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Impact of the homogeneous and heterogeneous risk factors on the incidence and survival outcome of bone metastasis in NSCLC patients

Qian Song[1,2] · Jun Shang[3] · Chufan Zhang[1,2] · Lanlin Zhang[1,2] · Xianghua Wu[1,2]

Abstract

Purpose Bone metastases (BM) is reported as the most frequent distant metastasis in non-small cell lung cancer (NSCLC), but the risk factors for the incidence and prognosis of BM patients in NSCLC have not been extensively elucidated. This study aimed to find risk factors to predict BM patients' morbidity and survival outcome in NSCLC.

Methods 63,505 patients of NSCLC in the Surveillance, Epidemiology and End Results database diagnosed from 2010 to 2015 were used to analyze risk factors for developing BM by conducting multivariable logistic regression. Of these patients, 6152 and 5664 BM patients diagnosed between 2010 and 2014 were selected to investigate predictive factors for BM overall survival (OS) and cancer-specific survival (CSS) using the multivariable Cox proportional hazards regression.

Results There were overall 7486 (11.79%) BM patients in NSCLC. The homogeneous risk factors for BM patients' morbidity and survival outcome included male, higher T stage, lymph node involvement, poor differentiation grade, brain metastases, and liver metastases. Married status, adenocarcinoma type and lung metastases were positively correlated with BM incidence, while older age, white race, unmarried status, and SCC and other NSCLC types could predict poor OS and CSS of BM in NSCLC.

Conclusions The homogeneous and heterogeneous risk factors for morbidity and survival outcome of BM patients could help physicians in more precise and individualized screening and therapies for BM patients in NSCLC.

Keywords Non-small cell lung cancer · Bone metastasis · Risk factors · Morbidity · Prognosis

Abbreviations

BM	Bone metastases
NSCLC	Non-small cell lung cancer
US	The United States
SEER	Surveillance, epidemiology and end results
OS	Overall survival
CSS	Cancer-specific survival
SREs	Skeletal-related events
NCCN	National comprehensive cancer network
K-M	Kaplan–Meier
OR	Odds ratio
CI	Confidence interval
MST	Median survival time

Qian Song and Jun Shang are first authors and equally contributed.

✉ Xianghua Wu
  wuxianghua2018@163.com

1 Department of Medical Oncology, Fudan University Shanghai Cancer Center, No. 270 Dong-An Road, Shanghai 200032, China

2 Department of Oncology, Shanghai Medical College, Fudan University, 130 Dong-An Road, Shanghai 200032, China

3 School of Life Sciences, Fudan University, Shanghai, China

Introduction

Worldwide, lung cancer has become the most common cancer type. In both developed and developing countries, lung cancer gradually becomes the leading cause of cancer death in male patients (Torre et al. 2015). In the United States (US), lung cancer is estimated to contribute to 26% of cancer deaths in men and 25% in women in 2018 (Siegel et al. 2018). With the development of surgical techniques, targeted therapies, chemotherapies, radiotherapies, and immunotherapies, the survival outcome of lung cancer patients, especially patients with non-small cell lung cancer (NSCLC), has increased (Hirsch et al. 2017). Despite these therapeutic improvements, recurrence is still common in NSCLC

patients, and 75% of recurrences are with distant metastases (Torok et al. 2017). Bone metastases (BM) occur in approximately 40% of advanced NSCLC patients (LeVasseur et al. 2016), which is one of the most common types of distant metastasis. Skeletal spread dramatically reduces NSCLC patients' life quality by causing patients severe bone pain and complications such as pathologic fracture and spinal cord compression (Costa et al. 2008). These skeletal-related events (SREs) develop at least once in 40% of BM patients of NSCLC (Tanvetyanon and Hines 2005).

Most of the NSCLC patients did not come to doctor until they had symptoms mentioned above. Besides, for those asymptomatic patients, guidelines for lung cancer screening from National Comprehensive Cancer Network (NCCN) do not propose to routinely assess BM (Wood et al. 2018). Therefore, the diagnosis of BM is usually missed until they develop severe SRE. Thus, it is essential to investigate reliable risk factors for screening of BM in NSCLC patients. Clinical factors indicating BM include elevated alkaline phosphatase, hypercalcemia, and skeletal pain (Erturan et al. 2005). But there is lack of evidence showing these factors have robust ability of predicting high BM risk. Hence, at present, there demand more clinically applied BM risk predictors as well as the metastatic characteristics of NSCLC in clinic.

The aim of this study was utilizing the Surveillance, Epidemiology, and End Results (SEER) database to investigate morbidity and risk factors of BM in patients with NSCLC. Besides, survival outcomes and prognostic predictors were assessed for those who had found BM when they were first diagnosed with NSCLC.

Methods

Patient selection

Patients were chosen from the SEER database from 2010 to 2015, which was released in April 2018. SEER-Medicare program is a public-use dataset that collects clinical information and data from 18 population-based cancer registries and accounts for about 28% of the United States population. Thus, the 18 registry populations can be generalized to the overall population. SEER includes clinical, demographic, pathological, insurance, therapeutic, and outcome data.

