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Risk and prognostic factors of brain metastasis in lung cancer patients: a Surveillance, Epidemiology, and End Results population-based cohort study

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Background **Brain is a common metastasis site in lung cancer patients. However, homogeneous and heterogeneous risk/prognostic factors of brain metastasis for lung cancer patients have not been comprehensively elucidated. This study aimed to explore the brain metastasis risk and prognostic factors in lung cancer patients using the Surveillance, Epidemiology, and End Results (SEER) database.**

Methods **Lung cancer data were downloaded from SEER database to investigate risk factors for developing brain metastasis using logistic regression analysis. Univariate and multivariate Cox analyses were used to identify potential prognostic factors. Kaplan–Meier analysis was conducted to evaluate the survival. Propensity score matching was conducted to eliminate baseline differences between two groups.**

Results **A total of 10 818 (14.1%) patients with brain metastasis were diagnosed among 76 483 lung cancer patients. For non–small-cell lung carcinoma (NSCLC), distant liver/bone/lymph node metastases, higher T, N stages were risk factors. Black race, bone metastases and distant lymph node metastases and T4 were brain metastasis risk factors for SCLC patients. Cox analysis suggested that older age, male, primary lesion at main bronchus, liver/ bone/distant lymph node metastases, T2-4, N1-3, no surgery/chemotherapy/radiotherapy were associated with worse prognosis of NSCLC-brain metastasis patients. Age older than 80, liver/bone metastases, without radiotherapy and chemotherapy were associated with worse prognosis of SCLC-brain metastasis patients. Surgery of primary site could prolong the overall survival (OS) of NSCLC patients with brain metastasis, but not SCLC.**

Conclusion **In this study, we analyzed the homogeneous and heterogeneous risk/prognostic factors of brain metastasis in lung cancer patients. What is more, our results showed that surgery of primary site was associated with longer OS of NSCLC patients with brain metastasis.** ***European Journal of Cancer Prevention*** **32: 498–511**

European Journal of Cancer Prevention 2023, **32**:498–511

Keywords: brain metastasis, lung cancer, risk factors, prognosis, surgery

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Received 13 January 2023 **Accepted** 20 January 2023.

Introduction

It is estimated that about 236 740 new cases of lung cancer will be diagnosed in the USA in 2022, with 130 180 cases of deaths. Lung cancer is the second most common cancer in both men and women, less than breast cancer (in female) or prostate cancer (in male), and is the leading cause of death of cancer patients, with low 5-year survival rate (Siegel *et al*., 2022). Metastasis is a characteristic of cancer and is responsible for the greatest number of cancer-related deaths (Fares *et al*., 2020). Brain is a common metastasis site of lung cancer. About 20% of cancer patients will develop brain metastases (Achrol *et al*., 2019), and brain metastases from lung cancer account for about 45% of total brain metastases (Schouten *et al*., 2002; Lowery and Yu, 2017). What is more, it is reported that about 10% of small-cell lung cancer (SCLC) patients have brain metastases at the time of initial diagnosis (Castrucci and Knisely, 2008).

Despite the rapid development of multiple therapies, such as targeted therapy and immunotherapy, the prognosis of patients with advanced lung cancer remains poor (Achrol *et al*., 2019). The median survival time of brain metastasis patients was about 6–10 months (Steeg *et al*., 2011; Bacha *et al*., 2018; Zhu *et al*., 2022). A study focusing on non–small-cell lung carcinoma (NSCLC) suggested that the median overall survival (OS) after NSCLC diagnosis was 13.33 months and the median OS after brain metastasis was 10.6 months (Bacha *et al*., 2018). Focusing on the high-risk population that is susceptible to brain metastasis and identifying potential brain metastasis before clinical symptoms could provide patients with

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the chance of receiving treatment timely and benefit the prognosis (Sanchez de Cos *et al.*, 2009). Therefore, it is very important to identify risk and prognostic factors, evaluate individual metastatic risk, and make diagnosis accurately, so as to improve the therapy.

Clinical characteristics including age, race, sex, Gleason score, smoking, histological type, T stage, N stage, insurance status, and marital status were found to correlate with survival of lung cancer patients with brain metastasis (Reddy *et al.*, 2020; Shen *et al.*, 2021; Sung *et al.*, 2021). The number and total volume of brain metastasis are also key factors that influence patient survival (Aoyama *et al.*, 2006; Sanchez de Cos *et al.*, 2009; Yamamoto *et al.*, 2013). Several nomograms predicting the brain metastasis of lung cancer patients based on clinical characteristics were proposed (Li *et al.*, 2021; Zuo *et al.*, 2021). However, few studies focused on the comparison of risk and prognostic value of different clinical factors. The purpose of our study was to investigate the risk factors for brain metastasis and prognostic factors for lung cancer patients with brain metastasis based on large data from the Surveillance, Epidemiology, and End Results (SEER) database. We further investigated homogeneous and heterogeneous risk and prognostic factors.

