Metastatic patterns and prognosis of young lung cancer patients: a population-based study by age

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Background: We aimed to examine the different metastatic patterns and corresponding survival outcomes between all ages of young (aged <60 years) and elderly lung cancer patients.

Methods: Lung cancer patients from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015 were divided into a young and elderly group. The young group was subdivided into four consecutive subgroups. Baseline characteristics were analyzed by the Chi-square test. Survival differences were evaluated by Kaplan-Meier curves and Cox proportional hazards models.

Results: Of the total 200,362 lung cancer patients, 155,348 were elderly patients and 45,014 were young patients, including 3,461 aged <45 years, 5,697 aged 45–49 years, 13,645 aged 50–54 years, and 22,211 aged 55–59 years. Compared with elderly lung cancer patients, extrathoracic metastases were significantly more frequent in each younger group, irrespective of the site and number of extrathoracic metastatic organs. Regardless of metastasis patterns, young ages were independent prognostic factors of lung cancer-specific survival (LCSS) [<45 years: hazard ratio (HR): 0.70; 45–49 years: HR: 0.87; 50–54 years: HR: 0.90; 55–59 years: HR: 0.93, all P values were <0.001]. In each age subgroup, patients with multi-organ extrathoracic metastasis had the worst LCSS.

Conclusions: Young lung cancer patients across all ages were at increased risk of extrathoracic metastasis, especially multi-organ patterns, but had a reduced risk of lung cancer-related death compared to elderly patients. Regular and meticulous monitoring of potential metastasized organs is required in young lung cancer patients throughout the follow-up period.

Keywords: Lung cancer; young; metastasis; prognosis; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Lung cancer is one of the leading causes of cancer morbidity worldwide, with a median age at diagnosis of 71 years (1). Previous studies assessing the metastatic patterns and prognosis of lung cancer are mainly based on elderly patients, but there are few studies examining these factors in young patients. Because of the potential interactions between metastatic patterns, prognosis, and age, a separate examination of this issue in young patients is important. Also, multiple studies have revealed that the incidence of lung cancer in young females has been on the rise in the evolution of the smoking epidemic worldwide (2), which further highlights the urgent need to assess this issue in young patients.

The definitions of age boundaries for young people vary markedly between studies on lung cancer, with the ages 35 years (3), 40 years (4), 45 years (5,6), 50 years (7,8), and even 60 years (9) all being used. Substantial disparities has been observed in clinical features, genomic alterations and prognosis between young and old lung cancer patients (5-8). Young patients with lung cancer may represent a distinct spectrum of the disease (10).

M descriptor is a strong prognostic marker for lung cancer patients (11), with a 5-year survival rate for localized stage disease of 57%, and a 5-year survival rate of only 5% for metastatic stage disease (12). Thus, a better understanding of patients who are more susceptible to metastasis and early detection of the potential metastasized organs have important implications for improving prognosis. Previous studies have revealed the extrathoracic metastatic patterns of octogenarians (9). However, the metastatic profiles of younger patients remain poorly understood and the predictions by extrapolation are challenging. Given the longer life expectancy, and the higher social and family participation of younger lung cancer patients (10), further studies are needed to characterize this subset of patients.

In this article, we conducted a population-based study in which we segregated relatively young patients (age at diagnosis less than 60 years) into four consecutive subgroups and sought to examine the relationship between different metastatic patterns and the corresponding prognostic value by age.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-2849).

Methods

Study population and data collection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients with invasive lung and bronchus cancer were identified from the Surveillance, Epidemiology, and End Results (SEER) 18-registry database between 2010 and 2015, on the basis of the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3). Informed consent was not required as there was no contact with study subjects. Any patient who met any of the following criteria were excluded: (I) patients who had a history of other malignancies, (II) patients under 18 years old at lung cancer diagnosis, (III) patients diagnosed at autopsy or death certificate only, (IV) metastatic status was not available. A total of 71,009 of the 271,371 lung cancer patients were excluded due to the exclusion criteria, resulting in 200,362 patients available for analysis. A detailed flow chart of the patient screening process is provided in Figure S1. Patients were divided into a young group and elderly group, the former of which was further subdivided into <45, 45–49, 50–54, and 55–59 age subgroups.

Variable classifications

Metastatic status was classed as non-metastasis, intrathoracic metastasis, and extrathoracic metastasis. Intrathoracic metastasis included contralateral lung tumor nodule(s) and malignant pleural (or pericardial) tumor nodules (or effusion) (13), while extrathoracic metastasis recorded in the SEER database involved bone, brain, liver, and distant lymph nodes (LNs).

We also collected baseline covariates, including sex, race, histology, grade, primary tumor site, stage at diagnosis, surgery, radiation, chemotherapy, and the follow-up records.

Statistical analysis

The baseline characteristics of the patients were summarized using descriptive statistics and compared using the Chi-square test and Fisher's exact test. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were determined using univariate logistic regression analyses. Kaplan-Meier curves and the log-rank test were used to compare the lung cancer-specific survival (LCSS) and overall survival (OS) between groups. Hazard ratios

(HRs) and 95% CIs for LCSS and OS were calculated by multivariate Cox proportional hazard models using all confounders which are listed in *Table 1*. Two-sided P values <0.05 were considered significant. Statistical analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA) and plotted by GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics

A total of 200,362 lung cancer patients were ultimately included in this study, comprising 45,014 younger and 155,348 elderly patients. We further categorized young patients into four consecutive subgroups: <45 years (n=3,461), 45–49 years (n=5,697), 50–54 years (n=13,645), and 55–59 years (n=22,211). The detailed baseline characteristics of included patients by age groups are described in *Table 1*. The youngest group (<45 years) included more females than males (52% *vs.* 48%), while all other age groups included more males than females. Adenocarcinoma was the dominant histological subtype across each age group, particularly in the youngest group. The proportion of squamous cell carcinoma had a significant positive association with age (9.3%, 13.5%, 15.8%, 18.5%, and 24.8% in aged <45, 45–49, 50–54, 55–59, and ≥60 years, respectively). With aging, there was a decreasing trend in the proportion of advanced lung cancer patients, but the proportion of patients undergoing treatment, including surgery, radiation, and chemotherapy, progressively declined.

