Clinical associations and prognostic value of site-specific metastases in non-small cell lung cancer: A population-based study

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Abstract. The prognosis of non-small cell lung cancer (NSCLC) is poor, particularly for patients with metastatic disease. Numerous efforts have been made to improve the prognosis of these patients; however, only a small number of studies have explored the occurrence rate and prognostic value of different patterns of distant metastasis (DM) in NSCLC systematically. To investigate these, information from patients diagnosed with NSCLC between 2010 and 2014 was collected from the Surveillance, Epidemiology and End Results database. Survival rate comparisons were performed using Kaplan-Meier analysis and log-rank tests. A Cox proportional hazard model was established to determine factors associated with improved overall survival (OS) and cancer-specific survival (CSS). The present study revealed that the most common site of single metastasis occurrence was bone, and the least common was the liver for NSCLC. As for multi-site metastases, the most common two-site metastasis involved bone and lung, and the most common three-site metastasis involved bone, liver and lung. As for NSCLC subtypes, large cell carcinoma (LCC) exhibited more specific metastatic features. The most common single metastatic site was the brain for patients with LCC, and the most common two-site metastatic combination was bone and liver. Patients with isolated liver metastasis exhibited the worst OS and CSS among patients with single metastasis. Furthermore, for patients with multi-site metastases, metastases involving the liver were associated with the worst OS and CSS among various combinations. To the best of our knowledge, the present study is the first to investigate the occurrence rate and prognostic value of different metastatic patterns of site-specific DM for NSCLC using a large population-based dataset. The findings of the present study may have vital implications for classifying patients with advanced NSCLC, thus laying a foundation for individualized precise treatment.

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Introduction

Lung cancer is a globally widespread disease and a leading cause of cancer-associated mortality, with ~1.6 million cases of lung cancer-associated mortality per year (1). Non-small cell lung cancer (NSCLC) accounts for ~85% of all primary cases, the majority of which present with advanced and unresectable disease at diagnosis, which is associated with a poor prognosis (2,3). In the past few years, targeted therapy and immunotherapy have led to promising results in patients with advanced NSCLC (4). However, the presence of distant metastasis (DM) remains a cause of high mortality in the majority of patients with NSCLC (5,6).

Out of all newly diagnosed NSCLC cases, ~40% present with metastatic disease at diagnosis (7), and the majority of these patients have a low 5-year survival rate (8). A previous study reported that patients with NSCLC with multi-site metastases exhibit worse outcomes than patients with a single metastatic site (9). Additionally, some studies have observed poor survival in patients with liver metastasis (10,11). However, for the majority of these studies, the main limitation was that the sample size was too small.

The most frequent metastatic site of NSCLC is bone, followed by the lung, brain, liver and adrenal glands (5). Sex, age at diagnosis and histological subtypes can effectively influence the metastasis of NSCLC (6). However, the clinical associations and prognostic values of site-specific metastases have not been well studied. Only a limited number of studies have been conducted to investigate the various metastatic patterns, and their occurrence rate and prognosis in NSCLC and its subtypes (5,6).

Therefore, studying the metastatic patterns is crucial for the management and treatment of clinical NSCLC cases. In the present study, which was based on the Surveillance,

Epidemiology and End Results (SEER) database, different metastatic patterns, and their incidence rates and influence on survival of patients with NSCLC were analyzed. The aim of the present study was to assess the occurrence patterns and prognostic value of site-specific DM for NSCLC.

Patients and methods

Patient selection. Specific data were collected from the SEER-18 registry of the US National Cancer Institute (12). The clinical information of ~34.6% of patients with cancer within the US are precisely collected and organized in the SEER database. The diagnosis time of selected patients was limited to the period between 2010 and 2014, since information regarding metastatic sites was not available prior to that period. The eligible patients were selected using the SEER*Stat v8.3.5 software (https://seer.cancer.gov).

To identify patients with NSCLC, cases with a primary site of 'lung and bronchus' were selected. Diagnosis was confirmed microscopically and only one primary tumor was identified. According to histological type, NSCLC cases were classified as: Adenocarcinoma (AD; histological codes 8140, 8230, 8250-8255, 8260, 8310, 8333, 8470, 8480, 8481, 8490 and 8550), squamous cell carcinoma (SQCC; histological codes 8052, 8070-8073, 8083 and 8084), adenosquamous carcinoma (ASC; histological code 8560), large cell carcinoma (LCC; histological codes 8012-8014, 8082, 8123 and 8310) and others (histological codes 8022, 8031, 8032, 8200, 8240, 8249, 8430, 8562, 8972 and 8980). All patients without information regarding cause of mortality and survival months were excluded. Additionally, patients with 'blanks' for metastatic site (n=6,952) and unknown American Joint Committee on Cancer stage T/N (n=9) were excluded (13).