Methods

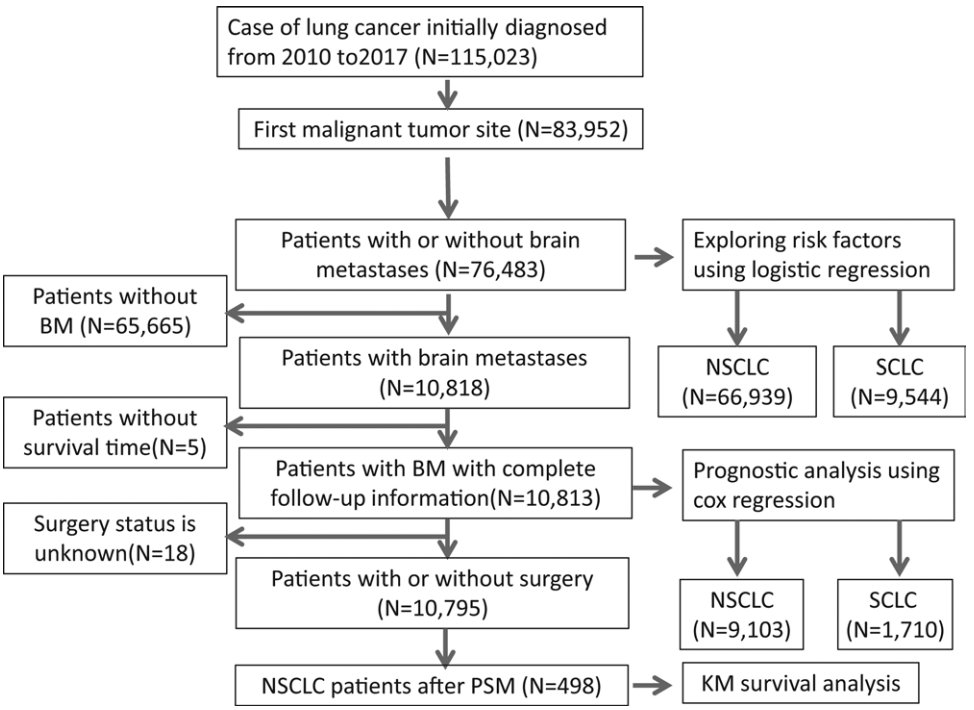
Population

In this population-based study, lung cancer data were downloaded from the SEER database. SEER*Stat version 8.4.0 (https://seer.cancer.gov/seerstat/) was used to get the patient information (Doll *et al.*, 2018). Lung cancer patients diagnosed with brain metastasis between 2010 and 2017 were included in this study. Patient information was excluded when it is not the first primary site or follow-up information is incomplete. The inclusion and exclusion process is shown in Fig. 1. A total of 76 483 patients diagnosed with lung cancer between 2010 and 2017 were used to investigate brain metastasis risk factors, and then prognostic factors were explored for 10 813 lung cancer patients with brain metastasis. Subgroup analysis was based on the pathology of lung cancer patients. Patient information with survival time was used to investigate the prognostic role of surgery for NSCLC patients with brain metastasis.

Statistical analysis

This study included the following variables: age (<50, 50–59, 60–69, 70–79, ≥80); sex (male and female); race [white, black, other (American Indian/AK Native, Asian/Pacific Islander), unknown]; pathology (adenocarcinoma,

Fig. 1



Flowchart of the process of data selection. BM, brain metastasis.

non–small-cell carcinoma, small-cell carcinoma, large-cell carcinoma, squamous-cell carcinoma, other); site of primary tumor (left main bronchus, left upper lobe, left lower lobe, right main bronchus, right upper lobe, right middle lobe, right lower lobe, other); T stage (T1, T2, T3, T4, other); N stage (N0, N1, N2, N3, other); liver metastasis status (Yes, No, unknown); bone metastasis (Yes, No, unknown); brain metastasis (Yes, No, unknown); surgical treatment (Yes, No, unknown); radiotherapy (Yes, No, unknown); and chemotherapy (Yes, No, unknown). Univariate and multivariate logistic regression were used to identify the risk factors for brain metastasis. Kaplan–Meier method was conducted to investigate OS outcomes. Univariate and multivariate Cox regression analyses were used to identify potential prognostic factors. Propensity score matching (PSM) (ratio 1:1, caliper: 0.2 SD of propensity score) was conducted to eliminate baseline differences between the two groups using the 'Matching' R package (Huber *et al.*, 2017; Zhao *et al.*, 2021). $P<0.05$ was considered to be statistically significant. All statistical analyses were conducted within R software (version 4.1.0).

Results

Patient characteristics

A total of 76 483 lung cancer patients were initially identified between 2010 and 2017. Of these patients, 10 818 (14.1%) patients were diagnosed with brain metastasis, and most patients were without brain metastasis (85.9%, $N=65\,665$). 13 960 (18.3%) patients were more than 80 years. A total of 39 642 (51.8%) patients were male. A total of 39.1% were diagnosed with lung adenocarcinoma ($N=29\,878$). Over half of the patients were white (76.7%, $N=155\,877$). As for the lesion site, the right upper lobe is the most common, about 28.6% ($N=21\,842$). Most patients were without bone metastases ($N=60\,706$, 79.4%), liver metastases ($N=66\,410$, 86.8%), or distant lymph node metastases ($N=17\,880$, 23.4%). 14.9 % of patients ($N=11\,363$) were T1 and 27.6% ($N=21\,129$) were N0. More details about patient clinical characteristics are shown in Table 1.

Risk factors for developing brain metastases

The univariate and multivariate logistic regression analyses were conducted to investigate the risk factors associated with brain metastases. Results showed that age, race, pathology, primary lesion site, bone metastases, liver metastases, distant lymph node metastases, T stage, N stage were all associated with the development of brain metastasis. The association between sex and brain metastasis was not significant. The multivariate logistic regression revealed that patients older than 60 were less likely to develop brain metastasis. Other races, non–squamous-cell carcinoma, bone metastases, liver metastases, distant lymph node metastases, higher T stage, and higher N stage were risk factors of brain metastasis. As for the primary site, compared with the left upper lobe, patients whose tumor were present in right middle lobe and right lower lobe had a lower risk of developing brain metastasis. The logistic regression analysis results are shown in Table 2.

Considering that there are significant differences in tissue behavior between SCLC and NSCLC, we divided the patients in the cohort into two groups according to the pathological type: NSCLC group and SCLC group, and carried out logistic regression in two subgroups. The results showed that there were significant differences between NSCLC and SCLC in the factors related to brain metastasis. In NSCLC, the results of univariate logistic regression suggested that age, race, location of primary lesion, presence of bone metastasis, liver metastasis, distant lymph node metastasis, T stage and N stage were related to the occurrence of brain metastasis. While in multivariate analysis, lesion in middle and lower lobe of the right lung were related to the lower risk of brain metastasis. The risk of synchronous brain metastasis is increased in patients with other races, synchronous distant metastasis (liver, bone, distant lymph node metastasis), higher T stage, and higher N stage. More details are shown in Table 3.