Metastatic patterns

Irrespective of the metastasis sites, extrathoracic metastasis was significantly more frequent in each younger group than in elderly patients, whereas intrathoracic metastasis showed contrasting trends. Among extrathoracic metastasis, bone was the most common organ of metastasis, with the highest occurrences in patients aged <45 years (24.4%). Similar tendencies were obtained in distant LN metastasis and multi-extrathoracic metastasis. The incidence rate of brain metastasis was highest in patients aged 50–54 years (20.1%), and the incidence rate of liver metastasis was highest in patients aged 55–59 years (13.7%) (*Figure 1*). Further univariate logistic regression analyses were concordant with these results. Compared

with elderly patients, younger patients tended to have less intrathoracic metastasis. The highest ORs of bone metastasis, and multi-extrathoracic metastasis were all observed in patients aged <45 years. Lung cancer patients aged 50–54 and 55–59 years were more likely to have brain metastasis (OR: 2.00, 95% CI: 1.91–2.09, P<0.001) and liver metastasis (OR: 1.22, 95% CI: 1.17–1.28, P<0.001), respectively (Figure S2).

Combination of metastases

All young groups had a higher proportion of patients with metastasis than elderly group (56.7% in <45 years, 59.4% in 45–49 years, 57.8% in 50–54 years, and 55.9% in 55–59 years *vs.* 50.2% in the elderly group) (Table S1). Among the cohort of metastatic patients, the majority of patients had extrathoracic metastasis (Table S1). Bone metastasis was the most common single-organ metastasis in the elderly group (18.1%), whereas brain metastasis was the leading single-organ metastasis in each younger group (16.6% in patients aged <45 years, 17.4% in 45–49 years, 18.8% in 50–54 years, 16.4% in 55–59 years). For multi-organ metastases, the bi-organ patterns (aged <45 years: 22.9%, aged 45–49 years: 20.0%, aged 50–54 years: 21.1%, aged 55–59 years: 21.7%, and aged ≥60 years: 16.9%) were significantly more common than tri-organ patterns (aged <45 years: 7.7%, aged 45–49 years: 6.9%, aged 50–54 years: 6.3%, aged 55–59 years: 6.6%, and aged ≥60 years: 4.4%) and tetra-organ patterns (aged <45 years: 1.0%, aged 45–49 years: 1.0%, aged 50–54 years: 0.8%, aged 55–59 years: 0.9%, and aged ≥60 years: 0.5%) (Figure S3).

Further analysis revealed that for bi-organ patterns, bone and brain metastases were the most common metastases in the youngest group (4.6%) and the second youngest group (3.7%). Bone and liver metastasis were more frequent in the other three groups (aged <45 years: 3.6%, aged 50–54 years: 3.7%, and aged 55–59 years: 4.2%). For tri-organ patterns, the bone, brain, and liver metastasis pattern was the most common combination in all age groups (aged <45 years: 2.3%, aged 45–49 years: 1.8%, aged 50–54 years: 1.8%, aged 55–59 years: 1.7%, and aged ≥60 years: 1.1%) (*Table 2*).

Patient survival across age groups

As age increased, there was a significant decrease in the median LCSS (mLCSS) of lung cancer patients (*Table 2, Figure 2A*). The youngest group had the best mLCSS of 25.0 months, with 1-, 2-, 3-, and 5-year LCSS rates

Table 1 Baseline characteristics of LC patients stratified by age

Characteristics	Younger LC patients (18–59 years)				Older LC patients (≥60 years) (n=155,348)	P value
	<45 years (n=3,461)	45–49 years (n=5,697)	50–54 years (n=13,645)	55–59 years (n=22,211)		
Sex, n (%)						<0.001
Male	1,662 (48.0)	2,857 (50.1)	7,062 (51.8)	12,231 (55.1)	81,560 (52.5)	
Female	1,799 (52.0)	2,840 (49.9)	6,583 (48.2)	9,980 (44.9)	73,788 (47.5)	
Race, n (%)						<0.001
White	2,513 (72.6)	4,217 (74.0)	10,258 (75.2)	16,873 (76.0)	126,920 (81.7)	
Black	479 (13.8)	953 (16.7)	2,430 (17.8)	3,749 (16.9)	16,222 (10.4)	
Other/unknown	469 (13.6)	527 (9.3)	957 (7.0)	1,589 (7.2)	12,206 (7.9)	
Histology, n (%)						<0.001
Adenocarcinoma	1,848 (53.4)	3,036 (53.3)	7,059 (51.7)	10,839 (48.8)	71,435 (46.0)	
Squamous cell carcinoma	321 (9.3)	768 (13.5)	2,155 (15.8)	4,100 (18.5)	38,559 (24.8)	
Large cell carcinoma	64 (1.8)	126 (2.2)	279 (2.0)	459 (2.1)	2,427 (1.6)	
SCLC	286 (8.3)	764 (13.4)	2,077 (15.2)	3,554 (16.0)	21,503 (13.8)	
Other NSCLC	942 (27.2)	1,003 (17.6)	2,075 (15.2)	3,259 (14.7)	21,424 (13.8)	
Grade, n (%)						<0.001
Unknown	1,677 (48.5)	2,943 (51.7)	7,092 (52.0)	11,300 (50.9)	76,505 (49.2)	
Grade I–II	961 (27.8)	1,131 (19.9)	2,626 (19.2)	4,337 (19.5)	35,318 (22.7)	
Grade III–IV	823 (23.8)	1,623 (28.5)	3,927 (28.8)	6,574 (29.6)	43,525 (28.0)	
Primary site, n (%)						<0.001
Main bronchus	227 (6.6)	389 (6.8)	792 (5.8)	1,317 (5.9)	6,810 (4.4)	
Upper lobe, lung	1,483 (42.8)	2,985 (52.4)	7,310 (53.6)	11,787 (53.1)	78,634 (50.6)	
Middle lobe, lung	217 (6.3)	237 (4.2)	645 (4.7)	1,010 (4.5)	6,590 (4.2)	
Lower lobe, lung	921 (26.6)	1,200 (21.1)	2,829 (20.7)	4,833 (21.8)	41,525 (26.7)	
Overlapping lesion of lung	59 (1.7)	105 (1.8)	153 (1.1)	269 (1.2)	1,601 (1.0)	
Unknown	554 (16.0)	781 (13.7)	1,916 (14.0)	2,995 (13.5)	20,188 (13.0)	
Surgery, n (%)						<0.001
No	2,340 (67.6)	4,388 (77.0)	10,609 (77.8)	17,253 (77.7)	121,840 (78.4)	
Yes	1,121 (32.4)	1,309 (23.0)	3,036 (22.2)	4,958 (22.3)	33,508 (21.6)	
Radiation, n (%)						<0.001
No	1,931 (55.8)	2,791 (49.0)	6,870 (50.3)	11,588 (52.2)	95,532 (61.5)	
Yes	1,530 (44.2)	2,906 (51.0)	6,775 (49.7)	10,623 (47.8)	59,816 (38.5)	
Chemotherapy, n (%)						<0.001
No	1,304 (37.7)	1,928 (33.8)	5,061 (37.1)	8,991 (40.5)	87,468 (56.3)	
Yes	2,157 (62.3)	3,769 (66.2)	8,584 (62.9)	13,220 (59.5)	67,880 (43.7)	