We first identified patients whose age ≥ 18 years, with site codes from C34.0 to C34.9. Then we narrowed our investigation to those who were initially diagnosed with NSCLC from the first day of the year 2010 to the last day of the year 2015, as the information of distant metastases was collected from 2010 to 2015 in SEER. The histologic types of NSCLC were limited by the 3rd edition of the International Classification of Disease for Oncology and included adenocarcinoma (8140–8147,

8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550, 8572), squamous cell carcinoma (8050, 8051, 8052, 8070–8078) and other types of NSCLC (8010, 8012, 8014, 8015, 8020, 8021, 8022, 8030, 8036) (Morgensztern et al. 2012). T and N staging were suggested by the AJCC 7th edition. As shown in Fig. 1, after a critical selection, there were overall 63,505 patients diagnosed as NSCLC without or with BM from 01/01/2010 to 12/31/2015, who were used for the identification of risk factors of BM. Then 6152 BM patients diagnosed between 2010 and 2014 (with more than 1-year follow-up) were collected from the 63,505 patients to analyze the prognostic factors of overall survival (OS) for BM in NSCLC. 5,664 patients were selected to predict prognostic factors for cancer-specific survival (CSS), after excluding 448 patients who were dead from other reasons (Fig. 1).

Demographic, pathological, and clinical variables

Demographic variables include age (< 50, 50–59, 60–69, 70–79, ≥ 80), marital status (unmarried and married), race [white, black, other (American Indian or AK Native, Asian or Pacific Islander)], and sex (male and female). Pathological variables contain tumor histology (adenocarcinoma, squamous cell carcinoma, other types of NSCLC) and laterality (left side, right side and paired sides). Clinical variables were classified by grade (1, 2, 3, 4), T stage (T1, T2, T3, T4), N stage (N0, N1, N2, N3), without or with brain metastases, without or with liver metastases and without or with lung metastases.

Statistical analysis

Multivariable logistic regression was utilized to find the risk factors for BM when initially diagnosed as NSCLC. Kaplan–Meier (K–M) analysis was utilized to compare survival duration of OS and CSS between different groups of BM patients, and the OS and CSS differences between different groups were assessed by log-rank test. Multivariable analyses with Cox proportional hazard regression were conducted to determine independent prognostic factors for BM patients. Data were collected using SEER*Stat Software version 8.3.5. All of our statistical analyses were conducted using SPSS Version 23.0 (IBM Corporation, Armonk, NY, USA). Two-tailed P values less than 0.05 were considered as statistical significance in all of the analyses.

Results

Morbidity of bone metastases

In the overall 63,505 patients that were initially diagnosed as NSCLC between 2010 and 2015, there were

Fig. 1 Flowchart of the study analyzing the risk factors for the incidence and survival outcome of BM patients in NSCLC, along with recording of the number of patients and the reasons for exclusion from our investigation. *OS* overall survival; *CSS* cancer-specific survival
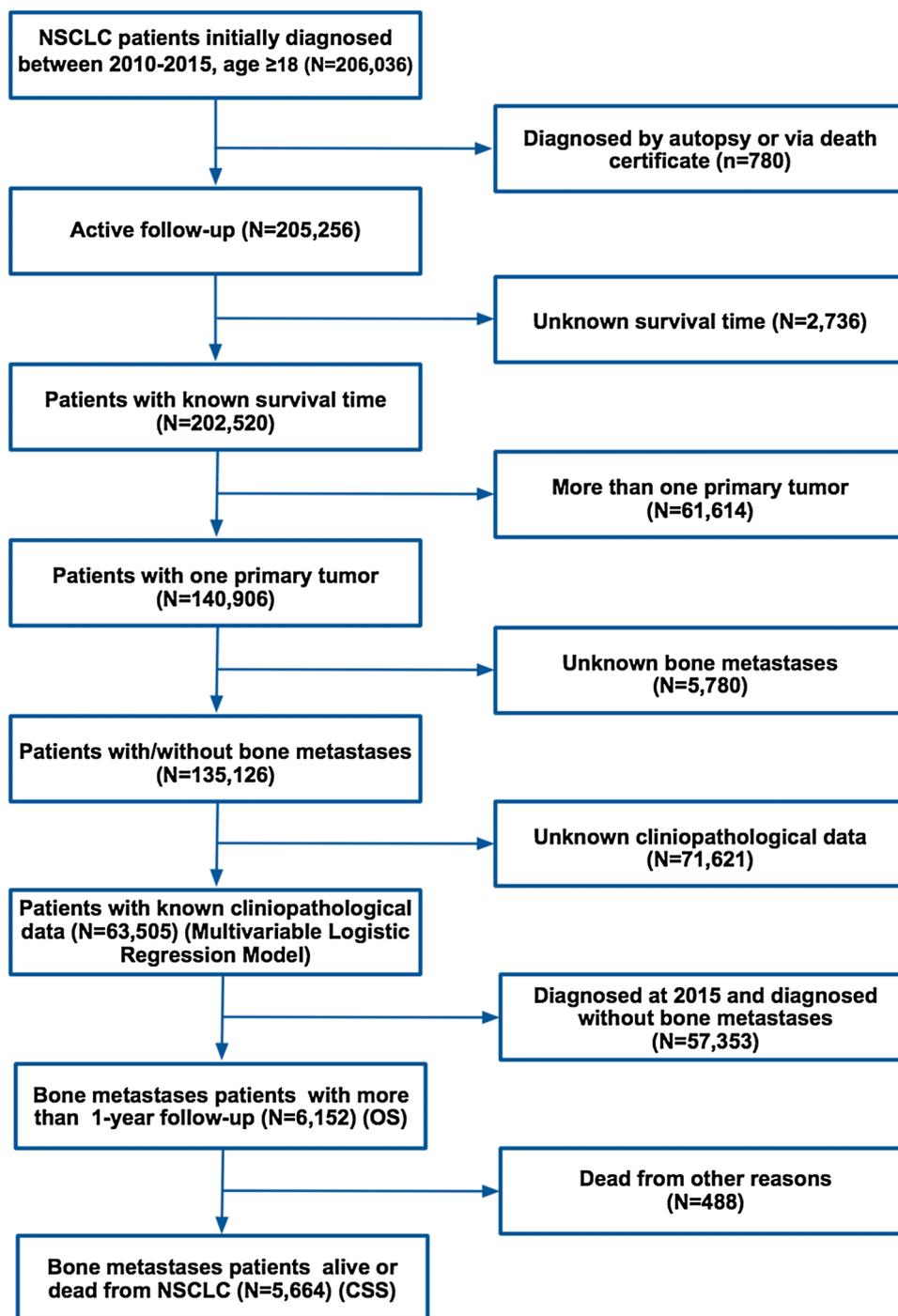
7486 (11.79%) BM patients and 56,019 (88.21%) patients without BM. The overall patients' mean age was 68.08 ± 10.49 years. There were 51,034 (80.36%) white patients. 34,261 (53.95%) patients were married and 33,508 (52.76%) patients were male. Patients with adenocarcinoma were composed of 60.61% of the total cohort (N = 38,493). And more patients tended to get NSCLC in the right side (58.57%, N = 37,197). Detailed data are demonstrated in Table 1.