In the SCLC group, we got different results. First of all, in the univariate logistic regression, the site of the primary lesion and N stage were not related to the occurrence of brain metastasis. In multivariate logistic regression, compared with patients younger than 50 years old, patients older than 70 years old have a lower risk of synchronous brain metastasis. Compared with white race, black race patients with SCLC have a higher risk of brain metastasis. There was no significant correlation between sex and brain metastasis. Patients with bone metastasis and distant lymph node metastasis were associated with a higher risk of brain metastasis, but not synchronous liver metastasis. It is worth noting that compared with T1, only T4 has significant correlation with the risk of synchronous brain metastasis, while T2 and T3 have no difference compared with T1. See Table 4 for more details of logistic regression analysis.

Prognostic factors for lung cancer patients with brain metastasis

A total of 10 813 lung cancer patients with brain metastasis and follow-up information between 2010 and 2017 were included to conduct Cox regression analysis and investigate potential prognostic factors. Treatment information was also collected, including surgery, radiotherapy and chemotherapy. Two hundred sixty-one patients (2.4%) received surgical treatment of primary lesions, 7861 patients (72.7%) received radiotherapy, and 6036 patients (55.8%) received chemotherapy. SEER database also provides the type of radiotherapy, as shown in Supplementary Table 1 and 2, Supplemental Digital Content 1, *http://links.lww.com/EJCP/*

Table 1 Clinical characteristics of lung cancer patients

	Brain metastases			
	Overall	No	Yes	*P*
n	76483	65665	10818	
Age (%)				<0.001
<50	3040 (4.0)	2397 (3.7)	643 (5.9)	
50–59	12290 (16.1)	9781 (14.9)	2509 (23.2)	
60–69	23822 (31.1)	20008 (30.5)	3814 (35.3)	
70–79	23371 (30.6)	20611 (31.4)	2760 (25.5)	
≥80	13960 (18.3)	12868 (19.6)	1092 (10.1)	
Race (%)				<0.001
Black	6948 (9.1)	5902 (9.0)	1046 (9.7)	
White	60578 (79.2)	52284 (79.6)	8294 (76.7)	
Other	8802 (11.5)	7340 (11.2)	1462 (13.5)	
Unknown	155 (0.2)	139 (0.2)	16 (0.1)	
Sex (%)				
Female	36841 (48.2)	31698 (48.3)	5143 (47.5)	0.162
Male	39642 (51.8)	33967 (51.7)	5675 (52.5)	
Pathology (%)				<0.001
Squamous-cell carcinoma	14957 (19.6)	14058 (21.4)	899 (8.3)	
Adenocarcinoma	29878 (39.1)	24393 (37.1)	5485 (50.7)	
Non–small-cell carcinoma	4894 (6.4)	3976 (6.1)	918 (8.5)	
Small-cell carcinoma	9544 (12.5)	7834 (11.9)	1710 (15.8)	
Large-cell carcinoma	1009 (1.3)	819 (1.2)	190 (1.8)	
Other	16201 (21.2)	14585 (22.2)	1616 (14.9)	
Location (%)				<0.001
Left lower	8995 (11.8)	7763 (11.8)	1232 (11.4)	
Left upper	17139 (22.4)	14747 (22.5)	2392 (22.1)	
Left main bronchus	1366 (1.8)	1163 (1.8)	203 (1.9)	
Right lower	11402 (14.9)	9993 (15.2)	1409 (13.0)	
Right middle	3530 (4.6)	3094 (4.7)	436 (4.0)	
Right upper	21842 (28.6)	18850 (28.7)	2992 (27.7)	
Right main bronchus	1841 (2.4)	1539 (2.3)	302 (2.8)	
Other	10368 (13.6)	8516 (13.0)	1852 (17.1)	
Bone metastasis (%)				<0.001
No	60706 (79.4)	53994 (82.2)	6712 (62.0)	
Yes	15094 (19.7)	11275 (17.2)	3819 (35.3)	
Unknown	683 (0.9)	396 (0.6)	287 (2.7)	
Liver metastasis (%)				<0.001
No	66410 (86.8)	58173 (88.6)	8237 (76.1)	
Yes	9274 (12.1)	7091 (10.8)	2183 (20.2)	
Unknown	799 (1.0)	401 (0.6)	398 (3.7)	
Distant lymph node metastasis (%)				<0.001
NO	17880 (23.4)	15616 (23.8)	2264 (20.9)	
Yes	1730 (2.3)	1267 (1.9)	463 (4.3)	
Unknown	56873 (74.4)	48782 (74.3)	8091 (74.8)	
T (%)				<0.001
T1	11363 (14.9)	10550 (16.1)	813 (7.5)	
T2	15451 (20.2)	13525 (20.6)	1926 (17.8)	
T3	11117 (14.5)	9386 (14.3)	1731 (16.0)	
T4	12184 (15.9)	9910 (15.1)	2274 (21.0)	
Other	26368 (34.5)	22294 (34.0)	4074 (37.7)	
N (%)				<0.001
N0	21129 (27.6)	19590 (29.8)	1539 (14.2)	
N1	4930 (6.4)	4246 (6.5)	684 (6.3)	
N2	19457 (25.4)	15985 (24.3)	3472 (32.1)	
N3	8164 (10.7)	6439 (9.8)	1725 (15.9)	
Other	22803 (29.8)	19405 (29.6)	3398 (31.4)	

A378. The vast majority of patients (71.9%) received beam radiation treatment, and a few patients also received radioactive implant or radioisotope treatment. The median survival of lung cancer patients with brain metastasis was 5 months. The 1-year, 3-year, and 5-year survival rates for brain metastasis patients were 25.27%, 8.19%, and 4.51%, respectively. The univariate Cox regression analysis suggested that older age, male, liver metastases, bone metastases, distant lymph node metastases, higher T or N stage, no surgery, no radiotherapy, no chemotherapy were risk factors of brain metastasis patient prognosis. Multivariable Cox regression analysis showed that older age, male, white race, SCC, liver metastases, bone metastases, distant lymph node metastases, T2-4, N1-3, no surgery, no chemotherapy were associated with worse prognosis. Compared with SCC, brain metastasis patients whose pathology was adenocarcinoma had a better prognosis. Brain metastasis patients with tumors that originated in the left upper lobe of lung had longer survival time than those in the right main bronchus. Cox analysis results are shown in Table 5.