Table 1 (*continued*)

Table 1 (continued)

Characteristics	Younger LC patients (18–59 years)				Older LC patients (≥60 years) (n=155,348)	P value
	<45 years (n=3,461)	45–49 years (n=5,697)	50–54 years (n=13,645)	55–59 years (n=22,211)		
Stage, n (%)						<0.001
I–II	835 (24.1)	1,037 (18.2)	2,637 (19.3)	4,633 (20.9)	41,273 (26.6)	
III–IV	2,525 (73.0)	4,536 (79.6)	10,718 (78.5)	17,052 (76.8)	108,298 (69.7)	
Unknown	101 (2.9)	124 (2.2)	290 (2.1)	526 (2.4)	5,777 (3.7)	

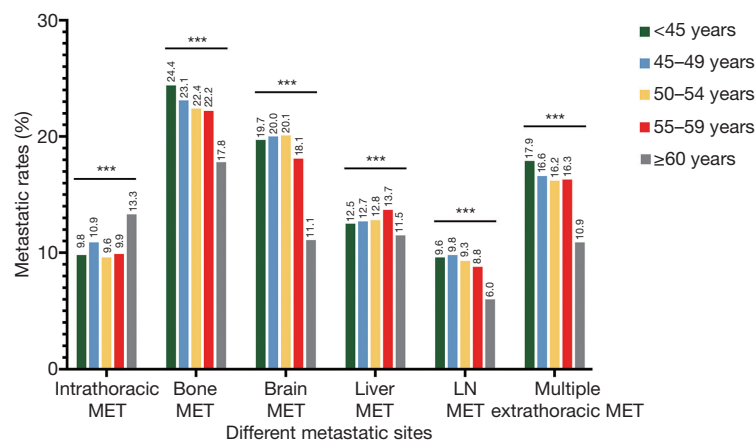LC, lung cancer; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

Figure 1 Comparison of the frequencies of different sites in different age groups. ***, P<0.001. MET, metastases; LN, lymph node.

of 64.7%, 50.0%, 43.1%, and 37.0%, respectively. The worst prognosis was observed in the oldest group, with a mLCSS of 12.0 months and 1-, 2-, 3-, and 5-year LCSS rates of 48.3%, 35.3%, 29.2%, and 23.2%, respectively (*Table 2*). Similar trends were observed in the corresponding OS (*Table 2*). Multivariate analysis demonstrated that ages younger than 60 years were independent prognostic factors for LCSS (aged <45 years: HR: 0.70, P<0.001; aged 45–49 years: HR: 0.87, P<0.001; aged 50–54 years: HR: 0.90, P<0.001; aged 55–59 years: HR: 0.93, P<0.001) (*Table 3*) and OS (aged <45 years: HR: 0.67, P<0.001; aged 45–49 years: HR: 0.84, P<0.001; aged 50–54 years: HR: 0.86, P<0.001; aged 55–59 years: HR: 0.91, P<0.001) (Table S2). We further assessed the LCSS disparity of lung cancer patients with and without metastasis stratified by age. Irrespective of metastasis patterns, significant differences were observed in the median survival for lung cancer patients across age groups (P<0.001) (*Figure 2B,C,D,E,F,G,H*).

Correlation of different metastasis patterns with survival

We compared the effects of metastasis patterns on the survival of lung cancer patients in each age group. Patients without metastasis had the best mLCSS, followed by patients with intrathoracic metastasis, then single-organ extrathoracic metastasis, and finally multi-organ extrathoracic metastasis (P<0.001), both in all patients (*Figure 3A*) and in each age subgroup (*Figure 3B,C,D,E,F*). In the Cox regression analysis of different extrathoracic sites, liver metastasis was most strongly associated with worse survival in all subgroups (aged <45 years: HR: 6.98, P<0.001; aged 45–49 years: HR: 5.64, P<0.001; aged 50–54 years: HR: 5.60, P<0.001; aged 55–59 years: HR: 5.83, P<0.001; aged ≥60 years: HR: 5.33, P<0.001) (Figure S4). The Kaplan-Meier survival curves for all patients by the metastatic organs indicated that there was a statistical difference (P<0.001) (Figure S5A). The same significant differences were found regardless of age

Table 2 Kaplan-Meier survival analysis in lung cancer patients across age groups

Survival status	<45 years (n=3,461)	45–49 years (n=5,697)	50–54 years (n=13,645)	55–59 years (n=22,211)	≥60 years (n=77,944)	P value
Median survival time (months)						
mLCSS	25.0 (22.7, 27.3)	15.0 (14.2, 15.8)	14.0 (13.5, 13.4)	13.0 (12.7, 13.4)	12.0 (11.9, 12.1)	<0.001
mOS	22.0 (20.2, 23.8)	13.0 (12.3, 13.7)	13.0 (12.6, 13.4)	12.0 (11.7, 12.3)	10.0 (9.9, 10.1)	<0.001
1-year (%)						
LCSS	64.7 (63.1, 66.3)	54.2 (52.8, 55.6)	52.9 (52.1, 53.7)	51.2 (50.6, 51.8)	48.3 (48.1, 48.5)	–
OS	62.9 (61.3, 64.5)	52.2 (50.8, 53.6)	50.7 (49.9, 51.5)	48.5 (47.9, 49.1)	44.5 (44.3, 44.7)	–
2-year (%)						
LCSS	50.0 (48.2, 51.8)	38.0 (36.6, 39.4)	37.2 (36.4, 38.0)	36.4 (35.8, 37.0)	35.3 (35.1, 35.5)	–
OS	47.6 (45.8, 49.4)	35.9 (34.5, 37.3)	34.8 (34.0, 35.6)	33.5 (32.9, 34.1)	30.9 (30.7, 31.1)	–
3-year (%)						
LCSS	43.1 (41.3, 44.9)	31.2 (29.8, 32.6)	30.5 (29.7, 31.3)	29.7 (29.1, 30.3)	29.2 (29.0, 29.4)	–
OS	40.5 (38.7, 42.3)	28.8 (27.6, 30.0)	27.8 (27.0, 28.6)	26.6 (26.0, 27.2)	24.2 (24.0, 24.4)	–
5-year (%)						
LCSS	37.0 (35.0, 39.0)	25.4 (24.0, 26.8)	24.8 (23.8, 25.8)	24.2 (23.4, 25.0)	23.2 (23.0, 23.4)	–
OS	33.8 (31.8, 35.8)	22.9 (21.5, 24.3)	21.8 (21.0, 22.6)	20.5 (19.9, 21.1)	17.4 (17.2, 17.6)	–

LCSS, lung cancer-specific survival; OS, overall survival; mLCSS, median LCSS; mOS, median OS.

