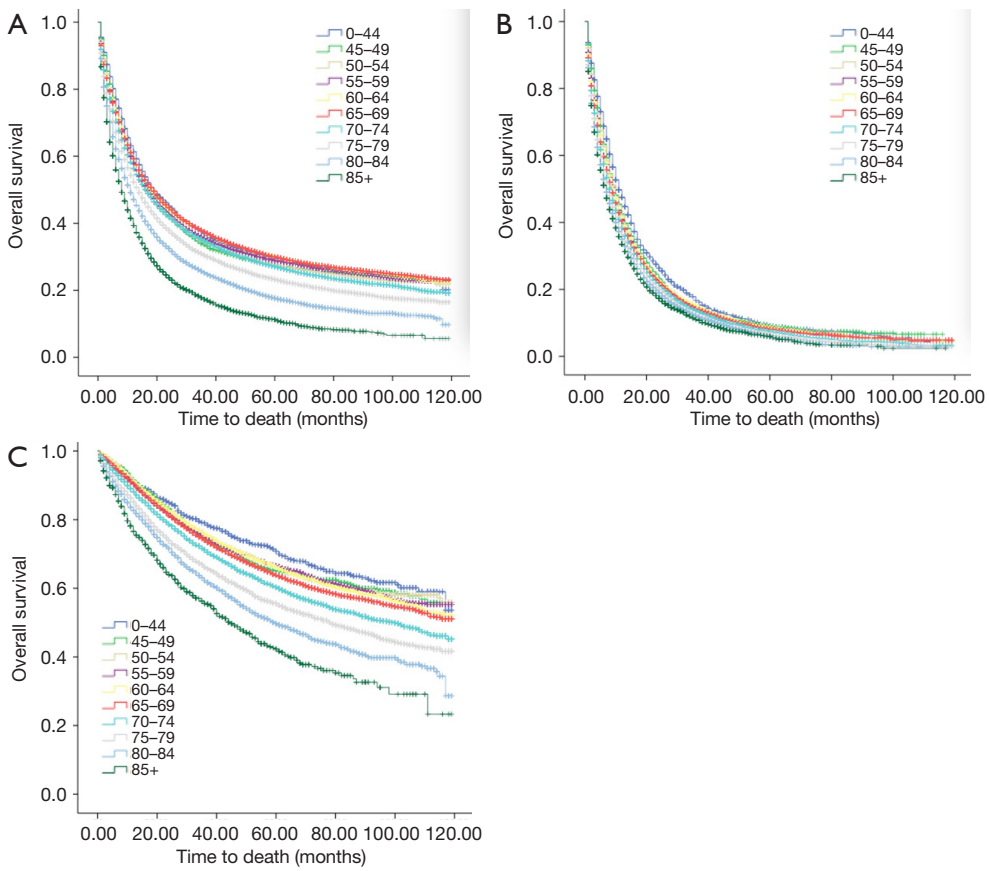

Figure 4 Kaplan-Meier survival curves for overall survival: all patients (A); patients with distant metastasis (B); patients with received surgery (C).

Table 3 Univariate and multivariate analyses of factors associated with OS

Factors	OS							
	Univariate				Multivariate			
	HR	95% CI	P value	P' value	HR	95% CI	P value	P' value
All patients								
Age at diagnosis								
0–44		1.000 (reference)		<0.001		1.000 (reference)		<0.001
45–49	1.071	1.013–1.131	<0.001		1.128	1.065–1.195	<0.001	
50–54	1.079	1.026–1.135	<0.001		1.164	1.105–1.227	<0.001	
55–59	1.061	1.011–1.114	<0.001		1.204	1.145–1.267	<0.001	
60–64	1.025	0.978–1.075	<0.001		1.236	1.176–1.299	<0.001	
65–69	1.027	0.980–1.077	<0.001		1.330	1.266–1.397	<0.001	
70–74	1.122	1.070–1.176	<0.001		1.469	1.398–1.544	<0.001	
75–79	1.255	1.197–1.315	<0.001		1.653	1.572–1.737	<0.001	
80–84	1.470	1.401–1.543	<0.001		1.855	1.763–1.953	<0.001	
85+	1.835	1.742–1.933	<0.001		2.141	2.026–2.262	<0.001	
Sex								
Female		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Male	1.325	1.309–1.342	<0.001		1.229	1.213–1.246	<0.001	
Race								
White		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Black	1.618	1.368–1.913	<0.001		1.040	1.019–1.061	<0.001	
Others	1.897	1.603–2.245	<0.001		0.755	0.736–0.775	<0.001	
Year of diagnosis								
2004		1.000 (reference)		<0.001		1.000 (reference)		<0.001
2005	0.950	0.924–0.976	<0.001		0.959	0.931–0.987	0.005	
2006	0.928	0.903–0.954	<0.001		0.915	0.889–0.942	<0.001	
2007	0.894	0.870–0.919	<0.001		0.896	0.871–0.922	<0.001	
2008	0.876	0.853–0.900	<0.001		0.860	0.836–0.885	<0.001	
2009	0.859	0.836–0.882	<0.001		0.827	0.804–0.851	<0.001	
2010	0.871	0.848–0.895	<0.001		0.822	0.799–0.845	<0.001	
2011	0.798	0.776–0.820	<0.001		0.746	0.725–0.768	<0.001	
2012	0.808	0.785–0.831	<0.001		0.750	0.728–0.773	<0.001	
2013	0.730	0.703–0.757	<0.001		0.689	0.663–0.715	<0.001	
Histology								
Adenocarcinoma		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Squamous	1.209	1.193–1.225	<0.001		1.143	1.127–1.160	<0.001	