Supplementary Table 1, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A378*. The type of radiotherapy that lung cancer-brain metastasis patients received.

Table 2 The logistic regression analysis results

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age				
<50	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
50–59	0.96 (0.87–1.05)	0.368	1 (0.9–1.11)	0.971
60–69	0.71 (0.65–0.78)	<0.001	0.8 (0.72–0.88)	<0.001
70–79	0.5 (0.45–0.55)	<0.001	0.6 (0.54–0.66)	<0.001
≥80	0.32 (0.28–0.35)	<0.001	0.38 (0.34–0.43)	<0.001
Race				
White	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Black	1.12 (1.04–1.2)	0.002	1 (0.93–1.08)	0.902
Other	1.26 (1.18–1.33)	<0.001	1.17 (1.09–1.24)	<0.001
Unknown	0.73 (0.43–1.22)	0.225	0.82 (0.48–1.39)	0.461
Sex				
Female	1 (Reference)	1 (Reference)		
Male	1.03 (0.99–1.07)	0.158		
Pathology				
Squamous-cell carcinoma	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Adenocarcinoma	3.52 (3.27–3.78)	<0.001	3.03 (2.81–3.27)	<0.001
Non–small-cell carcinoma	3.61 (3.27–3.98)	<0.001	3.04 (2.75–3.37)	<0.001
Small-cell carcinoma	3.41 (3.13–3.72)	<0.001	2.3 (2.1–2.51)	<0.001
Large-cell carcinoma	3.63 (3.06–4.31)	<0.001	2.92 (2.44–3.48)	<0.001
Other	1.73 (1.59–1.89)	<0.001	1.82 (1.67–1.99)	<0.001
Location				
Left upper	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Left lower	0.98 (0.91–1.05)	0.563	1.02 (0.94–1.1)	0.684
left main bronchus	1.08 (0.92–1.26)	0.354	0.88 (0.75–1.04)	0.126
Right upper	0.98 (0.92–1.04)	0.464	0.95 (0.89–1.01)	0.098
Right middle	0.87 (0.78–0.97)	0.012	0.84 (0.75–0.95)	0.003
Right lower	0.87 (0.81–0.93)	<0.001	0.9 (0.84–0.97)	0.005
Right main bronchus	1.21 (1.06–1.38)	0.004	0.95 (0.83–1.09)	0.505
Other	1.34 (1.25–1.43)	<0.001	0.95 (0.88–1.02)	0.126
Bone metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	2.72 (2.61–2.85)	<0.001	1.79 (1.71–1.88)	<0.001
Unknown	5.83 (5–6.8)	<0.001	2.54 (2.12–3.05)	<0.001
Liver metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	2.17 (2.06–2.29)	<0.001	1.4 (1.31–1.48)	<0.001
Unknown	7.01 (6.09–8.07)	<0.001	3.76 (3.19–4.44)	<0.001
Distant lymph node metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	2.52 (2.25–2.83)	<0.001	1.7 (1.51–1.92)	<0.001
Unknown	1.14 (1.09–1.2)	<0.001	1.54 (1.37–1.72)	<0.001
T				
T1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
T2	1.85 (1.7–2.01)	<0.001	1.58 (1.44–1.73)	<0.001
T3	2.39 (2.19–2.61)	<0.001	1.73 (1.58–1.9)	<0.001
T4	2.98 (2.74–3.24)	<0.001	1.92 (1.76–2.11)	<0.001
Other	2.37 (2.19–2.57)	<0.001	1.93 (1.74–2.15)	<0.001
N				
N0	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
N1	2.05 (1.86–2.26)	<0.001	1.65 (1.49–1.82)	<0.001
N2	2.76 (2.59–2.95)	<0.001	1.88 (1.75–2.01)	<0.001
N3	3.41 (3.17–3.67)	<0.001	1.98 (1.83–2.15)	<0.001
Other	2.23 (2.09–2.37)	<0.001	1.97 (1.76–2.2)	<0.001

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

Since our previous analysis results suggest that there is significant heterogeneity between SCLC group and NSCLC group, here we conducted subgroup analysis again, and compared the prognostic factors of patients with brain metastasis in SCLC and NSCLC groups through univariate and multivariate cox analysis. In NSCLC group, the prognosis of patients with brain metastasis was worse with older age, and the prognosis of female patients was better than that of male patients. Compared with white race, patients of black race and other races have better prognosis. As for the primary lesion, compared with the left upper lobe, the prognosis of patients with primary lesions in the left and right main bronchi was worse. Based on the existence of brain metastasis, synchronous liver metastasis, bone metastasis, distant lymph node metastasis, and higher T and N staging led to poor prognosis. Surgical treatment, radiotherapy and chemotherapy of primary lesions could prolong the survival of patients (Table 6).

In SCLC, gender and the site of the primary lesion did not affect the survival of patients with brain metastasis (Table 7). Patients older than 80 years old, with liver metastasis and bone metastasis had a worse prognosis,

Table 3 The logistic regression analysis results of brain metastasis in non–small-cell lung cancer patients