(Figure S5B,C,D,E,F).

Discussion

In this large retrospective population-based study, we performed, for the first time, consecutive age group-stratified analysis to investigate the different metastatic patterns among patients with lung cancer between age groups. We demonstrated that compared with elderly lung cancer patients, young patients of all ages were more likely to have more extrathoracic metastasis, both in terms of site and number of extrathoracic metastatic organs.

These findings may be attributed to the following reasons. Firstly, both the relatively low screening attendance (14-17) and the asymptomatic nature at the early stages of lung cancer currently make early diagnosis considerably more difficult for young patients. Secondly, clinical misdiagnosis, according to the low incidence of lung cancer in young patients, may further delay the cancer diagnosis of this subset of patients (6). Finally, lung cancer with earlier disease onset may present a distinct disease entity with more aggressive disease biology (8,18). As such, Li *et al.* recommend that age 45 may be the optimal screening cut-

off for initiating lung cancer screening (19), with the aim of earlier detection and treatment of young lung cancer patients.

In terms of the relationship between metastasis organs and different ages, previous studies have suggested that as two of the major extrathoracic lesions, bone and brain metastasis tend to occur in patients less than 60 years compared to patients greater than 60 years (20,21). Consistent with these findings, based on age-stratified analysis, we further revealed that bone metastasis was the most common lesion in patients of all ages, particularly in patients younger than 45 years, while brain metastasis was most commonly observed in patients aged 50–54 years. Since small-cell lung cancer (SCLC) tends to have liver metastasis (22), the highest incidence of liver metastasis in patients aged 55–59 years may be ascribed to the larger proportion of SCLC in this age group. In lung cancer patients across ages, single-organ metastasis was far more frequent than bi-organ, tri-organ, and tetra-organ metastasis. Similar patterns were also reported in pancreatic cancer (23), breast cancer (24), and extrahepatic bile duct cancer (25).

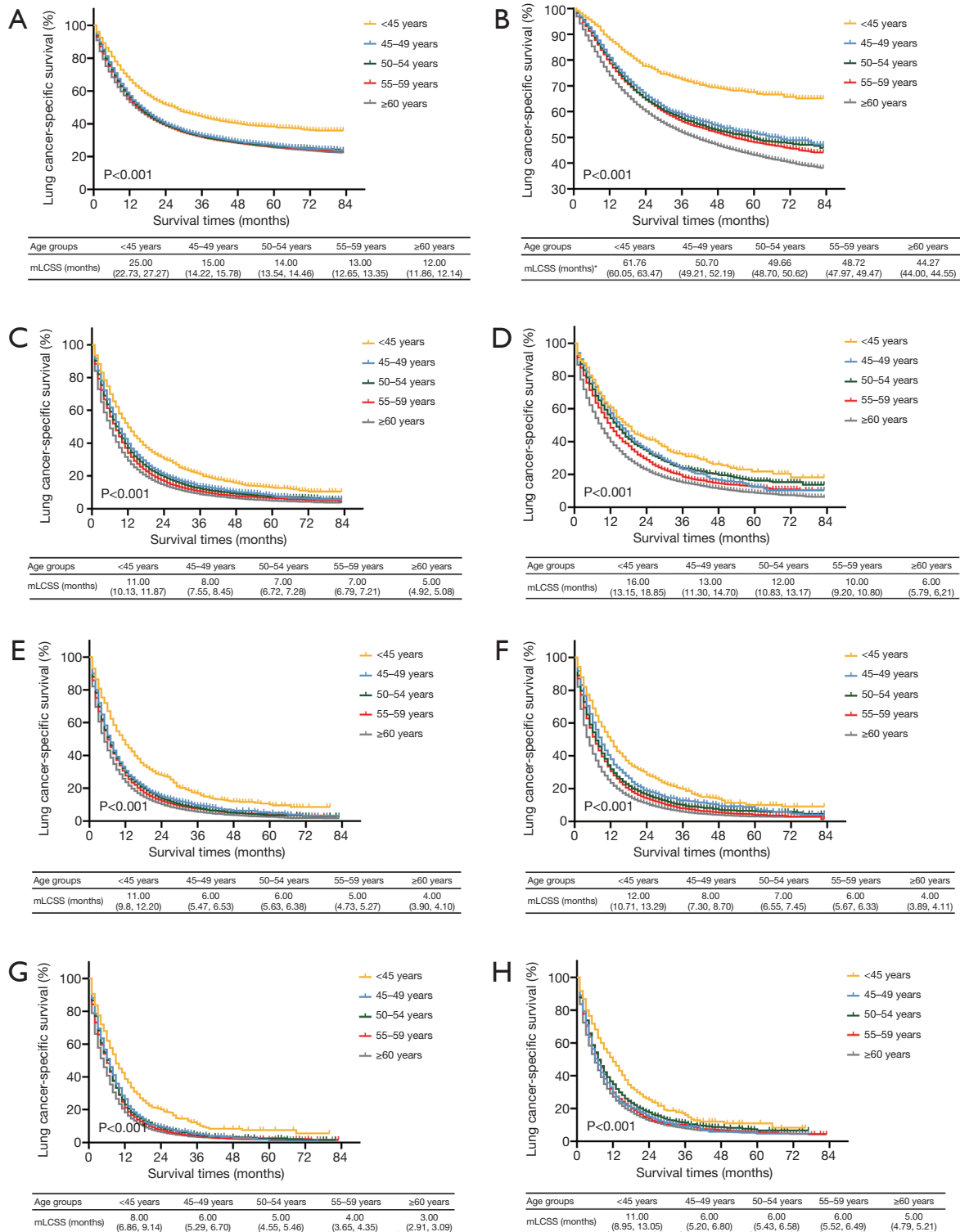In this study, younger age was associated with roughly

Figure 2 Comparison of Kaplan-Meier LCSS curves for patients across age groups. Kaplan-Meier plots for (A) all lung cancer patients, (B) patients without metastasis, (C) patients with metastasis, (D) patients with intrathoracic metastasis, (E) patients with bone metastasis, (F) patients with brain metastasis, (G) patients with liver metastasis, (H) patients with distant LNs metastasis. *, the median survival time of patients aged <45 years was not reached. LCSS, lung cancer-specific survival; mLCSS, median LCSS; LN, lymph node.