Table 3 (*continued*)

Table 3 (*continued*)

Factors	OS							
	Univariate				Multivariate			
	HR	95% CI	P value	P' value	HR	95% CI	P value	P' value
Surgery								
Yes		1.000 (reference)		<0.001		1.000 (reference)		<0.001
No	5.789	5.689–5.892	<0.001		0.336	0.328–0.344	<0.001	
Radiation								
Yes		1.000 (reference)		<0.001		1.000 (reference)		<0.001
No	1.742	1.719–1.764	<0.001		0.931	0.918–0.945	<0.001	
TNM stage								
Ia		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Ib	1.927	1.859–1.998	<0.001		1.424	1.361–1.490	<0.001	
IIa	2.097	1.953–2.252	<0.001		1.816	1.682–1.961	<0.001	
IIb	3.172	3.041–3.308	<0.001		1.930	1.831–2.034	<0.001	
IIIa	4.569	4.415–4.729	<0.001		1.836	1.7551.921	<0.001	
IIIb	6.516	6.314–6.924	<0.001		2.154	2.063–2.249	<0.001	
IV	10.282	9.982–10.592	<0.001		3.534	3.393–3.682	<0.001	
N stage								
N0		1.000 (reference)		<0.001		1.000 (reference)		<0.001
N1	1.670	1.632–1.710	<0.001		1.164	1.132–1.197	<0.001	
N2	2.877	2.833–2.921	<0.001		1.279	1.255–1.304	<0.001	
N3	3.358	3.290–3.428	<0.001		1.259	1.230–1.289	<0.001	
Tumor location								
Left		1.000 (reference)		<0.001		1.000 (reference)	<0.001	0.104
Right	1.001	0.989–1.014	0.827		1.005	0.992–1.019	0.452	
Paired sites	2.207	2.119–2.299	<0.001		1.049	1.002–1.097	0.039	
T stage								
T1		1.000 (reference)		<0.001		1.000 (reference)		<0.001
T2	1.982	1.943–2.023	<0.001		1.222	1.190–1.255	<0.001	
T3	3.154	3.066–3.244	<0.001		1.410	1.363–1.459	<0.001	
T4	4.179	4.099–4.261	<0.001		1.412	1.375–1.449	<0.001	
M stage								
M0		1.000 (reference)		<0.001		1.000 (reference)		<0.001
M1	3.320	3.277–3.364	<0.001		3.534	3.393–3.682	<0.001	

Table 3 (*continued*)

Table 3 (*continued*)