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95%CI)	*P*
Age				
<50	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
50–59	0.94 (0.85–1.04)	0.229	0.98 (0.88–1.09)	0.704
60–69	0.67 (0.61–0.74)	<0.001	0.74 (0.67–0.82)	<0.001
70–79	0.48 (0.43–0.53)	<0.001	0.54 (0.49–0.6)	<0.001
≥80	0.3 (0.27–0.33)	<0.001	0.34 (0.3–0.38)	<0.001
Race				
White	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Black	1.12 (1.04–1.2)	0.004	0.99 (0.91–1.07)	0.755
Other	1.3 (1.22–1.39)	<0.001	1.23 (1.15–1.31)	<0.001
Unknown	0.64 (0.35–1.15)	0.136	0.76 (0.41–1.39)	0.368
Sex				
Female	1 (Reference)	1 (Reference)		
Male	1.01 (0.97–1.06)	0.530		
Location				
Left upper	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Left lower	0.98 (0.9–1.06)	0.602	1.01 (0.93–1.1)	0.813
left main bronchus	1.1 (0.91–1.32)	0.319	0.83 (0.69–1.01)	0.063
Right upper	0.98 (0.92–1.04)	0.530	0.99 (0.92–1.05)	0.656
Right middle	0.87 (0.77–0.98)	0.017	0.86 (0.76–0.98)	0.019
Right lower	0.88 (0.81–0.95)	0.001	0.9 (0.83–0.98)	0.010
Right main bronchus	1.26 (1.08–1.47)	0.003	0.92 (0.78–1.08)	0.304
Other	1.41 (1.32–1.52)	<0.001	1.01 (0.93–1.1)	0.775
Bone metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	3.03 (2.89–3.18)	<0.001	2.08 (1.97–2.19)	<0.001
Unknown	6.68 (5.63–7.93)	<0.001	2.75 (2.24–3.37)	<0.001
Liver metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	2.66 (2.51–2.83)	<0.001	1.62 (1.51–1.73)	<0.001
Unknown	7.92 (6.79–9.24)	<0.001	4.03 (3.36–4.82)	<0.001
Distant lymph node metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	2.66 (2.34–3.02)	<0.001	1.75 (1.53–2)	<0.001
Unknown	1.14 (1.08–1.2)	<0.001	1.53 (1.36–1.73)	<0.001
T				
T1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
T2	1.92 (1.75–2.1)	<0.001	1.53 (1.39–1.68)	<0.001
T3	2.53 (2.3–2.78)	<0.001	1.62 (1.47–1.8)	<0.001
T4	3.19 (2.91–3.5)	<0.001	1.85 (1.67–2.04)	<0.001
Other	2.49 (2.29–2.71)	<0.001	1.94 (1.72–2.17)	<0.001
N				
N0	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
N1	2.08 (1.87–2.3)	<0.001	1.64 (1.47–1.82)	<0.001
N2	2.97 (2.77–3.17)	<0.001	2.05 (1.9–2.2)	<0.001
N3	3.77 (3.48–4.09)	<0.001	2.23 (2.05–2.43)	<0.001
Other	2.29 (2.14–2.45)	<0.001	1.96 (1.73–2.21)	<0.001

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

while patients of other race groups had a better prognosis. It should be noted that the T and N stages of the primary lesion and the metastatic status of distant lymph node were not related to the survival time of SCLC patients with brain metastasis. Primary lesion surgery cannot prolong the survival time of patients, while radiotherapy and chemotherapy were associated with a better prognosis for patients. This is different from the cox analysis results of NSCLC patients with brain metastasis, suggesting that there is heterogeneity between SCLC and NSCLC.

Effects of surgery on survival of non–small-cell lung carcinoma patients with brain metastasis

Since the cox results showed that surgery on primary tumor was associated with longer survival of NSCLC-brain metastasis patients, we then explored whether it still benefited patients after adjusting for other clinical factors. Among 10 813 patients with survival time, 10 795 patients were confirmed with or without surgery, and 9090 patients were NSCLC. Therefore, these patients were included in Kaplan–Meier survival analysis to explore the significance of surgery for primary lesion. In order to explore whether there were confounding bias, we analyzed the differences in clinical information between surgery and non-surgery groups. Results showed that all clinical characteristics, except sex, race, and distant lymph node metastases were unevenly distributed between two groups. Therefore, 1:1 PSM (caliper: 0.2 SD of propensity score) was then conducted using the 'Matching' package in R software. All the clinical factors including age, race, sex, location, bone metastasis, liver metastasis, Distant lymph node metastasis, T, N, radiotherapy, chemotherapy were included to calculate propensity score. Clinical characteristics

Table 4 The logistic regression analysis results of brain metastasis in small-cell lung cancer patients

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age				
<50	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
50–59	1.08 (0.79–1.46)	0.634	1.11 (0.82–1.51)	0.493
60–69	0.97 (0.72–1.3)	0.843	0.99 (0.73–1.33)	0.930
70–79	0.69 (0.51–0.93)	0.016	0.71 (0.53–0.97)	0.031
≥80	0.54 (0.39–0.76)	<0.001	0.57 (0.41–0.8)	0.001
Race				
White	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Black	1.27 (1.05–1.54)	0.015	1.24 (1.02–1.51)	0.032
Other	1.09 (0.9–1.32)	0.385	1.11 (0.92–1.35)	0.281
Unknown	1.34 (0.44–4.09)	0.604	1.31 (0.43–4.02)	0.636
Sex				
Female	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Male	1.14 (1.02–1.26)	0.017	1.08 (0.97–1.21)	0.141
Location				
Left upper	1 (Reference)	1 (Reference)		
Left lower	1.01 (0.83–1.24)	0.892		
left main bronchus	0.82 (0.61–1.1)	0.186		
Right upper	1 (0.86–1.17)	0.981		
Right middle	0.9 (0.67–1.2)	0.481		
Right lower	0.87 (0.71–1.05)	0.146		
Right main bronchus	0.88 (0.68–1.14)	0.341		
Other	0.94 (0.8–1.11)	0.480		
Bone metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.42 (1.27–1.6)	<0.001	1.4 (1.23–1.58)	<0.001
Unknown	2.86 (2–4.08)	<0.001	2.11 (1.41–3.14)	<0.001
Liver metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.01 (0.9–1.13)	0.847	0.89 (0.79–1.01)	0.063
Unknown	3.27 (2.31–4.65)	<0.001	2.36 (1.6–3.49)	<0.001
Distant lymph node metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.81 (1.39–2.36)	<0.001	1.7 (1.3–2.23)	<0.001
Unknown	1.15 (1.01–1.32)	0.038	1.19 (0.98–1.44)	0.076
T				
T1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
T2	1.21 (0.95–1.53)	0.125	1.16 (0.91–1.47)	0.231
T3	1.33 (1.04–1.69)	0.023	1.27 (0.99–1.62)	0.057
T4	1.46 (1.16–1.83)	0.001	1.33 (1.06–1.68)	0.014
Other	1.34 (1.08–1.67)	0.008	1.32 (1.03–1.7)	0.029
N				
N0	1 (Reference)	1 (Reference)		
N1	1.18 (0.9–1.54)	0.223		
N2	1.12 (0.92–1.35)	0.250		
N3	1.21 (0.98–1.49)	0.083		
Other	1.18 (0.97–1.43)	0.099		

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

between surgery and non-surgery groups are shown in Table 8. After PSM, 498 patients were selected and the baseline differences between two groups were balanced.