Bone metastasis patients' characteristics

There were 6152 eligible patients diagnosed as NSCLC with BM from 2010 to 2014. The mean age for those patients was 66.42 ± 11.02 years. White patients made up 77.50% of the total population (N = 4768). There were 3433 (55.80%) married patients and 3600 (58.52%) male patients. BM patients diagnosed as adenocarcinoma accounted for 69.38% of the total cohort (N = 4268), and right-side NSCLC patients

Table 1 Multivariable logistic regression for analyzing the demographic and related clinical characteristics for developing BM in patients diagnosed with initial primary NSCLC

Variables	Number of NSCLC patients (2010–2015)		OR (95% CI)	P value
	With bone metastases (%)	Without bone metastases (%)		
Age			0.976 (0.951–1.001)	0.055
< 50	448 (0.71%)	2143 (3.37%)	1.00	–
50–59	1547 (2.44%)	9401 (14.80%)	0.938 (0.824–1.067)	0.331
60–69	2443 (3.85%)	18,108 (28.51%)	0.929 (0.821–1.051)	0.243
70–79	2134 (3.36%)	18,060 (28.44%)	0.927 (0.818–1.051)	0.236
≥ 80	914 (1.44%)	8307 (13.08%)	0.881 (0.768–1.011)	0.070
Race			1.038 (0.994–1.083)	0 0.089
White	5782 (9.10%)	45,252 (71.26%)	1.00	–
Black	1004 (1.58%)	6467 (10.18%)	1.014 (0.935–1.099)	0.741
Other	700 (1.10%)	4300 (6.77%)	1.060 (0.964–1.166)	0.226
Marital status				
Unmarried	3315 (5.22%)	25,929 (40.83%)	1.00	–
Married	4171 (6.57%)	30,090 (47.38%)	1.061 (1.004–1.121)	0.036
Sex				
Male	4375 (6.89%)	29,133 (45.88%)	1.00	–
Female	3111 (4.90%)	26,886 (42.34%)	0.815 (0.771–0.861)	< 0.001
Tumor histology			0.675 (0.641–0.710)	< 0.001
Adenocarcinoma	5231 (8.24%)	33,262 (52.38%)	1.00	–
Squamous cell carcinoma	1874 (2.95%)	21,274 (33.50%)	0.516 (0.485–0.549)	< 0.001
Other	381 (0.60%)	1483 (2.34%)	1.005 (0.873–1.156)	0.948
Laterality			0.972 (0.923–1.023)	0 0.269
Left	3008 (4.74%)	22,705 (35.75%)	1.00	–
Right	4326 (6.81%)	32,871 (51.76%)	0.964 (0.913–1.019)	0.194
Paired	152 (0.24%)	443 (0.70%)	0.860 (0.695–1.063)	0.164
T stage			1.287 (1.251–1.324)	< 0.001
T1	616 (0.97%)	15,456 (24.34%)	1.00	–
T2	2039 (3.21%)	19,431 (30.60%)	1.798 (1.631–1.983)	< 0.001
T3	2088 (3.29%)	11,120 (17.51%)	2.272 (2.052–2.516)	< 0.001
T4	2743 (4.32%)	10,012 (15.77%)	2.536 (2.290–2.809)	< 0.001
N stage			1.568 (1.527–1.610)	< 0.001
N0	1484 (2.34%)	30,334 (47.77%)	1.00	–
N1	650 (1.02%)	5881 (9.26%)	1.709 (1.544–1.892)	< 0.001
N2	3732 (5.88%)	15,400 (24.25%)	2.862 (2.671–3.068)	< 0.001
N3	1620 (2.55%)	4404 (6.93%)	3.457 (3.170–3.771)	< 0.001
Grade			1.272 (1.218–1.328)	< 0.001
1	356 (0.56%)	6088 (9.59%)	1.00	–
2	2282 (3.59%)	22,606 (35.60%)	1.470 (1.298–1.666)	< 0.001
3	4681 (7.37%)	26,428 (41.62%)	1.695 (1.500–1.915)	< 0.001
4	167 (0.26%)	897 (1.41%)	1.568 (1.247–1.971)	< 0.001
Brain metastases				
No	5735 (9.03%)	52,082 (82.01%)	1.00	–
Yes	1751 (2.76%)	3937 (6.20%)	1.946 (1.812–2.089)	< 0.001
Liver metastases				
No	5818 (9.16%)	54,583 (85.95%)	1.00	–
Yes	1668 (2.63%)	1436 (2.26%)	5.846 (5.383–6.349)	< 0.001
Lung metastases				
No	5155 (8.12%)	51,079 (80.43%)	1.00	–
Yes	2331 (3.67%)	4940 (7.78%)	2.052 (1.917–2.197)	< 0.001