Factors	OS							
	Univariate				Multivariate			
	HR	95% CI	P value	P' value	HR	95% CI	P value	P' value
Patients received surgery								
Age at diagnosis								
0–44		1.000 (reference)		<0.001		1.000 (reference)		<0.001
45–49	1.085	1.022–1.151	0.007		1.275	1.094–1.486	0.002	
50–54	1.114	1.055–1.176	<0.001		1.266	1.100–1.457	0.001	
55–59	1.136	1.078–1.196	<0.001		1.328	1.161–1.520	<0.001	
60–64	1.127	1.070–1.186	<0.001		1.428	1.251–1.629	<0.001	
65–69	1.158	1.101–1.219	<0.001		1.592	1.396–1.815	<0.001	
70–74	1.216	1.156–1.279	<0.001		1.926	1.690–2.196	<0.001	
75–79	1.275	1.211–1.342	<0.001		2.404	2.108–2.743	<0.001	
80–84	1.332	1.264–1.403	<0.001		2.812	2.454–3.221	<0.001	
85+	1.394	1.319–1.474	<0.001		3.895	3.322–4.566	<0.001	
Sex								
Female		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Male	1.474	1.429–1.520	<0.001		1.352	1.308–1.396	<0.001	
Race								
White		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Black	1.029	0.974–1.088	0.303		1.063	1.004–1.125	0.037	
Others	0.831	0.779–0.886	<0.001		0.792	0.741–0.846	<0.001	
Unknown	0.269	0.145–0.500	<0.001		0.371	0.193–0.714	0.003	
Year of diagnosis								
2004		1.000 (reference)		<0.001		1.000 (reference)		<0.001
2005	0.973	0.943–1.004	0.089		0.982	0.925–1.042	0.551	
2006	0.941	0.913–0.971	<0.001		0.903	0.850–0.959	0.001	
2007	0.921	0.894–0.950	<0.001		0.832	0.782–0.884	<0.001	
2008	0.876	0.850–0.903	<0.001		0.827	0.777–0.880	<0.001	
2009	0.846	0.820–0.871	<0.001		0.744	0.698–0.794	<0.001	
2010	0.840	0.816–0.865	<0.001		0.697	0.651–0.746	<0.001	
2011	0.754	0.731–0.777	<0.001		0.645	0.598–0.695	<0.001	
2012	0.746	0.724–0.770	<0.001		0.645	0.590–0.704	<0.001	
2013	0.686	0.660–0.713	<0.001		0.551	0.476–0.638	<0.001	

Table 3 (*continued*)

Table 3 (*continued*)

Factors	OS							
	Univariate				Multivariate			
	HR	95% CI	P value	P' value	HR	95% CI	P value	P' value
Histology								
Adenocarcinoma		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Squamous	1.380	1.336–1.425	<0.001		1.198	1.157–1.240	<0.001	
M stage								
M0		1.000 (reference)		<0.001		1.000 (reference)		<0.001
M1	1.763	1.738–1.788	<0.001		1.758	1.730–1.786	<0.001	
Radiation								
No		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Yes	2.590	2.491–2.694	<0.001		1.485	1.421–1.552	<0.001	
TNM stage								
Ia		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Ib	1.764	1.682–1.849	<0.001		1.221	1.113–1.339	<0.001	
IIa	2.453	2.250–2.673	<0.001		1.680	1.505–1.876	<0.001	
IIb	3.346	3.165–3.536	<0.001		1.540	1.386–1.710	<0.001	
IIIa	3.986	3.775–4.208	<0.001		1.402	1.263–1.556	<0.001	
IIIb	3.721	3.508–3.947	<0.001		1.315	1.170–1.479	<0.001	
IV	6.718	6.362–7.093	<0.001		3.055	2.785–3.351	<0.001	
N stage								
N0		1.000 (reference)		<0.001		1.000 (reference)		<0.001
N1	2.145	2.059–2.235	<0.001		1.446	1.351–1.548	1.548	
N2	3.097	2.977–3.222	<0.001		2.003	1.863–2.152	2.152	
N3	6.129	5.415–6.938	<0.001		3.026	2.645–3.461	3.461	
Tumor location								
Left				<0.001		1.000 (reference)		0.053
Right	1.023	0.992–1.056	0.148		0.970	0.939–1.001	0.058	
Paired sites	4.171	3.268–5.323	<0.001		1.218	0.9281.600	0.156	
T stage								
T1		1.000 (reference)		<0.001		1.000 (reference)		<0.001
T2	1.883	1.816–1.954	<0.001		1.334	1.233–1.444	<0.001	
T3	3.594	3.375–3.826	<0.001		1.949	1.772–2.142	<0.001	
T4	3.681	3.511–3.860	<0.001		1.967	1.780–2.172	<0.001	

Table 3 (*continued*)

Table 3 (*continued*)