Kaplan–Meier survival analysis suggested that for NSCLC patients with brain metastasis, surgical treatment of the primary lesion could prolong patients' survival. A similar result was obtained after removing the influence of other clinical factors (Fig. 2). NSCLC patients with brain metastasis who received surgery for primary lesion had longer median survival time than those who did not have surgery (16.0 months vs. 4.0 months $P < 0.001$ and 16.0 months vs. 8.0 months $P < 0.001$ after PSM). This result suggests that surgery on primary site could bring survival benefits to NSCLC-brain metastasis patients. Further clinical trials are required to explore its therapeutic value and side effects in the future.

Considering that the T and N stage of tumor, liver metastasis and bone metastasis status all affected the survival time of patients with brain metastasis, we divided the patients cohort after PSM into T1-2 or T3-4 groups, N0-1 or N2-3 groups, with or without liver metastasis groups, with or without bone metastasis groups, and further explored the impact of primary lesion surgery on the prognosis in subgroups. The results showed that for NSCLC-brain metastasis patients with different T and N groups, the resection of the primary lesion could prolong the survival time of patients (Fig. 3).

The metastasis of other organs affected the prognosis of patients. For NSCLC-brain metastasis patients with no liver metastasis or bone metastasis, surgical treatment of the primary focus could significantly prolong the survival of patients. However, for patients with liver

Table 5 Univariate and multivariate Cox regression analysis results. $P<0.05$ was considered statistically significant

	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
<50	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
50–59	1.42 (1.30–1.56)	<0.001	1.38 (1.26–1.52)	<0.001
60–69	1.66 (1.51–1.81)	<0.001	1.55 (1.42–1.70)	<0.001
70–79	2.12 (1.93–2.32)	<0.001	1.81 (1.65–1.99)	<0.001
≥80	3.16 (2.84–3.50)	<0.001	2.31 (2.07–2.57)	<0.001
Sex				
Female	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Male	1.22 (1.18–1.27)	<0.001	1.18 (1.14–1.23)	<0.001
Race				
Wihte	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Black	0.95 (0.89–1.01)	0.114	0.92 (0.86–0.99)	0.018
Other	0.73 (0.69–0.78)	<0.001	0.73 (0.69–0.77)	<0.001
Unknown	0.76 (0.44–1.30)	0.312	0.94 (0.54–1.62)	0.817
Pathology				
Squamous-cell carcinoma	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Adenocarcinoma	0.61 (0.57–0.66)	<0.001	0.71 (0.66–0.76)	<0.001
Non–small-cell carcinoma	0.88 (0.80–0.96)	0.005	0.88 (0.80–0.97)	0.011
Small-cell carcinoma	0.81 (0.75–0.88)	<0.001	0.94 (0.86–1.02)	0.132
Large-cell carcinoma	0.82 (0.70–0.96)	0.014	1.03 (0.88–1.21)	0.736
Other	0.98 (0.90–1.07)	0.686	0.85 (0.78–0.92)	<0.001
Primary lesion site				
Left upper	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Left lower	1.02 (0.95–1.09)	0.682	1.01 (0.94–1.09)	0.768
Left main bronchus	1.22 (1.06–1.42)	0.007	1.16 (1.00–1.34)	0.055
Right upper	1.03 (0.98–1.09)	0.236	1.02 (0.96–1.07)	0.589
Right middle	0.99 (0.89–1.10)	0.860	0.95 (0.85–1.05)	0.316
Right lower	1.05 (0.98–1.13)	0.154	1.04 (0.97–1.11)	0.273
Right main bronchus	1.27 (1.13–1.44)	<0.001	1.14 (1.01–1.29)	0.040
Other	1.26 (1.18–1.34)	<0.001	1.07 (1.00–1.14)	0.053
Bone metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.17 (1.12–1.22)	<0.001	1.23 (1.18–1.29)	<0.001
Unknown	1.38 (1.22–1.55)	<0.001	1.00 (0.86–1.18)	0.973
Liver metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.51 (1.44–1.58)	<0.001	1.47 (1.40–1.55)	<0.001
Unknown	1.29 (1.16–1.43)	<0.001	0.94 (0.82–1.08)	0.369
Distant lymph node metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.18 (1.06–1.31)	0.002	1.16 (1.04–1.30)	0.006
Unknown	1.24 (1.18–1.30)	<0.001	1.08 (0.97–1.20)	0.144
T				
T1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
T2	1.17 (1.07–1.27)	<0.001	1.16 (1.07–1.27)	<0.001
T3	1.34 (1.23–1.46)	<0.001	1.30 (1.19–1.42)	<0.001
T4	1.38 (1.27–1.50)	<0.001	1.32 (1.22–1.44)	<0.001
Other	1.17 (1.08–1.27)	<0.001	1.09 (0.99–1.20)	0.096
N				
N0	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
N1	1.05 (0.96–1.15)	0.301	1.12 (1.02–1.23)	0.015
N2	1.15 (1.08–1.22)	<0.001	1.24 (1.17–1.32)	<0.001
N3	1.17 (1.10–1.26)	<0.001	1.31 (1.22–1.41)	<0.001
Other	1.01 (0.95–1.08)	0.762	1.08 (0.98–1.20)	0.126
Surgery				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.43 (0.38–0.50)	<0.001	0.53 (0.46–0.61)	<0.001
Unknown	1.59 (0.99–2.56)	0.056	1.07 (0.66–1.74)	0.788
Radiotherapy				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.39 (0.32–0.46)	<0.001	0.99 (0.82–1.19)	0.896
None/unknown	0.73 (0.61–0.87)	<0.001	1.15 (0.96–1.38)	0.137
Chemotherapy				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.35 (0.34–0.37)	<0.001	0.38 (0.36–0.39)	<0.001

CI, confidence interval; HR, hazard ratio.

metastasis and bone metastasis, there was no significant difference in survival time between surgery and non-surgery groups (Fig. 4). These results suggested that for NSCLC patients with brain metastasis, if there is no other organ metastasis, the operation of the primary focus can benefit the patient's survival, while if there is other organ metastasis, the surgical treatment is meaningless.