occupied 57.62% of the total BM patients ($N = 3545$). Detailed data are shown in Table 2.

Risk factors for progressing into bone metastases

As demonstrated in Table 1, patients of married [OR (odds ratio) = 1.061, 95% CI (confidence interval) = 1.004–1.121, $P = 0.036$], higher T stage (OR = 1.287, 95% CI = 1.251–1.324, $P < 0.001$), lymph nodes metastases (OR = 1.568, 95% CI = 1.527–1.610, $P < 0.001$), poor differentiation grade (OR = 1.272, 95% CI = 1.218–1.328, $P < 0.001$), brain metastases (OR = 1.946, 95% CI = 1.812–2.089, $P < 0.001$), liver metastases (OR = 5.846, 95% CI = 5.383–6.349, $P < 0.001$), and lung metastasis (OR = 2.052, 95% CI = 1.917–2.197, $P < 0.001$) were significantly associated with higher BM risk. Female NSCLC patients had lower BM risk compared with male NSCLC patients (OR = 0.815, 95% CI = 0.771–0.861, $P < 0.001$), and patients with squamous cell carcinoma (SCC) were less likely to have BM than those with adenocarcinoma (OR = 0.675, 95% CI = 0.641–0.710, $P < 0.001$).

Prognostic factors for bone metastasis patients' overall survival (OS) and cancer-specific survival (CSS)

The median survival time (MST) for OS and CSS of different BM patient groups is listed in Tables 2 and 3. BM patients of other race had the longest MST for OS (MST = 10 months, 95% CI = 8.451–11.549 months) and for CSS(MST = 10 months, 95% CI = 8.408–11.592 months), while those of other tumor histology showed the shortest MST for OS (MST = 2 months, 95% CI = 1.628–2.372 months) and for CSS (MST = 2 months, 95% CI = 1.616–2.384 months). The OS and CSS of BM patients classified according to age (Figs. 2a, 3a), race (Figs. 2b, 3b), marital status (Figs. 2c, 3c), sex (Figs. 2d, 3d), tumor histology (Figs. 2e, 3e), laterality (Figs. 2f, 3f), T stage (Figs. 2g, 3g), N stage (Figs. 2h, 3h), grade (Figs. 2i, 3i), brain metastases (Figs. 2j, 3j), liver metastases (Figs. 2k, 3k), and lung metastases (Figs. 2l, 3l) were illustrated in a graphic way. The results of multivariable Cox proportional hazard model demonstrated that older age, SCC and other NSCLC types, higher T stage, lymph node involvement, poor differentiation grade, brain metastases, and liver metastases were associated with poor survival outcomes of OS and CSS for BM patients, whereas patients of other races, married and female had better OS and CSS for BM patients (Tables 2, 3). Laterality and lung metastases were not correlated with patients' OS and CSS.

As shown in Fig. 4, male, higher T stage, lymph node involvement, poor differentiation grade, brain metastases, and liver metastases were homogeneous risk factors for the incidence and survival outcome of BM in NSCLC. Patients of married status were more likely to have BM, and those patients tended to have a better OS and CSS than unmarried patients. Patients with adenocarcinoma were more likely to be associated with the development of BM, but those with SCC and other NSCLC types had a poor survival outcome. Patients with lung metastases were tended to develop BM, but not associated with BM patients' prognosis. Older age and other races were significantly correlated with OS and CSS of BM patients but could not predict BM risk.

Discussion

In the present study, we utilized the SEER database collecting a large population of NSCLC patients to find the homogeneous and heterogeneous risk factors for the morbidity and survival outcome of BM patients. According to our investigations, there were 11.79% of NSCLC patients who had BM when they were initially diagnosed. This is lower than the reported BM incidence (20%–40%) (Kuchuk et al. 2013; Quint et al. 1996; Tsuya et al. 2007). This may contribute to the underestimation of BM morbidity in the SEER database since this database is lacking the record of patients who are asymptomatic, while the reported BM incidence was mainly calculated after a systematic evaluation of the presence of BM. This highlighted the importance of basic bone screening for those asymptomatic NSCLC patients clinically.