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Table 3 Multivariate analysis of LCSS of lung cancer patients

Characteristics	HR	95% CIs	P value
Age			<0.001
≥60 years	Ref.		
55–59 years	0.93	0.92–0.95	<0.001
50–54 years	0.90	0.88–0.91	<0.001
45–49 years	0.87	0.84–0.90	<0.001
<45 years	0.70	0.67–0.73	<0.001
Sex			<0.001
Male	Ref.		
Female	0.82	0.82–0.83	<0.001
Race			<0.001
White	Ref.		
Black	0.97	0.95–0.99	<0.001
Other/unknown	0.79	0.77–0.80	<0.001
Histology			<0.001
Adenocarcinoma	Ref.		
Squamous cell carcinoma	1.21	1.20–1.23	<0.001
Large cell carcinoma	1.35	1.30–1.41	<0.001
SCLC	1.43	1.40–1.45	<0.001
Other NSCLC	1.15	1.13–1.17	<0.001
Grade			<0.001
Unknown	Ref.		
Grade I–II	0.76	0.75–0.77	<0.001
Grade III–IV	1.12	1.11–1.14	<0.001
Primary site			<0.001
Main bronchus	Ref.		
Upper lobe, lung	0.81	0.79–0.83	<0.001
Middle lobe, lung	0.76	0.73–0.78	<0.001
Lower lobe, lung	0.83	0.81–0.85	<0.001
Overlapping lesion of lung	1.06	1.00–1.12	0.046
Unknown	0.94	0.92–0.97	<0.001
Surgery			<0.001
No	Ref.		
Yes	0.22	0.21–0.22	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	HR	95% CIs	P value
Radiation			<0.001
No	Ref.		
Yes	0.83	0.82–0.84	<0.001
Chemotherapy			<0.001
No	Ref.		
Yes	0.53	0.52–0.53	<0.001
Metastasis status			<0.001
No	Ref.		
Yes	2.70	2.67–2.74	<0.001

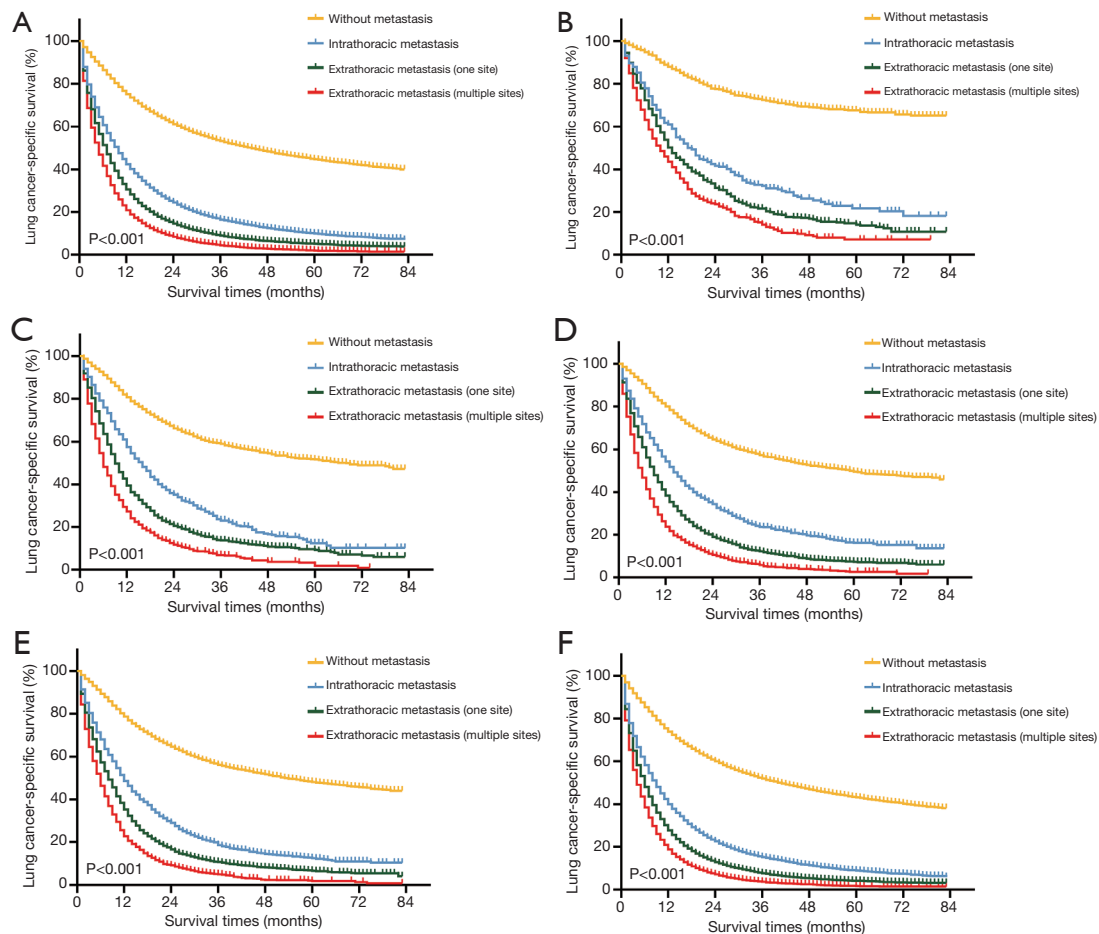LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

Figure 3 Kaplan-Meier LCSS curves of lung cancer patients at different ages stratified by different metastasis patterns. (A) All lung cancer patients; (B) patients aged <45 years; (C) patients aged 45–49 years; (D) patients aged 50–54 years; (E) patients aged 55–59 years; (F) patients ≥60 years. LCSS, lung cancer-specific survival.