Table 6 Univariate and multivariate Cox regression analysis results of non–small-cell lung carcinoma-brain metastasis patients

	Univariate cox		Multivariate cox	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
<50	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
50–59	1.43 (1.29–1.58)	<0.001	1.4 (1.27–1.55)	<0.001
60–69	1.7 (1.54–1.87)	<0.001	1.6 (1.45–1.77)	<0.001
70–79	2.13 (1.93–2.35)	<0.001	1.82 (1.64–2.01)	<0.001
≥80	3.14 (2.81–3.5)	<0.001	2.32 (2.07–2.6)	<0.001
Sex				
Female	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Male	1.25 (1.2–1.3)	<0.001	1.2 (1.15–1.26)	<0.001
Race				
White	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Black	0.97 (0.9–1.04)	0.361	0.92 (0.86–0.99)	0.035
Other	0.73 (0.69–0.78)	<0.001	0.7 (0.66–0.74)	<0.001
Unknown	0.9 (0.48–1.67)	0.728	1.15 (0.62–2.14)	0.661
Location				
Left upper	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Left lower	1.02 (0.94–1.1)	0.677	1.01 (0.94–1.1)	0.714
left main bronchus	1.35 (1.13–1.61)	0.001	1.31 (1.09–1.56)	0.003
Right upper	1.06 (0.99–1.12)	0.074	1.03 (0.97–1.09)	0.381
Right middle	0.98 (0.88–1.11)	0.785	0.94 (0.84–1.06)	0.298
Right lower	1.05 (0.98–1.13)	0.173	1.05 (0.98–1.13)	0.181
Right main bronchus	1.32 (1.14–1.52)	<0.001	1.21 (1.05–1.4)	0.010
Other	1.29 (1.21–1.39)	<0.001	1.11 (1.03–1.19)	0.006
Bone metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.16 (1.11–1.22)	<0.001	1.22 (1.17–1.28)	<0.001
Unknown	1.38 (1.2–1.57)	<0.001	1.04 (0.87–1.24)	0.648
Liver metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.49 (1.41–1.57)	<0.001	1.48 (1.4–1.57)	<0.001
Unknown	1.3 (1.16–1.45)	<0.001	0.93 (0.8–1.08)	0.350
Distant lymph node metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.16 (1.03–1.3)	0.017	1.15 (1.02–1.3)	0.020
Unknown	1.24 (1.18–1.31)	<0.001	1.21 (1.08–1.35)	0.001
T				
T1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
T2	1.19 (1.09–1.3)	<0.001	1.19 (1.08–1.3)	<0.001
T3	1.39 (1.26–1.52)	<0.001	1.34 (1.22–1.48)	<0.001
T4	1.42 (1.3–1.56)	<0.001	1.37 (1.25–1.51)	<0.001
Other	1.21 (1.11–1.32)	<0.001	1.17 (1.05–1.3)	0.004
N				
N0	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
N1	1.07 (0.97–1.19)	0.165	1.18 (1.06–1.3)	0.002
N2	1.14 (1.07–1.22)	<0.001	1.24 (1.16–1.33)	<0.001
N3	1.16 (1.08–1.25)	<0.001	1.32 (1.22–1.43)	<0.001
Other	1.01 (0.94–1.08)	0.851	1.12 (1–1.25)	0.045
Surgery				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.44 (0.38–0.51)	<0.001	0.51 (0.44–0.59)	<0.001
Unknown	1.62 (0.92–2.85)	0.097	1.22 (0.69–2.16)	0.500
Radiotherapy				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.4 (0.33–0.49)	<0.001	0.77 (0.63–0.93)	0.008
None/unknown	0.76 (0.63–0.93)	0.006	1.08 (0.89–1.32)	0.419
Chemotherapy				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.35 (0.33–0.36)	<0.001	0.35 (0.34–0.37)	<0.001

CI, confidence interval.

Discussion

Our results showed that brain metastases occurred in 14.1% of patients with lung cancer. Adenocarcinoma is the most common pathological type of lung cancer (Yang *et al*., 2018). Our logistic regression analysis and cox analysis results showed that SCLC and NSCLC were quite different. Furthermore, by combining the results, we found several homogeneous and heterogeneous factors, which have never been discussed in detail in previous studies. The homogeneous brain metastasis risk and prognostic factors in NSCLC were distant metastases (including liver/bone/distant lymph node), T/N stage and were bone metastases in SCLC. Our results showed that both older NSCLC and SCLC patients had a lower risk of brain metastases, but worse survival. A similar result was also obtained in a previous study (Barnholtz-Sloan *et al*., 2004; Reddy *et al*., 2020). As for the pathology, patients with lung adenocarcinoma

Table 7 Univariate and multivariate Cox regression analysis results of small-cell lung cancer-brain metastasis patients