As shown in our study, there were nine risk factors that were able to predict high BM risk for NSCLC, including married status, male, adenocarcinoma, higher T stage, lymph node involvement, poor differentiation grade, brain metastases, liver metastases, and lung metastases. These risk factors were able to guied doctors paying more attention to those with high BM risk. For these patients, a more frequent skeletal inspection may help early diagnosis of BM, which can lead to the appropriate use of bone-targeting agents and thus reduce the rate of SREs. Besides, these clinical factors may be combined with biological markers for more accurate prediction of BM for NSCLC patients in the future.

Apart from this, we found 11 risk factors that could predict both OS and CSS of BM patients in NSCLC, including older age, white race, unmarried status, male, SCC and other NSCLC types, higher T stage, lymph node involvement, poor differentiation grade, brain metastases, and liver metastases. Using these predictive factors, doctors are able to estimate the prognosis of BM patients in NSCLC. Our investigation is in accordance with M.Riihimäki's study, which found BM patients with SCC demonstrated poorer survival outcomes than those with adenocarcinoma (Riihimaki et al. 2014). For the homogeneous risk factors, special attention should be paid by physicians, considering their predictive ability of both high BM risk and poor

Table 2 Multivariable Cox regression for the OS among primary NSCLC patients with BM (diagnosed 2010–2014)

Variables	Number of patients with BM (2010–2014)		Median survival time (95% CI, month)	HR (95% CI)	P value
	Overall (OS)	Deceased (%, OS)			
Age				1.159 (1.131–1.188)	<0.001
<50	374	326 (87.17%)	7 (5.961–8.039)	1.00	–
50–59	1287	1181 (91.76%)	5 (4.531–5.469)	1.269 (1.122–1.435)	<0.001
60–69	1998	1820 (91.09%)	5 (4.588–5.412)	1.344 (1.194–1.514)	<0.001
70–79	1748	1653 (94.57%)	3 (2.726–3.274)	1.665 (1.477–1.878)	<0.001
≥80	745	709 (95.17%)	3 (2.702–3.298)	1.891 (1.654–2.161)	<0.001
Race				0.866 (0.831–0.903)	<0.001
White	4768	4461 (93.56%)	4 (3.808–4.192)	1.00	–
Black	817	764 (93.51%)	3 (2.564–3.436)	1.047 (0 0.968–1.133)	0.252
Other	567	464 (81.83%)	10 (8.451–11.549)	0.670 (0.608–0.738)	<0.001
Marital status					
Unmarried	2719	2554 (93.93%)	3 (2.768–3.232)	1.00	–
Married	3433	3135 (91.32%)	5 (4.705–5.295)	0.820 (0.777–0.866)	<0.001
Sex					
Male	3600	3382 (93.94%)	4 (3.798–4.202)	1.00	–
Female	2552	2307 (90.40%)	5 (4.645–5.355)	0.805 (0.762–0.850)	<0.001
Tumor histology				1.304 (1.245–1.366)	<0.001
Adenocarcinoma	4268	3861 (90.46%)	5 (4.715–5.285)	1.00	–
Squamous cell carcinoma	1560	1511 (96.86%)	3 (2.706–3.294)	1.354 (1.271–1.442)	<0.001
Other	324	317 (97.84%)	2 (1.628–2.372)	1.558 (1.378–1.761)	<0.001
Laterality				1.041 (0.991–1.094)	0.112
Left	2476	2291 (92.53%)	4 (3.663–4.337)	1.00	–
Right	3545	3274 (92.36%)	4 (3.777–4.223)	1.033 (0.979–1.090)	0.233
Paired	131	124 (94.66%)	3 (1.610–4.390)	1.146 (0.954–1.377)	0.145
T stage				1.075 (1.045–1.106)	<0.001
T1	506	449 (88.74%)	7 (6.021–7.979)	1.00	–
T2	1674	1540 (92.00%)	5 (4.633–5.367)	1.190 (1.070–1.323)	0.001
T3	1728	1601 (92.65%)	4 (3.691–4.309)	1.251 (1.124–1.393)	<0.001
T4	2244	2099 (93.54%)	4 (3.737–4.263)	1.302 (1.171–1.448)	<0.001
N stage				1.050 (1.023–1.078)	<0.001
N0	1218	1102 (90.48%)	5 (4.466–5.534)	1.00	–
N1	531	479 (90.21%)	5 (4.273–5.727)	0.970 (0.871–1.081)	0.584
N2	3118	2909 (93.30%)	4 (3.763–4.237)	1.139 (1.061–1.222)	<0.001
N3	1285	1199 (93.31%)	4 (3.535–4.465)	1.114 (1.024–1.212)	0.012
Grade				1.143 (1.093–1.194)	<0.001
1	287	261 (90.94%)	6 (4.570–7.430)	1.00	–
2	1870	1686 (90.16%)	6 (5.484–6.516)	1.056 (0.927–1.204)	0.414
3	3845	3596 (93.52%)	4 (3.810–4.190)	1.247 (1.098–1.416)	0.001
4	150	146 (97.33%)	3 (2.298–3.702)	1.350 (1.093–1.668)	0.005
Brain metastases					
No	4722	4357 (92.27%)	4 (3.765–4.235)	1.00	–
Yes	1430	1332 (93.15%)	4 (3.713–4.287)	1.209 (1.134–1.289)	<0.001
Liver metastases					
No	4778	4363 (91.31%)	5 (4.744–5.256)	1.00	–
Yes	1374	1326 (96.51%)	3 (2.761–3.239)	1.378 (1.294–1.468)	<0.001
Lung metastases					
No	4234	3904 (92.21%)	4 (3.767–4.233)	1.00	–
Yes	1918	1785 (93.07%)	4 (3.695–4.305)	1.036 (0.974–1.101)	0.262