Factors	OS							
	Univariate				Multivariate			
	HR	95% CI	P value	P' value	HR	95% CI	P value	P' value
Patients with distant metastasis								
Age at diagnosis								
0–44		1.000 (reference)		<0.001		1.000 (reference)		<0.001
45–49	1.133	0.977–1.314	0.100		1.113	1.046–1.184	0.001	
50–54	1.132	0.988–1.297	0.075		1.156	1.092–1.223	<0.001	
55–59	1.152	1.011–1.313	0.034		1.194	1.130–1.261	<0.001	
60–64	1.151	1.013–1.308	0.031		1.215	1.152–1.282	<0.001	
65–69	1.236	1.089–1.402	0.001		1.295	1.228–1.366	<0.001	
70–74	1.423	1.254–1.614	<0.001		1.395	1.323–1.472	<0.001	
75–79	1.689	1.487–1.917	<0.001		1.528	1.448–1.613	<0.001	
80–84	1.976	1.733–2.253	<0.001		1.679	1.589–1.774	<0.001	
85+	2.522	2.162–2.941	<0.001		1.884	1.776–1.999	<0.001	
Sex								
Female		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Male	1.202	1.185–1.218	<0.001		1.202	1.185–1.220	<0.001	
Race								
White		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Black	0.993	0.973–1.014	0.523		1.032	1.010–1.054	0.004	
Others	0.814	0.793–0.835	<0.001		0.750	0.729–0.771	<0.001	
Unknown	0.667	0.560–0.793	<0.001		0.666	0.549–0.808	<0.001	
Year of diagnosis								
2004		1.000 (reference)		<0.001		1.000 (reference)		<0.001
2005	0.949	0.896–1.006	0.078		0.960	0.928–0.992	0.015	
2006	0.878	0.828–0.931	<0.001		0.926	0.896–0.956	<0.001	
2007	0.814	0.767–0.864	<0.001		0.919	0.889–0.949	<0.001	
2008	0.797	0.750–0.847	<0.001		0.877	0.849–0.905	<0.001	
2009	0.730	0.685–0.778	<0.001		0.851	0.824–0.878	<0.001	
2010	0.687	0.643–0.735	<0.001		0.850	0.824–0.877	<0.001	
2011	0.624	0.580–0.672	<0.001		0.769	0.745–0.794	<0.001	
2012	0.635	0.583–0.693	<0.001		0.768	0.743–0.793	<0.001	
2013	0.525	0.455–0.605	<0.001		0.705	0.677–0.734	<0.001	

Table 3 (*continued*)

Table 3 (*continued*)

Factors	OS							
	Univariate				Multivariate			
	HR	95% CI	P value	P' value	HR	95% CI	P value	P' value
Histology								
Adenocarcinoma		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Squamous	1.039	1.024–1.054	<0.001		1.136	1.118–1.154	<0.001	
M stage								
M0		1.000 (reference)		<0.001		1.000 (reference)		<0.001
M1	3.475	3.324–3.633	<0.001		2.830	2.681–2.987	<0.001	
Radiation								
No		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Yes	0.777	0.766–0.788	<0.001		0.872	0.859–0.885	0.885	
TNM stage								
Ia		1.000 (reference)		<0.001		1.000 (reference)		<0.001
Ib	1.787	1.689–1.890	<0.001		1.415	1.328–1.508	<0.001	
IIa	1.533	1.351–1.741	<0.001		1.370	1.201–1.564	<0.001	
IIb	2.143	2.008–2.286	<0.001		1.559	1.449–1.678	<0.001	
IIIa	2.032	1.932–2.137	<0.001		1.447	1.365–1.535	<0.001	
IIIb	2.695	2.570–2.826	<0.001		1.795	1.697–1.899	<0.001	
IV	3.808	3.637–3.987	<0.001		2.830	2.681–2.987	<0.001	
N stage								
N0		1.000 (reference)		<0.001		1.000 (reference)		<0.001
N1	1.254	1.219–1.290	<0.001		1.131	1.097–1.166	<0.001	
N2	1.375	1.352–1.298	<0.001		1.235	1.211–1.260	<0.001	
N3	1.419	1.388–1.450	<0.001		1.212	1.184–1.242	<0.001	
Tumor location								
Left		1.000 (reference)		<0.001		1.000 (reference)		0.261
Right	1.003	0.988–1.017	0.729		1.004	0.990–1.019	0.562	
Paired sites	1.387	1.331–1.446	<0.001		1.038	0.992–1.087	0.110	
T stage								
T1		1.000 (reference)		<0.001		1.000 (reference)		<0.001
T2	1.441	1.406–1.476	<0.001		1.213	1.179–1.249	1.249	
T3	1.640	1.588–1.693	<0.001		1.380	1.33–1.431	1.431	
T4	1.903	1.861–1.947	<0.001		1.383	1.346–1.422	1.422	