Statistical analysis. In the present study, patients with metastatic NSCLC were sorted according to metastatic site, including bone, brain, liver and lung. Overall survival (OS; defined as the time from diagnosis to mortality due to any reason) and cancer-specific survival (CSS; defined as the time from diagnosis to NSCLC-associated mortality) were set as primary endpoints of the present study. Comparison of the associations between clinicopathological characteristics and different metastatic sites was achieved using a χ^2 test. Curve plotting and analysis of survival were accomplished by the Kaplan-Meier method and log-rank tests, respectively. Multivariate analyses and hazard ratios with corresponding 95% confidence interval (CI) on behalf of the prognostic factors affecting OS and CSS were carried out using a Cox proportional hazard model. All tests were performed using SPSS Statistics v21.0 software (IBM Corp., Armonk, NY, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. From the SEER database, 108,464 patients diagnosed with NSCLC between 2010 and 2014 were identified. Details of the selection procedure are shown in Fig. 1. Within the identified group, 51,788 patients (47.7%) exhibited DM at diagnosis. Table I summarizes the clinical characteristics of patients with and without DM at diagnosis. Patients with the characteristics of male, African descent, higher clinical T stage, positive nodes or adenocarcinoma histological type were more likely to exhibit metastasis at diagnosis (all P<0.001). Patients with metastatic disease at diagnosis were less likely to undergo surgery and more likely to undergo chemotherapy and/or radiotherapy (all P<0.001). For the whole cohort, mean and median follow-up were 17.2 and 12 months, respectively. The mean follow-up for patients with and without metastatic disease was 8.7 and 21.8 months, respectively.

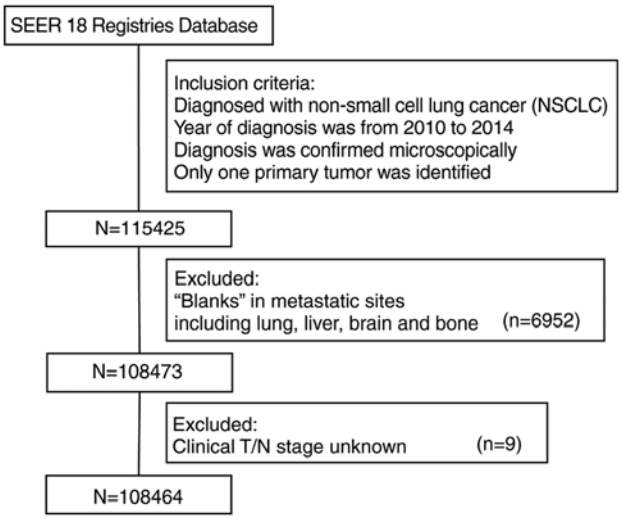

Figure 1. Flowchart of patient selection based on the SEER database. NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology and End Results.

Metastatic patterns. At the time of diagnosis, stage IV cases accounted for 47.75% (51,788/108,464) of all patients with NSCLC. The database only included information for liver, lung, bone and brain metastasis. Patients who exhibited metastasis to any of the four sites accounted for 74.84% (38,756/51,788) of stage IV cases. The clinical characteristics of all included patients with different metastatic sites are listed in Table II. For patients with and without bone metastasis, the distribution of age (P=0.002) and ethnicity (P<0.001) were significantly different. The same phenomenon was observed for patients with brain and lung metastases (all P<0.01) but not for patients with liver metastasis (P>0.05). In addition, the distribution of sex, clinical T/N stage, tumor grade and histology were significantly associated with metastasis at these four metastatic sites (all P<0.001).

Frequency differences among different metastatic patterns. Fig. 2 shows the proportion of different metastatic combination patterns for the included patients with site-specific metastasis. A total of 8,654 (22.3%), 7,699 (19.9%), 6,109 (15.8%) and 2,264 (5.8%) patients presented with isolated bone, lung, brain and liver metastasis at the time of diagnosis, respectively (Fig. 2A). Among patients with two metastatic sites, bone and lung metastasis was the most common combination, and brain and liver metastasis was the least common combination, accounting for 7.4 and 1.4% of all metastatic cases, respectively

Table I. Patient characteristics, stratified by presence of metastases at time of diagnosis.

Characteristic	No metastases at diagnosis, n=56,676 (%)	Metastases at diagnosis, n=51,788 (%)	P-value
Age (years)			<0.001
<50	2,419 (4.27)	3,020 (5.83)	
≥50	54,257 (95.73)	48,768 (94.17)	
Sex			<0.001
Male	27,863 (49.16)	28,364 (54.77)	
Female	28,813 (50.84)	23,424 (45.23)	
Ethnicity			<0.001
Caucasian	46,098 (81.34)	39,986 (77.21)	
African descent	6,441 (11.36)	6,964 (13.45)	
Others	4,137 (7.30)	4,838 (9.34)	
T stage			<0.001
T0, T1, T2	37,435 (66.05)	17,341 (33.48)	
T3, T4	16,585 (29.27)	28,142 (54.34)	
TX	2,656 (4.69)	6,305 (12.17)	
N stage			<0.001
N0	32,690 (57.68)	12,543 (24.22)	
N positive	23,047 (40.67)	36,311 (70.12)	
NX	939 (1.66)	2,934 (5.67)	
Tumor grade			<0.001
I	6,385 (11.27)	1,379 (2.66)	
II	16,862 (29.75)	6,561 (12.67)	
III	16,913 (29.84)	13,090 (25.28)	
IV	597 (1.05)	545 (1.05)	
Unknown	15,919 (28.09)	30,213 (58.34)	
Histology			<0.001
AD	30,592 (53.98)	36,942 (71.33)	
SQCC	21,399 (37.76)	12,150 (23.46)	
ASC	1,110 (1.96)	836 (1.61)	
LCC	1,158 (2.04)	1,390 (2.68)	
Others	2,417 (4.26)	470 (0.91)	
Chemotherapy			<0.001
Yes	21,141 (37.30)	27,966 (54.00)	
No/Unknown	35,535 (62.70)	23,822 (46.00)	
Radiotherapy			<0.001
Yes	21,167 (37.35)	22,658 (43.75)	
No/Unknown	35,509 (62.65)	29,130 (56.25)	
Surgery			<0.001
Yes	27,789 (49.03)	1,923 (3.71)	
No/Unknown	28,887 (50.97)	49,865 (96.28)	

AD, adenocarcinoma; ASC, adenosquamous carcinoma; LCC, large cell carcinoma; N, node; SQCC, squamous cell carcinoma; T, tumor.