Table 3 Multivariable Cox regression for analyzing the CSS among primary NSCLC patients with BM (diagnosed 2010–2014)

| Variables	Number of patients with BM (2010–2014)		Median survival time (95% CI, month)	HR (95% CI)	P value
	Overall (CSS)	Deceased (%, CSS)			
Age				1.166 (1.137–1.197)	< 0.001
< 50	351	303 (86.32%)	7 (5.913–8.087)	1.00	–
50–59	1190	1084 (91.09%)	5 (4.500–5.500)	1.265 (1.113–1.437)	< 0.001
60–69	1844	1666 (90.35%)	5 (4.574–5.426)	1.342 (1.187–1.518)	< 0.001
70–79	1600	1505 (94.06%)	4 (3.718–4.282)	1.676 (1.479–1.899)	< 0.001
≥80	679	643 (94.70%)	3 (2.687–3.313)	1.930 (1.679–2.218)	< 0.001
Race				0.864 (0.827–0.902)	< 0.001
White	4388	4081 (93.00%)	4 (3.802–4.198)	1.00	–
Black	739	686 (92.83%)	4 (3.550–4.450)	1.028 (0.947–1.117)	0.507
Other	537	434 (80.82%)	10 (8.408–11.592)	0.675 (0.610–0.747)	< 0.001
Marital status					
Unmarried	2491	2326 (93.38%)	3 (2.765–3.235)	1.00	–
Married	3173	2875 (90.61%)	5 (4.692–5.308)	0.817 (0.772–0.865)	< 0.001
Sex					
Male	3303	3085 (93.40%)	4 (3.767–4.233)	1.00	–
Female	2361	2116 (89.62%)	5 (4.629–5.371)	0.805 (0.760–0.852)	< 0.001
Tumor histology				1.305 (1.242–1.370)	< 0.001
Adenocarcinoma	3962	3555 (89.73%)	5 (4.703–5.297)	1.00	–
Squamous cell carcinoma	1414	1365 (96.53%)	3 (2.704–3.296)	1.363 (1.276–1.456)	< 0.001
Other	288	281 (97.57%)	2 (1.616–2.384)	1.534 (1.346–1.747)	< 0.001
Laterality				1.035 (0.983–1.090)	0 0.189
Left	2262	2077 (91.82%)	5 (4.645–5.355)	1.00	–
Right	3292	3021 (91.77%)	4 (3.772–4.228)	1.038 (0.982–1.099)	0.189
Paired	110	103 (93.64%)	4 (2.473–5.527)	1.053 (0.861–1.287)	0.614
T stage				1.077 (1.046–1.109)	< 0.001
T1	472	415 (87.92%)	7 (6.010–7.990)	1.00	–
T2	1549	1415 (91.35%)	5 (4.557–5.443)	1.203 (1.077–1.344)	0.001
T3	1568	1441 (91.90%)	4 (3.679–4.321)	1.244 (1.113–1.392)	< 0.001
T4	2075	1930 (93.01%)	4 (3.728–4.272)	1.319 (1.181–1.473)	< 0.001
N stage				1.077 (1.046–1.109)	< 0.001
N0	1098	982 (89.44%)	5 (4.449–5.551)	1.00	–
N1	492	440 (89.43%)	5 (4.251–5.749)	1.007 (0.899–1.127)	0.904
N2	2884	2675 (92.75%)	4 (3.754–4.246)	1.162 (1.079–1.252)	< 0.001
N3	1190	1104 (92.77%)	4 (3.514–4.486)	1.153 (1.055–1.259)	0.002
Grade				1.141 (1.090–1.195)	< 0.001
1	264	238 (90.15%)	6 (4.535–7.465)	1.00	–
2	1733	1549 (89.38%)	6 (5.456–6.544)	1.049 (0.914–1.203)	0.497
3	3529	3280 (92.94%)	4 (3.804–4.196)	1.234 (1.081–1.410)	0.002
4	138	134 (97.10%)	3 (2.330–3.670)	1.387 (1.112–1.731)	0.004
Brain metastases					
No	4331	3966 (91.57%)	4 (3.756–4.244)	1.00	–
Yes	1333	1235 (92.65%)	4 (3.698–4.302)	1.214 (1.136–1.297)	< 0.001
Liver metastases					
No	4393	3978 (90.55%)	5 (4.731–5.269)	1.00	–
Yes	1271	1223 (96.22%)	3 (2.715–3.285)	1.392 (1.303–1.487)	< 0.001
Lung metastases					
No	3892	3562 (91.52%)	5 (4.760–5.240)	1.00	–
Yes	1772	1639 (92.49%)	4 (3.648–4.352)	1.029 (0.965–1.098)	0.376
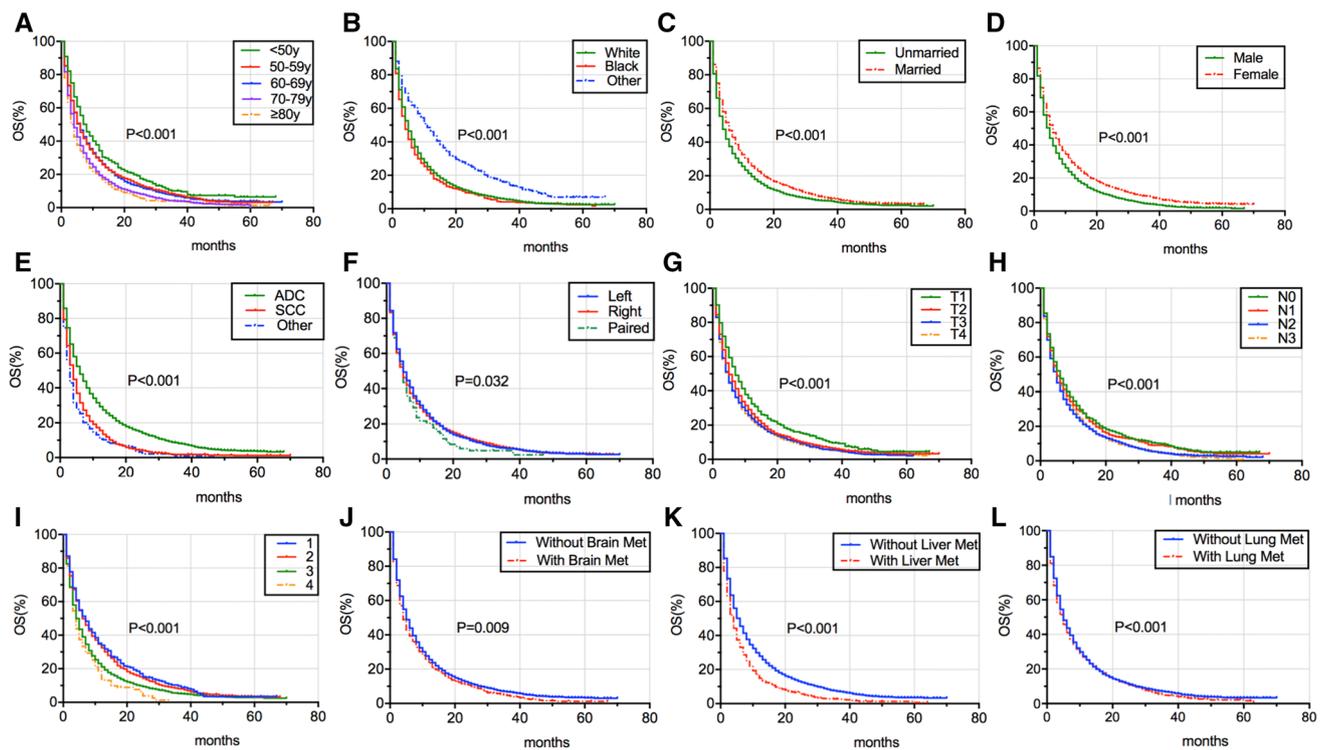
Fig. 2 Kaplan–Meier survival curve analysis of risk factors' impact on the OS of BM patients in NSCLC, which were stratified according to age (**a**), race (**b**), marital status (**c**), sex (**d**), tumor histology (**e**), laterality (**f**), T stage (**g**), N stage (**h**), grade (**i**), brain metastases (**j**), liver metastases (**k**), and lung metastases (**l**). *OS* overall survival, *BM* bone metastases, *NSCLC* non-small cell lung cancer, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *Brain Met* brain metastases, *Liver Met* liver metastases, *Lung Met* lung metastases, *y* years