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increasing trends of LCSS and OS, regardless of the metastasis patterns. Although young patients of all ages presented with extensive disease more often, multivariate analysis confirmed that younger ages were significant positive predictors of LCSS and OS. This finding could be in large part due to the different percentages of lung cancer patients who received treatments across age groups. Sacher *et al.* emphasized that the younger the age at diagnosis, the more patients harboring a targetable genotype (8). Therefore, besides surgery, radiation, and chemotherapy, the emergence of targeted therapy may widen the survival gap between age groups. Further survival analyses stratified by age revealed that in all age groups, the most significant survival advantage was in non-metastatic lung cancer patients, worse survival was in intrathoracic metastasis and single-organ extrathoracic metastasis, and the poorest survival was in multi-organ extrathoracic metastasis. In view of the higher incidence of multi-organ extrathoracic metastasis in young patients, regular imaging of distant organs including bone, brain, and liver among others requires closer attention throughout the follow-up period.

Several limitations should be mentioned. Firstly, although population-based data were used, this present study is a retrospective analysis. Given that detailed metastasis statuses were collected in 2010 in the SEER database, we used 2010 as the starting year to enroll patients. Secondly, for metastatic lesions, only intrathoracic, bone, brain, liver, and distant LN metastasis are recorded in the SEER database. The current results confirmed that metastasis which occurred in other organs accounted for approximately 7.3% to 8.1% in the metastasis for lung cancer patients of different ages, such as the adrenal gland (26). Finally, the exact numbers of metastatic lesions in different organs were not available in the SEER database. Therefore, we could not further categorize patients with single-organ metastasis into M1b (single lesion) and M1c (multiple lesions) on the basis of the eighth edition of TNM classification (11).

In conclusion, we found that compared to elderly patients, young patients across all ages were at increased risk of extrathoracic metastasis, especially multi-organ metastasis, but manifested a reduced risk of lung cancer-related death. Young lung cancer patients of different ages exhibited different clinicopathological features and metastatic patterns, together with survival disparities. Considering the more favorable outcome and longer potential years of life saved, more meticulous long-term monitoring of potential metastasis organs are required in young lung cancer patients.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-2849

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-2849). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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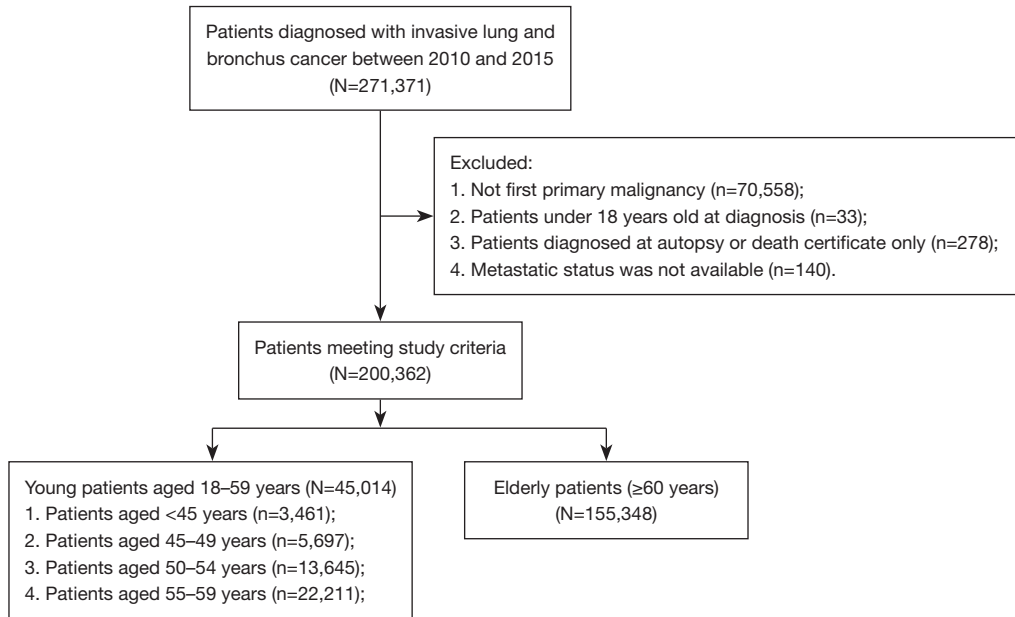
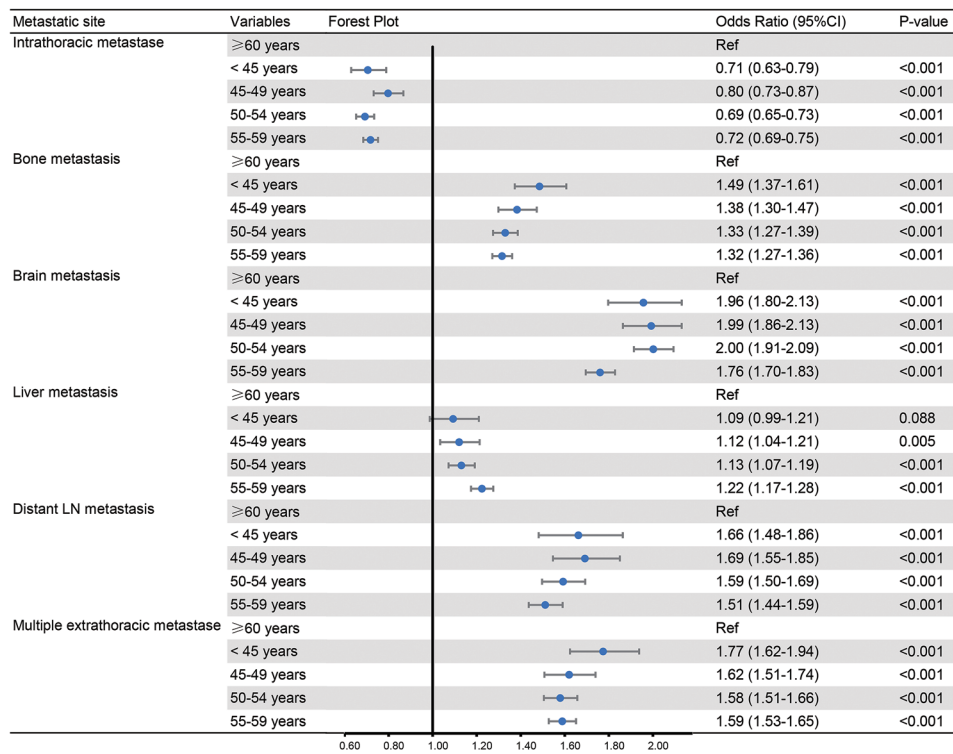**Figure S1** Flowchart of the patient selection process in this study.