(Fig. 2B). The frequency of three-site metastasis combination was low. The most common three-site metastasis combination comprised bone, liver and lung, accounting for 3.1% of all metastatic cases (Fig. 2C). Four-site metastasis was relatively rare, and was diagnosed in 652 (1.7%) patients (Fig. 2D). Notably, patients with NSCLC who presented with bone metastasis were more likely to exhibit multi-site metastases.

Metastatic features based on different NSCLC subtypes. Subsequently, the metastatic characteristics of patients with different NSCLC subtypes were investigated (Fig. 3). The results revealed that the most common single metastatic site was bone for patients with AD and ASC, accounting for 36.13 and 42.08%, respectively. For patients with SQCC and other subtypes, single lung metastasis was most common, accounting for 37.68 and

Table II. Clinical features and metastatic sites.

	Liver metastasis (%)			Brain metastasis (%)			Bone metastasis (%)			Lung metastasis (%)		
Characteristic	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value
Age (years)			0.246			<0.001			0.002			0.003
<50	1,859 (78.51)	509 (21.49)		1,331 (56.21)	1,037 (43.79)		1,107 (46.75)	1,261 (53.25)		1,451 (61.28)	917 (38.72)	
≥50	28,193 (77.48)	8,195 (22.52)		24,341 (66.89)	12,047 (33.11)		18,180 (49.96)	18,208 (50.04)		21,161 (58.15)	15,227 (41.85)	
Sex			<0.001			<0.001			<0.001			<0.001
Male	16,347 (76.84)	4,926 (23.16)		14,548 (68.39)	6,725 (31.61)		10,125 (47.60)	11,148 (52.40)		12,612 (59.29)	8,661 (40.71)	
Female	13,705 (78.39)	3,778 (21.61)		11,124 (63.63)	6,359 (36.37)		9,162 (52.41)	8,321 (47.59)		10,000 (57.20)	7,483 (42.80)	
Ethnicity			0.321			<0.001			<0.001			<0.001
Caucasian	23,204 (77.37)	6,787 (22.63)		19,982 (66.63)	10,009 (33.37)		14,902 (49.69)	15,089 (50.31)		17,816 (59.40)	12,175 (40.60)	
African descent	3,979 (78.07)	1,118 (21.93)		3,375 (66.22)	1,722 (33.78)		2,668 (52.34)	2,429 (47.66)		2,902 (56.94)	2,195 (43.06)	
Others	2,869 (78.22)	799 (21.78)		2,315 (63.11)	1,353 (36.89)		1,717 (46.81)	1,951 (53.19)		1,894 (51.64)	1,774 (48.36)	
T stage			<0.001			<0.001			<0.001			<0.001
T0, T1, T2	9,738 (78.12)	2,727 (21.88)		7,568 (60.71)	4,897 (39.29)		5,829 (46.76)	6,636 (53.24)		9,981 (80.07)	2,484 (19.93)	
T3, T4	17,166 (77.94)	4,858 (22.06)		15,209 (69.06)	6,815 (30.94)		11,546 (52.42)	10,478 (47.58)		9,482 (43.05)	12,542 (56.95)	
TX	3,148 (73.78)	1,119 (26.22)		2,895 (67.85)	1,372 (32.15)		1,912 (44.81)	2,355 (55.19)		3,149 (73.80)	1,118 (26.20)	
N stage			<0.001			<0.001			<0.001			<0.001
N0	7,283 (82.31)	1,565 (17.69)		5,982 (67.61)	2,866 (32.39)		4,880 (55.15)	3,968 (44.85)		5,451 (61.61)	3,397 (38.39)	
N positive	21,210 (76.23)	6,612 (23.77)		18,197 (65.41)	9,625 (34.59)		13,402 (48.17)	14,420 (51.83)		15,881 (57.08)	11,941 (42.92)	
NX	1,559 (74.74)	527 (25.26)		1,493 (71.57)	593 (28.43)		1,005 (48.18)	1,081 (51.82)		1,280 (61.36)	806 (38.64)	
Tumor grade			<0.001			<0.001			<0.001			<0.001
I	918 (85.71)	153 (14.29)		828 (77.31)	243 (22.69)		678 (63.31)	393 (36.69)		408 (38.10)	663 (61.90)	
II	4,064 (83.86)	782 (16.14)		3,294 (67.97)	1,552 (32.03)		2,573 (53.10)	2,273 (46.90)		2,631 (54.29)	2,215 (45.71)	
III	7,727 (78.04)	2,174 (21.96)		6,284 (63.47)	3,617 (36.53)		5,331 (53.84)	4,570 (46.16)		5,852 (59.11)	4,049 (40.89)	
IV	312 (79.59)	80 (20.41)		238 (60.71)	154 (39.29)		195 (49.74)	197 (50.26)		252 (64.29)	140 (35.71)	
Unknown	17,031 (75.54)	5,515 (24.46)		15,028 (66.65)	7,518 (33.35)		10,510 (46.62)	12,036 (53.38)		13,469 (59.74)	9,077 (40.26)	
Histology			<0.001			<0.001			<0.001			<0.001
AD	22,149 (78.80)	5,959 (21.20)		17,754 (63.16)	10,354 (36.84)		13,451 (47.85)	14,657 (52.15)		16,471 (58.60)	11,637 (41.40)	
SQCC	6,449 (75.04)	2,145 (24.96)		6,617 (77.00)	1,977 (23.00)		4,736 (55.11)	3,858 (44.89)		4,815 (56.03)	3,779 (43.97)	
ASC	494 (77.67)	142 (22.33)		414 (65.09)	222 (34.91)		270 (42.45)	366 (57.55)		400 (62.89)	236 (37.11)	
LCC	709 (66.08)	364 (33.92)		623 (58.06)	450 (41.94)		618 (57.60)	455 (42.40)		749 (69.80)	324 (30.20)	
Others	251 (72.75)	94 (27.25)		264 (76.52)	81 (23.48)		212 (61.45)	133 (38.55)		177 (51.30)	168 (48.70)	

AD, adenocarcinoma; ASC, adenosquamous carcinoma; LCC, large cell carcinoma; N, node; SQCC, squamous cell carcinoma; T, tumor.