OS, overall survival; CI, confidence interval.

lung cancer patients has decreased. Improvements in medical treatment and increased public awareness have been considered to play a role. Previous studies showed that elderly NSCLC patients represent a heterogeneous group (10) with unfavorable clinicopathologic characte ristics (11). For example, elderly patients have significantly more chemotherapy-related toxicity (12,13), and less possibility for adenocarcinoma histology compared with younger patients (4). However, the impact of age on clinicopathologic characteristics was assessed in small-scale populations, and there is still debate as to what this means for lung cancer patients. To address this, we assessed the effects of age on N stage and M stage using the SEER Database.

TNM stage is an independent prognostic factor for all solid cancers, including NSCLC (14,15). The relationship between the age at diagnosis and the risk of lymph node positivity in NSCLC has not been previous described. In this study, we demonstrated that younger patients diagnosed with NSCLC have an increased predisposition for lymph node positivity compared with older patients. The risk of metastasis in older patients is nearly double of the younger patients. We also assessed the incidence of distant metastasis in our cohort. The risk of distant metastasis followed a similar trend as that of lymph node metastasis in NSCLC patients. In order to further validate our results, patients were divided into four subgroups according to T stages. Remarkably, the inverse relationship between age and distant metastasis, and lymph node metastasis remained. These results support the idea that younger patients have a higher malignant potential compared to the elderly.

The relationship between age and survival is still controversial. In some small-scale studies, age as a continuous variable, was not a prognostic factor for advanced or metastatic NSCLC (10,16,17). Other studies have drawn the opposite conclusion that age is a prognostic factor for patients with NSCLC, and elderly patients have a worse outcome compared to younger individuals (3,18,19). In our current analysis, a large population-based study, we find that age is in fact a prognostic factor for this population (as assessed by the cancer-specific survival). We find an unexpected link between survival and lymph node metastasis. This is because younger patients may respond better to treatments, like surgery and chemoradiotherapy (20,21). Previous studies analyzed age as binary variable. In order to better assess the associations between age and clinicopathological characteristics, patients were classified by 5-year intervals.

Our data present an interesting phenomenon. However, we are unable to address the underlying mechanisms in our current study. One possible explanation for our results is a genetic difference between our patients. Tumor cells in younger patients may exhibit more aggressive behavior than those in older patients (22). Secondly, age-related changes are presented in immunologic surveillance, such as decreased lymphatic flow to nodes and/or nodal involution. It was reported that tumor-associated neutrophil is related to a metastatic disease (23,24), and age-related changes in natural killer cells can impact on their ability to perform immune surveillance (25). We must also consider that a higher proportion of elderly patients take aspirin regularly because of cardiovascular diseases, such as myocardial infarction (26,27), and coronary artery disease (28,29). Aspirin can inhibit the aggregation of platelet by influencing the activity of cyclooxygenase-1 (COX-1) (30). Platelets have been shown to promote tumor metastasis (31). Future studies will need to elucidate whether these variables support our findings.

Our study is inherently limited by its retrospective design. Although our study is based on a large population and multicenter analysis, some of the patients' files have been miscoded. These clerical errors can lead to patients being excluded from the study. Additionally, some important information, such as details of treatment, surgery type and smoking status, were not available in the SEER Database. Previous studies reported that neoadjuvant chemotherapy increases pathological response and lymph nodal downstage, so it could reduce the incidence of lymph node metastasis (32). In this study, we excluded patients who received neoadjuvant radiotherapy to eliminate the effect of preoperative radiation on lymph node harvest and positivity. Another consideration is that incomplete lymph node dissections may lead to misdiagnosing a lymph node metastasis. Finally, the records were obtained from the SEER Database did not provide the sites of tumor invasion. Thus, it is not possible to accommodate the latest edition of TNM, and the T stage of these patients was defined by the 8th AJCC TNM staging classification (33).

In conclusion, age at diagnosis is a heterogeneous factor for NSCLC patients. This study demonstrates that young age is associated with increased rates of lymph node and distant metastases. However, in spite of this, we also find that age is an independent factor for predicting outcome: younger patients have a better prognosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics committee of Shanghai Pulmonary Hospital (No. K16-264).

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