survival outcomes. In the six homogeneous risk factors, liver metastases rank highest in both odds ratio and hazard ratio. This is also in accordance with the study showing that lung cancer patients with liver metastases conferred the worst prognosis (Riihimaki et al. 2014). It also highlights the close contact between BM and liver metastases in NSCLC. Further mechanism researches are needed to unearth their possible interaction. According to the heterogeneous risk factors, physicians can focus on different aspects of their predictive abilities. For adenocarcinoma patients, the main focus should be the risk of BM, but the main concentration should be on the prognosis of BM for SCC. Interestingly, we found that married patients were more likely to develop BM than unmarried patients, while unmarried BM patients were with poorer prognosis than those married. Studies have shown that marriage can bring survival benefits for cancer patients because of the health insurance status, psychological supports from the family, and neighborhood socioeconomic status (Aizer et al. 2013; Gomez et al. 2016). These can explain why married BM patients of NSCLC have a better survival outcome than those unmarried. Nevertheless, we found married patients had higher possibility of developing BM, which has not been reported before. We hypothesize that this may

be caused by the higher rate of exposure to secondhand smoke and kitchen fume of married women patients when they were diagnosed of NSCLC with BM, after which they were more likely to get the family support. This may explain why married patients were more likely diagnosed with BM while they were less likely to die from NSCLC.

Nevertheless, our investigations have some limitations that need to be mentioned. First of all, the SEER database only offered us with BM patients that were initially diagnosed, which may cause underestimation of those who progressed into BM later in their disease duration. Then, as demonstrated above, the SEER database may cause the underestimation of BM rate since the asymptomatic BM patients are unable to be captured. Third, the SEER database does not provide the detailed diagnostic standards for BM. Besides, the SEER database does not contain some important clinicopathologic factors of NSCLC like driven mutations, which need further investigations.