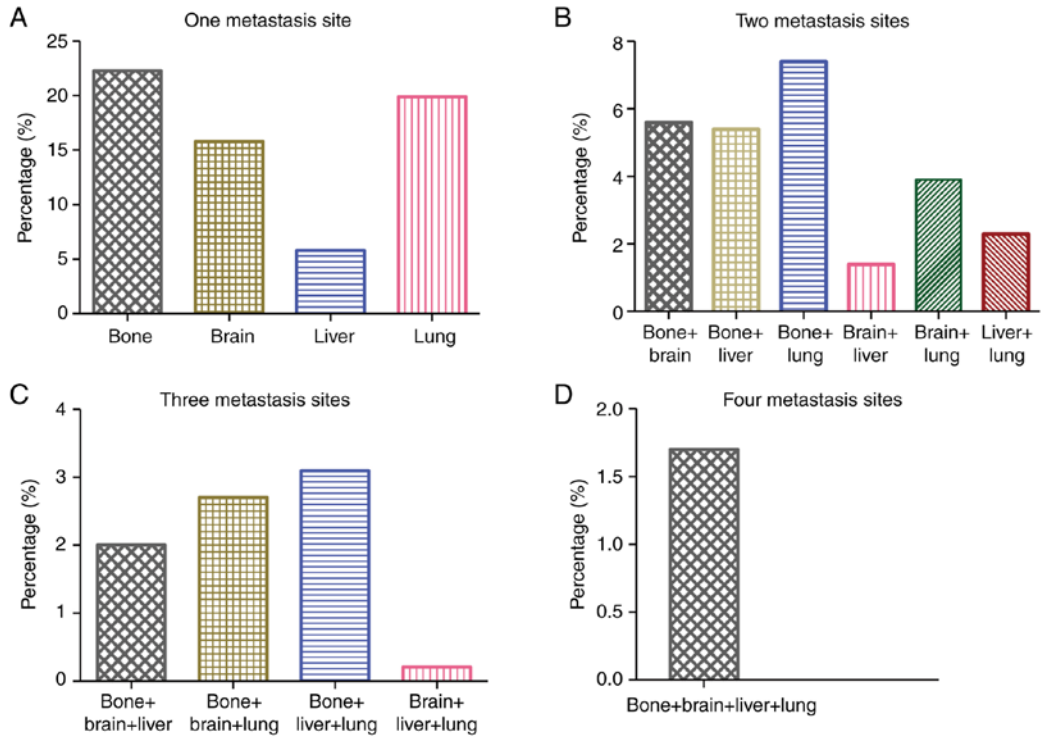

Figure 2. Different metastatic patterns of patients with non-small cell lung cancer. Percentages of patients with observed metastasis at (A) one metastatic site, (B) two metastatic sites, (C) three metastatic sites and (D) four metastatic sites for different combinations of bone, brain, liver and lung metastatic sites.