Figure S2 Multivariate regression analyses of the independent effects of age on different metastasis sites. CI, confidence interval.
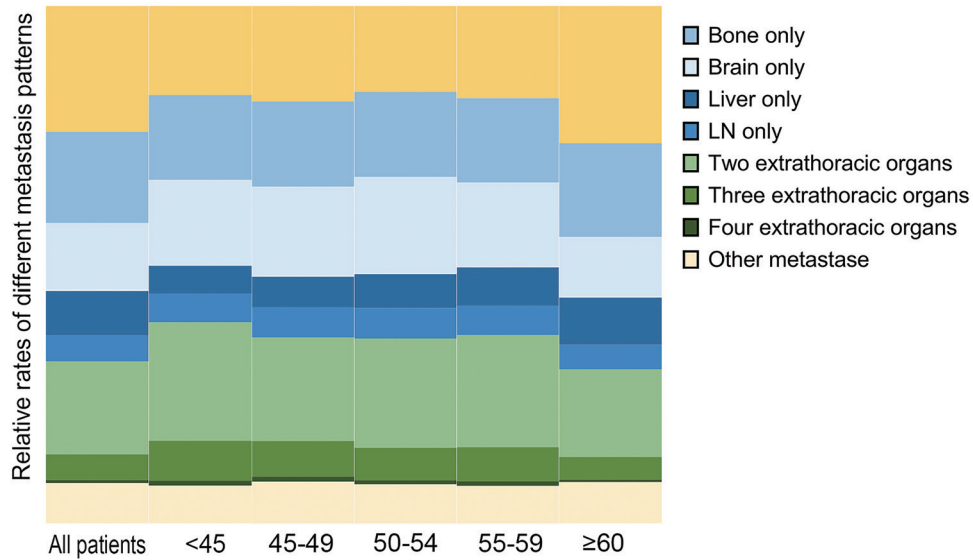
Figure S3 Relative rates of intrathoracic metastasis and single- and multi-extrathoracic organs in different age groups. LN, lymph node.
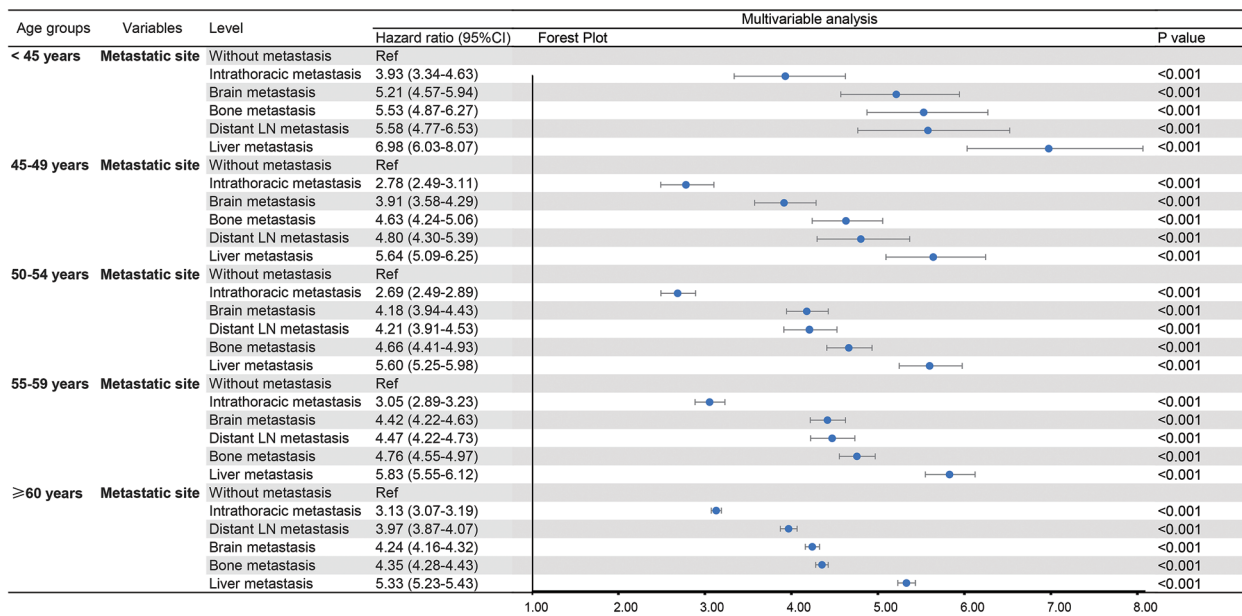

Figure S4 Multivariate analyses of the impact of age on LCSS for lung cancer patients. LCSS, lung cancer-specific survival; CI, confidence interval.
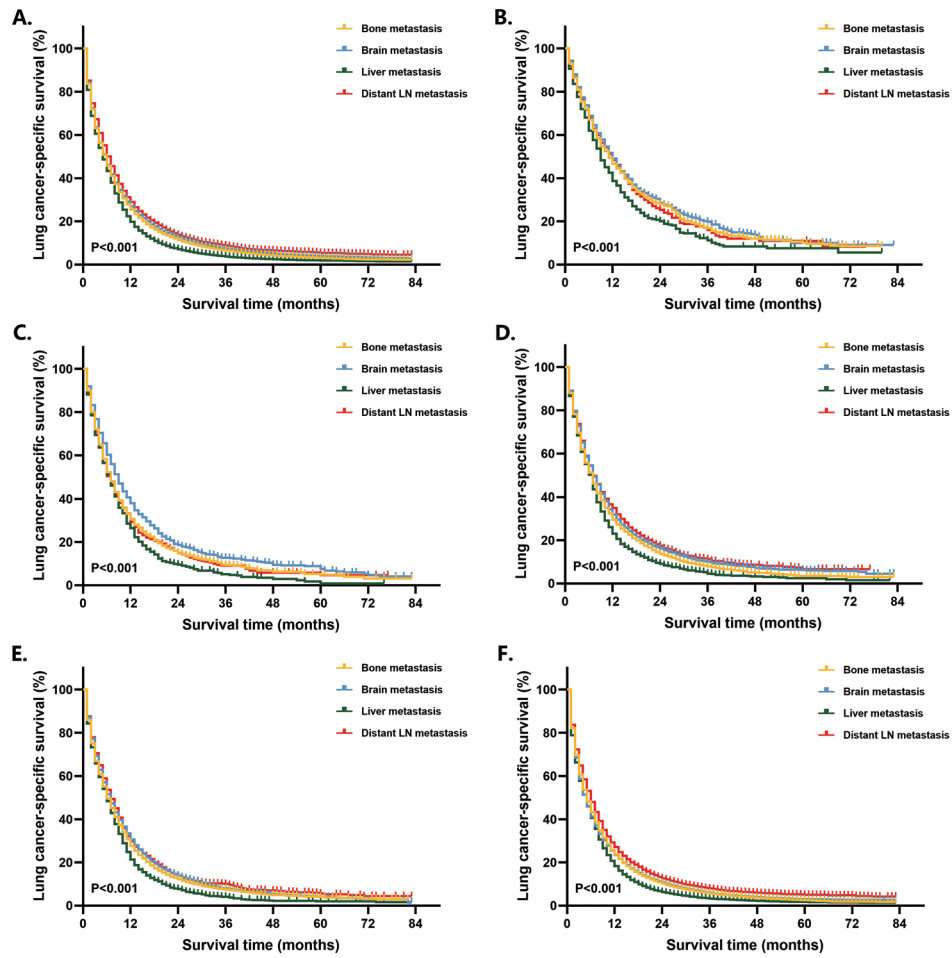
Figure S5 Kaplan-Meier LCSS curves for lung cancer patients at different ages stratified by extrathoracic metastasis organs. (A) All lung cancer patients; (B) patients aged <45 years; (C) patients aged 45–49 years; (D) patients aged 50–54 years; (E) patients aged 55–59 years; (F) patients ≥60 years. LCSS, lung cancer-specific survival; LN, lymph node.