In conclusion, despite the limitations, our analyses used a large cohort of NSCLC patients in SEER database to demonstrate that there were homogeneous and heterogeneous risk factors for BM incidence and survival outcomes. Our study may provide a framework for clinical prediction and to provide patients with personzed treatment in clinical practice.
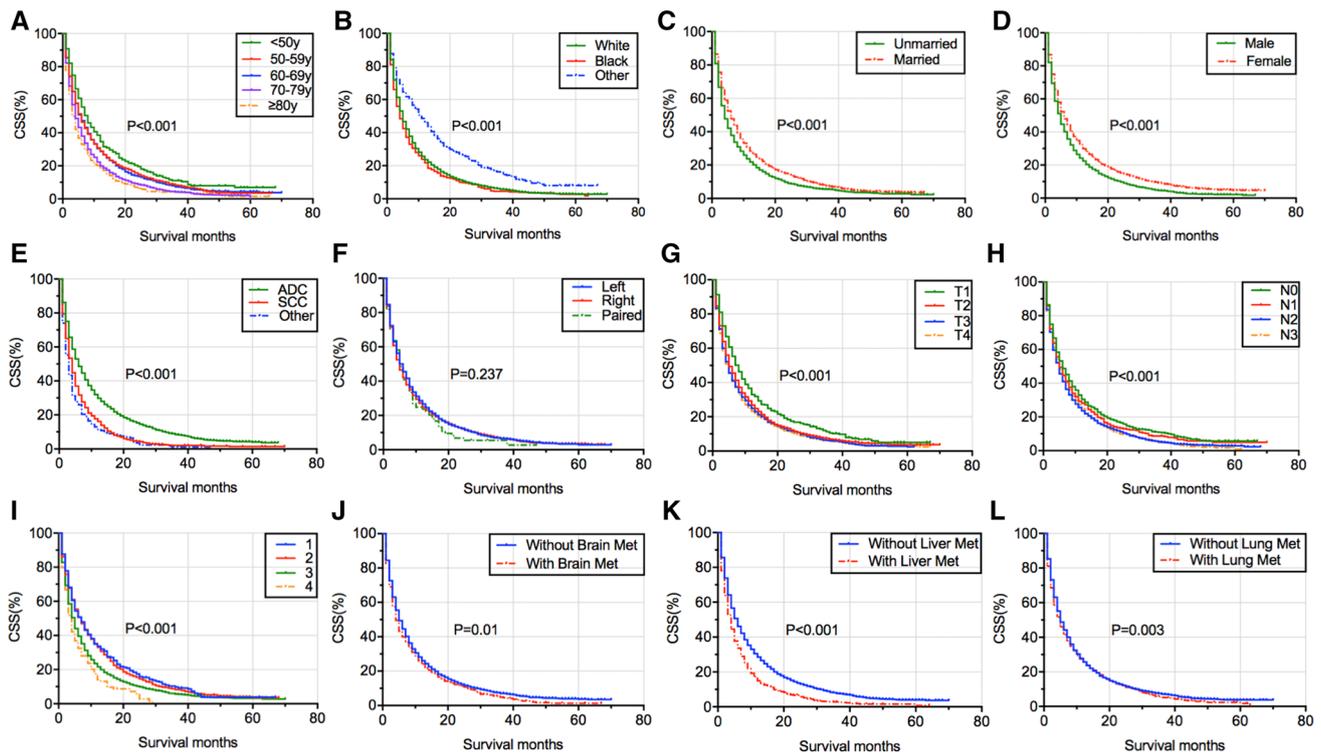
Fig. 3 Kaplan–Meier survival curve analysis of risk factors' impact on the CSS of BM patients in NSCLC, which were stratified according to age (**a**), race (**b**), marital status (**c**), sex (**d**), tumor histology (**e**), laterality (**f**), T stage (**g**), N stage (**h**), grade (**i**), brain metastases (**j**), liver metastases (**k**), and lung metastases (**l**). *CSS* cancer-specific survival, *BM* bone metastases, *NSCLC* non-small cell lung cancer, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *Brain Met* brain metastases, *Liver Met* liver metastases, *Lung Met* lung metastases, *y* years
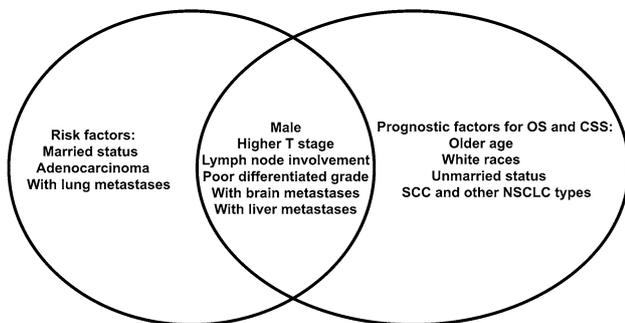

Fig. 4 The homogeneous and heterogeneous risk factors for the incidence and survival outcome of BM patients in NSCLC. The left circle was the risk factors for the incidence of BM patients. The right circle was the risk factors for the prognosis factors of BM patients' OS and CSS. The intersection of two circles meant the homogeneous risk factors including male, higher T stage, lymph node involvement, poor differentiation grade, brain metastases, and liver metastases. *OS* overall survival, *CSS* cancer-specific survival, *BM* bone metastases, *SCC* squamous cell carcinoma, *NSCLC* non-small cell lung cancer

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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