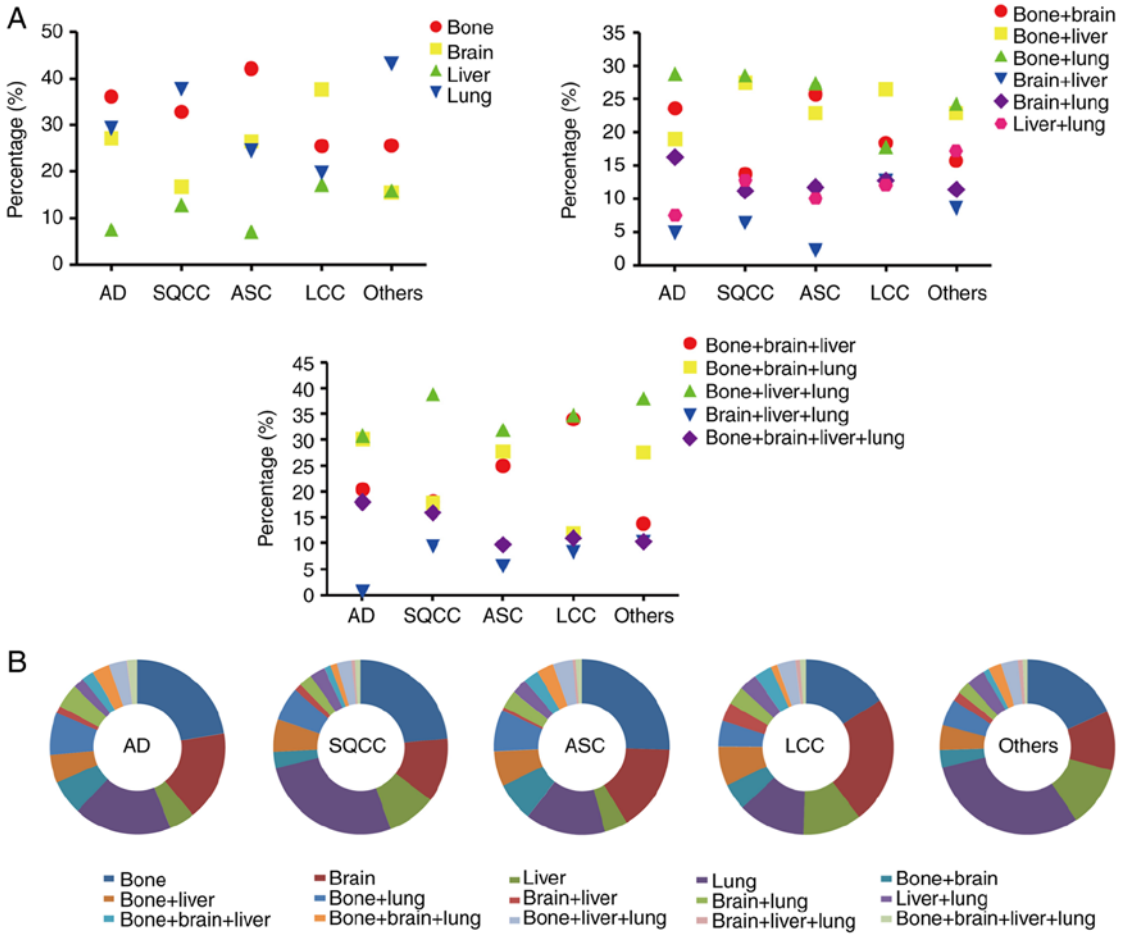

Figure 3. Percentages of distant metastasis combinations for NSCLC subtypes. (A) Occurrence of metastasis at different sites in NSCLC subtypes. (B) Relative rates of combination of metastatic sites in AD, SQCC, ASC, LCC and other subtypes. AD, adenocarcinoma; ASC, adenosquamous carcinoma; LCC, large cell carcinoma; NSCLC, non-small cell lung cancer; SQCC, squamous cell carcinoma.