Table S1 Relative rates of different metastatic patterns across age groups

Metastasis site	<45 years (n=3,461)	45–49 years (n=5,697)	50–54 years (n=13,645)	55–59 years (n=22,211)	≥60 years (n=155,348)	P value
Metastasis	1,961 (56.7)	3,384 (59.4)	7,883 (57.8)	12,416 (55.9)	77,944 (50.2)	<0.001
Intrathoracic metastasis	338 (9.8)	621 (10.9)	1,311 (9.6)	2,205 (9.9)	20,671 (13.3)	<0.001
Extrathoracic metastasis	1,481 (42.8)	2,487 (43.7)	5,973 (43.8)	9,288 (41.8)	51,045 (32.9)	<0.001
One site	862 (24.9)	1,542 (27.1)	3,757 (27.5)	5,663 (25.5)	34,055 (21.9)	<0.001
Bone only	322 (9.3)	559 (9.8)	1,296 (9.5)	2,021 (9.1)	14,075 (9.1)	0.167
Brain only	326 (9.4)	589 (10.3)	1,483 (10.9)	2,034 (9.2)	9,138 (5.9)	<0.001
Liver only	104 (3.0)	195 (3.4)	516 (3.8)	903 (4.1)	7,067 (4.5)	<0.001
Distant LN only	110 (3.2)	199 (3.5)	462 (3.4)	705 (3.2)	3,775 (2.4)	<0.001
Two sites	449 (13.0)	676 (11.9)	1,662 (12.2)	2,693 (12.1)	13,166 (8.5)	<0.001
Bone + brain	160 (4.6)	210 (3.7)	492 (3.6)	757 (3.4)	3,181 (2.0)	<0.001
Bone + liver	124 (3.6)	202 (3.5)	511 (3.7)	937 (4.2)	5,245 (3.4)	<0.001
Bone + distant LN	73 (2.1)	84 (1.5)	232 (1.7)	325 (1.5)	1,577 (1.0)	<0.001
Brain + liver	33 (1.0)	73 (1.3)	173 (1.3)	287 (1.3)	1,323 (0.9)	<0.001
Brain + distant LN	36 (1.0)	68 (1.2)	159 (1.2)	225 (1.0)	910 (0.6)	<0.001
Liver + distant LN	23 (0.7)	39 (0.7)	95 (0.7)	162 (0.7)	930 (0.6)	0.127
Three sites	151 (4.4)	235 (4.1)	493 (3.6)	821 (3.7)	3,444 (2.2)	<0.001
Bone + brain + liver	79 (2.3)	102 (1.8)	239 (1.8)	388 (1.7)	1,661 (1.1)	<0.001
Bone + brain + distant LN	23 (0.7)	53 (0.9)	99 (0.7)	170 (0.8)	497 (0.3)	<0.001
Bone + liver + distant LN	43 (1.2)	70 (1.2)	123 (0.9)	219 (1.0)	1,066 (0.7)	<0.001
Brain + liver + distant LN	6 (0.2)	10 (0.2)	32 (0.2)	44 (0.2)	220 (0.1)	0.037
Four sites	19 (0.5)	34 (0.6)	61 (0.4)	111 (0.5)	380 (0.2)	<0.001

LN, lymph node.

Table S2 Multivariate analysis of OS of lung cancer patients

Characteristics	HR	95% CIs	P value
Age			<0.001
≥60 years	Ref.		
55–59 years	0.91	0.89–0.92	<0.001
50–54 years	0.86	0.85–0.88	<0.001
45–49 years	0.84	0.81–0.86	<0.001
<45 years	0.67	0.64–0.70	<0.001
Sex			
Male	Ref.		
Female	0.81	0.80–0.82	<0.001
Race			
White	Ref.		
Black	0.98	0.97–1.00	0.033
Other/unknown	0.79	0.77–0.80	<0.001
Histology			<0.001
Adenocarcinoma	Ref.		
Squamous cell carcinoma	1.24	1.22–1.26	<0.001
Large cell carcinoma	1.35	1.29–1.40	<0.001
SCLC	1.42	1.40–1.45	<0.001
Other NSCLC	1.14	1.12–1.16	<0.001
Grade			<0.001
Unknown	Ref.		
Grade I–II	0.78	0.77–0.79	<0.001
Grade III–IV	1.11	1.10–1.13	<0.001
Primary site			<0.001
Main bronchus	Ref.		
Upper lobe, lung	0.82	0.80–0.84	<0.001
Middle lobe, lung	0.77	0.74–0.79	<0.001
Lower lobe, lung	0.84	0.82–0.86	<0.001
Overlapping lesion of lung	1.05	0.99–1.10	0.082
Unknown	0.96	0.94–0.99	0.002
Surgery			<0.001
No	Ref.		
Yes	0.24	0.24–0.25	<0.001
Radiation			<0.001
No	Ref.		
Yes	0.82	0.81–0.82	<0.001
Chemotherapy			<0.001
No	Ref.		
Yes	0.51	0.51–0.52	<0.001
Metastasis status			<0.001
No	Ref		
Yes	2.46	2.43–2.49	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.