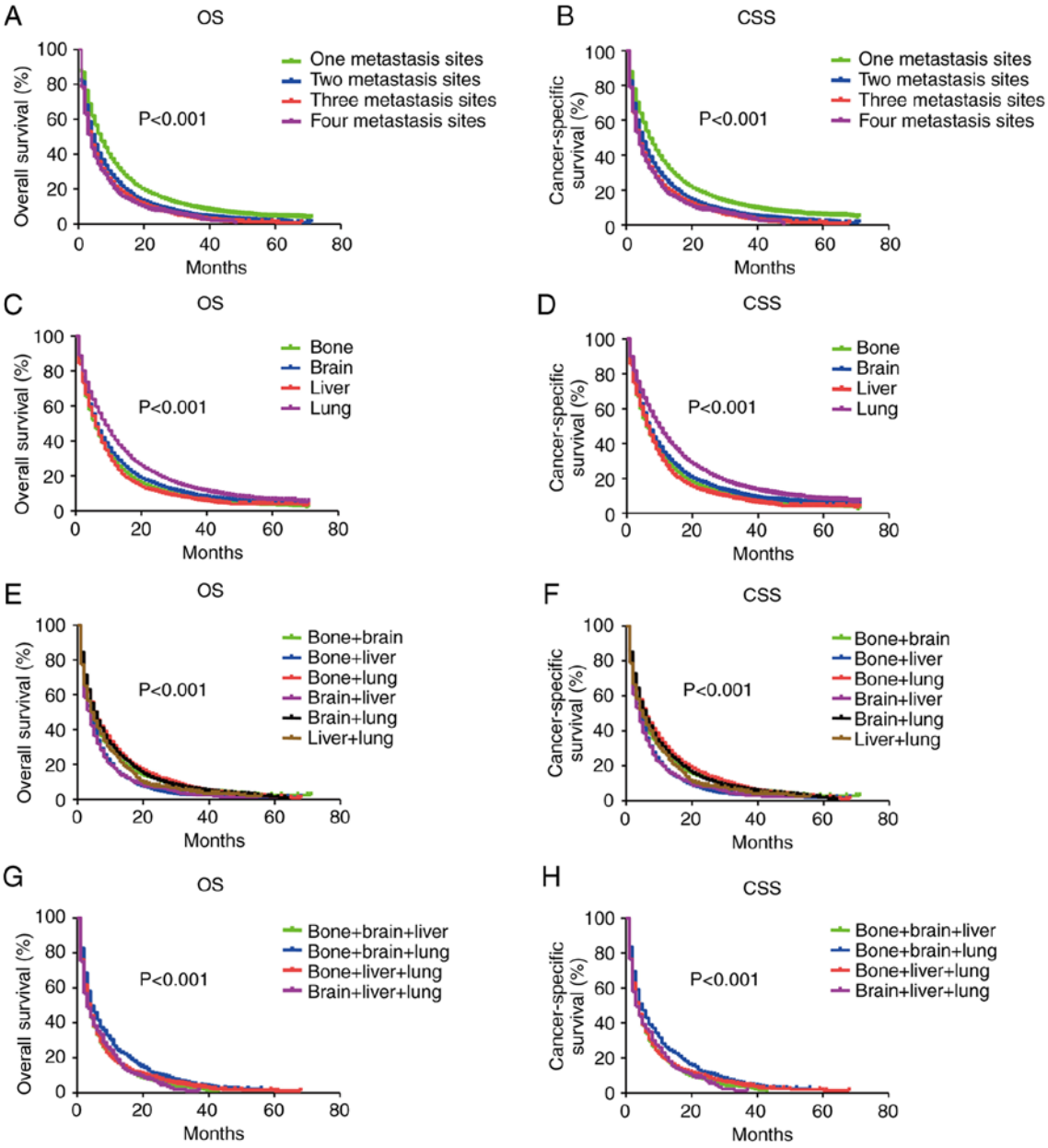

Figure 4. Survival curves of patients with NSCLC with different metastatic site combination patterns. (A and B) OS and CSS in patients with NSCLC with different numbers of distant metastases. (C and D) OS and CSS in patients with NSCLC with single metastasis. (E and F) OS and CSS in patients with NSCLC with two-site metastasis. (G and H) OS and CSS in patients with NSCLC with three-site metastasis. CSS, cancer-specific survival; NSCLC, non-small cell lung cancer; OS, overall survival.

43.09%, respectively. Notably, in patients with LCC the most common single metastatic site was the brain, accounting for 37.57%. The most common two-site metastasis combination was bone and lung, accounting for 28.79% of patients with AD, 28.51% of patients with SQCC, 27.37% of patients with ASC and 24.29% of patients with other subtypes. However, the most common two-site metastasis combination for patients with LCC was bone and liver, accounting for 26.42%. For three-site metastasis, bone, liver and lung was the most common combination for all subtypes, accounting for 30.77 (AD), 38.85 (SQCC), 31.94 (ASC), 34.86 (LCC) and 37.93% (other subtypes).

Survival analysis for different metastatic patterns of NSCLC. Differences in the prognosis of patients with different metastatic patterns were evaluated by Kaplan-Meier analysis. OS and CSS were compared among patients with NSCLC with different metastatic sites (Fig. 4). Patients with two-site metastasis exhibited better OS and CSS than those with three- or four-site metastasis, but exhibited worse OS and CSS than patients with single metastasis (P<0.001; Fig. 4A and B). There was no significant difference in survival identified between patients with three- and four-site metastasis (P=0.380). Among patients with a single metastatic site, patients with isolated lung metastasis exhibited the best outcome, followed by single brain and bone metastasis (all P<0.001). Isolated liver metastasis was associated with the worst outcome (P<0.001; Fig. 4C and D). For two-site metastasis, patients with liver-combined metastasis exhibited worse OS and CSS compared with patients with other metastatic patterns (all P<0.001). By contrast, no significant differences in survival among patients with bone

and lung, bone and brain, and brain and lung metastases were identified (all P>0.05; Fig. 4E and F). Additionally, no significant differences among patients with bone and liver, brain and liver, and liver and lung metastases were identified (all P>0.05; Fig. 4E and F). Similar findings were observed in patients with three-site metastasis. Patients with bone, brain and lung metastasis exhibited improved OS and CSS compared with those with liver-combined three-site metastatic patterns (all P<0.001; Fig. 4G and H). However, log-rank tests identified no significantly different effect on prognosis among patients with liver-combined three-site metastatic patterns. Therefore, patients with isolated liver or liver-combined metastasis exhibited a poorer prognosis than those with other metastatic patterns.

Cox regression analysis based on OS and CSS. In multivariate analysis, increased age, being male, positive nodes, higher tumor grade and more metastatic sites were associated with worse outcomes. Additionally, patients receiving appropriate treatments, including chemotherapy, radiotherapy or surgery, had a significantly lower risk of mortality than those without treatment (Table III).

Additionally, multivariate analyses indicated that SQCC, ASC and LCC were significantly associated with decreased OS and CSS compared with AD. Among them, LCC had the highest risk of mortality referring to AD [OS: Hazard ratio (HR), 1.227; 95% CI, 1.149-1.310; CSS: HR, 1.287; 95% CI, 1.206-1.374; P<0.001 for the two endpoints; Table III].

Notably, patients with isolated liver metastasis exhibited the worst outcomes (OS: HR, 1.385; 95% CI, 1.318-1.455; CSS: HR, 1.507; 95% CI, 1.432-1.585; P<0.001 for the two endpoints). As for multi-site metastasis, patients with liver-combined metastases exhibited a significantly higher risk of mortality than those without liver metastasis (Table IV).

Discussion

Postmus *et al* (14) reported that the median OS for patients with NSCLC with DM is only 6 months. The incidence of DM of NSCLC at diagnosis is ~40%, and the most common metastatic site is the bone, followed by the lung, brain, liver and adrenal glands (5,8). The present retrospective study, investigating patients with NSCLC, demonstrated major differences in the frequency of metastases to one, two, three or four organs, and further identified the prognostic influence of different site-specific metastatic combinations.

Only a small number of studies have investigated the incidence of different metastatic patterns in patients with metastatic NSCLC (6,15). A retrospective study reported that among the 729 patients with metastatic NSCLC, 250 (34.3), 234 (32.1), 207 (28.4), 122 (16.7), 98 (13.4) and 69 (9.5%) exhibited bone, lung, brain, adrenal gland, liver and distant lymph node metastasis, respectively (5). Another study based on the Swedish Family Cancer Database demonstrated that ~38% of all deceased patients with lung cancer had one metastatic site, and 19% had two or more reported metastases (6). However, in the present study, ~63.8% of all metastatic cohorts exhibited metastasis to one site. Ren *et al* (11) reported that the most common combination for two-site metastasis for AD was bone and brain (11.4%), and that for SQCC was bone and liver (11.8%). However, in the present study, the most common two-site metastatic combination was bone and lung for AD (28.79), SQCC (28.51), ASC (27.37), and other subtypes (24.29%). Bone and liver was the most common two-site metastatic combination for patients with LCC, and accounted for 26.42%. A previous study identified that the incidence of bone metastasis is as high as 34.3% in patients with metastatic NSCLC (5). Notably, the present study revealed that patients with bone metastasis accounted for more than a half of all patients with metastatic NSCLC. However, the patients with isolated liver metastasis at the initial diagnosis accounted for 5.8%, which was lower than the 13-24% reported previously (5,16). In addition, the present study revealed that bone in combination with other sites accounted for most of the multi-site metastases.

In the present study, LCC exhibited specific metastatic characteristics, which were entirely different from those of other histological subtypes. The most common single metastatic site was the brain for LCC. Notably, the most common two-site metastatic combination was bone and liver, which did not involve the most common single metastatic site. This result may be associated with the averaged incidence of metastasis to each site in LCC. Analysis of single metastatic sites revealed that LCC was more frequently associated with brain and liver metastases than other histological subtypes, whereas bone metastasis was less common in LCC. Similar findings have been confirmed in another study (17). Additionally, a previous study reported an association between liver and bone metastasis in major histological types of NSCLC, which was particularly evident in LCC (18). This may explain why the most common two-site metastasis combination in LCC identified in the present study was bone and liver.

Only a small number of studies have reported that the differences in survival among patients with metastatic NSCLC may be associated with different metastatic patterns (5,19). A previous study reported that patients with NSCLC with liver metastasis exhibit worse prognosis (5). Another study demonstrated that AD patients with liver metastasis at diagnosis have a shorter progression-free survival (PFS) and OS than those without liver metastasis (2.5 and 6.3 months, respectively) (20). As expected, the results of the present study also confirmed that liver metastasis was associated with the worst outcomes in patients with metastatic NSCLC, which was consistent with the findings from other types of cancer (21,22). Notably, in the present study, the hazard ratio for isolated liver metastasis was 1.385-fold and 1.507-fold higher than that for isolated lung metastasis in terms of OS and CSS, respectively. Additionally, patients with liver-combined metastases exhibited worse survival rates than those with other metastatic patterns. Although liver metastasis accounted for the smallest number of patients with metastatic NSCLC, it is a metastatic type that is of great concern due to its poor prognosis. Previous studies have demonstrated that patients with liver metastasis gain limited therapeutic benefit with checkpoint-inhibitor monotherapy (23-25). However, a recent phase 3 randomized trial revealed that a benefit in regard to PFS was observed with atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP) in patients with NSCLC with liver metastasis subgroups (median, 7.4 months with ABCP vs. 4.9 months with bevacizumab plus carboplatin plus paclitaxel; unstratified HR, 0.42; 95% CI, 0.26-0.66) (26). Notably, liver metastasis became

Table III. Multivariate analysis of OS and CSS in patients with metastatic non-small cell lung cancer.

	OS		CSS	
Feature	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (years)				
<50	1.000 (reference)		1.000 (reference)	
≥50	1.236 (1.183-1.292)	<0.001	1.282 (1.223-1.344)	<0.001
Sex				
Female	1.000 (reference)		1.000 (reference)	
Male	1.166 (1.141-1.191)	<0.001	1.183 (1.157-1.209)	<0.001
Ethnicity				
Caucasian	1.000 (reference)		1.000 (reference)	
African descent	0.984 (0.954-1.015)	0.306	0.970 (0.939-1.002)	0.063
Others	0.770 (0.743-0.799)	<0.001	0.690 (0.663-0.718)	<0.001
T stage				
T0, T1, T2	1.000 (reference)		1.000 (reference)	
T3, T4	1.055 (1.031-1.081)	<0.001	1.061 (1.035-1.087)	<0.001
TX	1.149 (1.106-1.193)	<0.001	1.149 (1.105-1.195)	<0.001
N stage				
N0	1.000 (reference)		1.000 (reference)	
N positive	1.252 (1.220-1.285)	<0.001	1.281 (1.247-1.316)	<0.001
NX	1.225 (1.163-1.298)	<0.001	1.243 (1.178-1.311)	<0.001
Tumor grade				
I	1.000 (reference)		1.000 (reference)	
II	1.176 (1.097-1.260)	<0.001	1.233 (1.142-1.331)	<0.001
III	1.405 (1.315-1.502)	<0.001	1.514 (1.407-1.629)	<0.001
IV	1.537 (1.356-1.743)	<0.001	1.655 (1.455-1.883)	<0.001
Unknown	1.356 (1.271-1.447)	<0.001	1.440 (1.341-1.547)	<0.001
Histology				
AD	1.000 (reference)		1.000 (reference)	
SQCC	1.187 (1.156-1.218)	<0.001	1.200 (1.168-1.232)	<0.001
ASC	1.123 (1.033-1.221)	0.006	1.135 (1.043-1.235)	0.003
LCC	1.227 (1.149-1.310)	<0.001	1.287 (1.206-1.374)	<0.001
Other	0.605 (0.541-0.677)	<0.001	0.477 (0.415-0.548)	<0.001
Chemotherapy				
No/Unknown	1.000 (reference)		1.000 (reference)	
Yes	0.405 (0.396-0.414)	<0.001	0.387 (0.378-0.396)	<0.001
Radiotherapy				
No/Unknown	1.000 (reference)		1.000 (reference)	
Yes	0.923 (0.904-0.943)	<0.001	0.937 (0.917-0.958)	<0.001
Surgery				
No/Unknown	1.000 (reference)		1.000 (reference)	
Yes	0.597 (0.561-0.635)	<0.001	0.523 (0.487-0.562)	<0.001
Number of distant metastases				
One metastatic site	1.000 (reference)		1.000 (reference)	
Two metastatic sites	1.299 (1.267-1.332)	<0.001	1.336 (1.302-1.371)	<0.001
Three metastatic sites	1.572 (1.511-1.635)	<0.001	1.631 (1.567-1.696)	<0.001
Four metastatic sites	1.674 (1.541-1.818)	<0.001	1.745 (1.607-1.896)	<0.001

AD, adenocarcinoma; ASC, adenosquamous carcinoma; CI, confidence interval; CSS, cancer-specific survival; LCC, large cell carcinoma; N, node; OS, overall survival; SQCC, squamous cell carcinoma; T, tumor.

Table IV. Multivariate analysis of the association among different metastatic patterns and OS and CSS in patients with metastatic non-small cell lung cancer.

	OS		CSS	
Metastatic pattern	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
One metastatic site				
Lung	1.000 (reference)		1.000 (reference)	
Brain	1.111 (1.072-1.151)	<0.001	1.162 (1.119-1.206)	<0.001
Bone	1.218 (1.179-1.258)	<0.001	1.295 (1.252-1.340)	<0.001
Liver	1.385 (1.318-1.455)	<0.001	1.507 (1.432-1.585)	<0.001
Two metastatic sites				
Bone + lung	1.000 (reference)		1.000 (reference)	
Brain + lung	1.001 (0.973-1.068)	0.981	1.018 (0.953-1.088)	0.595
Bone + brain	1.050 (0.990-1.114)	0.102	1.059 (0.997-1.125)	0.061
Liver + lung	1.277 (1.179-1.382)	<0.001	1.279 (1.180-1.387)	<0.001
Brain + liver	1.357 (1.233-1.493)	<0.001	1.358 (1.232-1.496)	<0.001
Bone + liver	1.328 (1.251-1.409)	<0.001	1.379 (1.299-1.464)	<0.001
Three/four metastatic sites				
Bone + brain + lung	1.000 (reference)		1.000 (reference)	
Bone + liver + lung	1.228 (1.127-1.339)	<0.001	1.282 (1.175-1.399)	<0.001
Bone + brain + liver	1.189 (1.078-1.311)	0.001	1.249 (1.132-1.378)	<0.001
Brain + liver + lung	1.214 (1.055-1.397)	0.007	1.273 (1.108-1.464)	0.001
Bone + brain + liver + lung	1.176 (1.061-1.303)	0.002	1.215 (1.096-1.347)	<0.001

CI, confidence interval; CSS, cancer-specific survival; OS, overall survival.

a stratified factor for improved PFS with ABCP, suggesting that patients with NSCLC with liver metastasis may be a more special subgroup and may require a specific treatment strategy. In addition, patients with isolated lung metastasis possessed the best prognosis, which was consistent with the findings of a previous study (27). Therefore, knowledge of the prognostic effects of different metastatic sites may be valuable for classifying patients with advanced NSCLC and may serve as a reference for individualized precise treatment.

Additionally, the present study investigated the prognosis of patients with metastatic NSCLC with single or multiple metastatic sites. A recent study demonstrated that metastasis to a single site is associated with significantly improved OS compared with multiple sites in patients with NSCLC (28). It has been previously reported that the most common two-site metastatic combinations were nervous system and bone, bone and liver, and nervous system and liver, but differences in survival rates among them are unknown (6). However, in the present study, the most common two-site metastatic combination involved bone and lung. Notably, among patients with two-site metastasis, those with liver-combined two-site metastasis exhibited worse OS and CSS than those with other metastatic patterns. Similar findings were observed in three-site metastasis. Combined two- or three-site metastasis involving liver was associated with worse OS and CSS in patients with metastatic NSCLC. Therefore, identifying patients with multi-site DM involving the liver is crucial to improve outcomes or treatment value in these specific cohorts. In addition, men and elderly patients had a shorter survival, which is consistent with previously published retrospective studies (22,29).

There were several limitations in the present study. First, there was lack of information regarding details of systemic treatment administered; in particular, no information regarding targeted therapy and immunotherapy was available. During the past decade, through improved understanding of the molecular and immunological features of cancer, novel targeted therapies and immunotherapies have been available to treat patients with metastatic NSCLC and have brought unprecedented survival benefits in selected cohorts (30,31). Second, there was a lack of information regarding co-morbidities, performance status and gene mutations. This information will be discussed in future studies. Finally, the present study only included metastatic sites associated with the bone, brain, liver and lung. Metastasis to other sites, including the adrenal glands, may also influence the outcomes of patients with NSCLC.

In conclusion, the present study demonstrated that in patients with NSCLC, bone was the most commonly targeted site for single- or multi-organ metastases. As for NSCLC subtypes, the most common single metastatic site was bone for AD and ASC, and lung for SQCC and other subtypes. Additionally, bone and lung was the most common combination for two-site metastasis for AD, SQCC, ASC and other subtypes. Notably, for LCC, the brain was the most common single metastatic site, and bone and liver were most commonly involved in two-site metastasis. The present study demonstrated that metastasis to the liver alone or in combination with other organs was a factor for poor prognosis of patients

with metastatic NSCLC, while isolated lung metastasis was associated with the best outcomes. Knowledge regarding the prognostic value of different sites of DM may be valuable for classifying patients with advanced NSCLC, laying a foundation for individualized precise treatment.

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Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZX, JS, XC and QYa designed the study. ZX, LuZ and MC participated in data selection and assembly. LiZ, YY and QYo performed the data analysis. ZX, QYa and XC were involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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