	Univariate cox regression		Multivariate cox regression	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age				
<50	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
50–59	1.16 (0.88–1.53)	0.303	1.03 (0.78–1.37)	0.812
60–69	1.2 (0.91–1.57)	0.198	1.03 (0.78–1.36)	0.825
70–79	1.73 (1.31–2.28)	<0.001	1.29 (0.98–1.71)	0.074
≥80	2.94 (2.16–4.01)	<0.001	1.61 (1.17–2.21)	0.004
Sex				
Female	1 (Reference)	1 (Reference)		
Male	1.08 (0.98–1.19)	0.111		
Race				
White	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Black	0.85 (0.71–1.01)	0.063	0.87 (0.73–1.04)	0.115
Other	0.83 (0.7–0.99)	0.037	0.78 (0.65–0.93)	0.006
Unknown	0.45 (0.14–1.39)	0.163	0.7 (0.22–2.21)	0.549
Location				
Left upper	1 (Reference)	1 (Reference)		
Left lower	1.03 (0.86–1.23)	0.779		
left main bronchus	0.88 (0.67–1.16)	0.374		
Right upper	0.89 (0.78–1.03)	0.125		
Right middle	1.04 (0.79–1.37)	0.758		
Right lower	1.07 (0.89–1.28)	0.479		
Right main bronchus	1.05 (0.83–1.33)	0.693		
Other	1.03 (0.89–1.2)	0.701		
Bone metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.3 (1.17–1.45)	<0.001	1.13 (1–1.27)	0.042
Unknown	1.4 (1.05–1.86)	0.022	1.02 (0.7–1.5)	0.909
Liver metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.59 (1.43–1.77)	<0.001	1.59 (1.42–1.79)	<0.001
Unknown	1.23 (0.94–1.62)	0.136	0.93 (0.65–1.34)	0.699
Distant lymph node metastases				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.25 (0.98–1.59)	0.070	1.03 (0.81–1.32)	0.796
Unknown	1.19 (1.05–1.35)	0.008	1.14 (1–1.29)	0.053
T				
T1	1 (Reference)	1 (Reference)		
T2	0.99 (0.79–1.24)	0.941		
T3	1.04 (0.83–1.31)	0.713		
T4	1.1 (0.89–1.36)	0.370		
Other	0.91 (0.74–1.11)	0.360		
N				
N0	1 (Reference)	1 (Reference)		
N1	0.86 (0.67–1.1)	0.228		
N2	1.15 (0.96–1.37)	0.128		
N3	1.21 (1–1.47)	0.056		
Other	1 (0.83–1.2)	0.978		
Surgery				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.39 (0.21–0.74)	0.003	0.54 (0.29–1.01)	0.054
Unknown	1.51 (0.63–3.64)	0.356	0.93 (0.37–2.34)	0.880
Radiotherapy				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.23 (0.14–0.39)	<0.001	0.58 (0.34–0.99)	0.047
None/unknown	0.44 (0.26–0.75)	0.003	0.86 (0.5–1.47)	0.571
Chemotherapy				
No	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	0.26 (0.23–0.29)	<0.001	0.29 (0.26–0.33)	<0.001

CI, confidence interval; HR, hazard ratio.

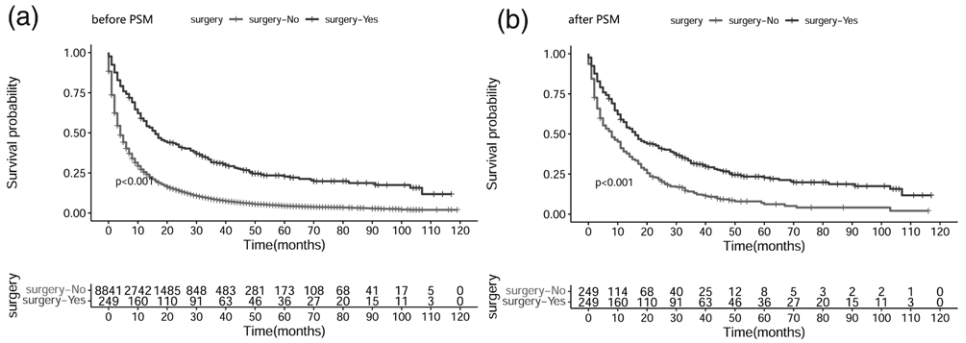
have a higher risk of developing brain metastasis. However, among patients with brain metastasis, adenocarcinoma patients have longer survival time. A similar result was achieved when investigating the role of race. NSCLC patients with other races were at higher risk for developing brain metastasis, but had a better prognosis among patients with brain metastasis. Previous research exploring the risk factor for brain metastasis from esophageal cancer revealed that other races (American Indian/Alaska Native race) were positively associated with the occurrence of brain metastases (Cheng *et al.*, 2021). These results showed that race may influence tumor metastasis. Interestingly, the T and N stages of the primary lesion and the distant lymph node status were not related to the survival time of SCLC patients with brain metastasis, but were closely associated with the prognosis of NSCLC, which indicated the heterogeneity between SCLC and NSCLC.

Table 8 The clinical characters of surgery and non-surgery groups, before Propensity score matching and after Propensity score matching

	Before PSM					After PSM			
	Overall	Surgery – No	Surgery – Yes	*P*		Overall	Surgery – No	Surgery – Yes	*P*
	9090	8841	249			498	249	249	
Age				<0.001	Age				0.62
<50	583 (6.4)	553 (6.3)	30 (12.0)		<50	54 (10.8)	24 (9.6)	30 (12.0)	
50–59	2101 (23.1)	2031 (23.0)	70 (28.1)		50–59	147 (29.5)	77 (30.9)	70 (28.1)	
60–69	3141 (34.6)	3041 (34.4)	100 (40.2)		60–69	199 (40.0)	99 (39.8)	100 (40.2)	
70–79	2316 (25.5)	2274 (25.7)	42 (16.9)		70–79	79 (15.9)	37 (14.9)	42 (16.9)	
≥80	949 (10.4)	942 (10.7)	7 (2.8)		≥80	19 (3.8)	12 (4.8)	7 (2.8)	
Sex				0.058	Sex				1
Female	4336 (47.7)	4202 (47.5)	134 (53.8)		Female	267 (53.6)	133 (53.4)	134 (53.8)	
Male	4754 (52.3)	4639 (52.5)	115 (46.2)		Male	231 (46.4)	116 (46.6)	115 (46.2)	
Race				0.087	Race				0.704
White	904 (9.9)	881 (10.0)	23 (9.2)		White	42 (8.4)	19 (7.6)	23 (9.2)	
Black	6859 (75.5)	6656 (75.3)	203 (81.5)		Black	406 (81.5)	203 (81.5)	203 (81.5)	
Other	1315 (14.5)	1292 (14.6)	23 (9.2)		Other	50 (10.0)	27 (10.8)	23 (9.2)	
Unknown	12 (0.1)	12 (0.1)	0 (0.0)		Unknown				
Location				0.008	Location				0.808
Left upper	2022 (22.2)	1955 (22.1)	67 (26.9)		Left upper	134 (26.9)	67 (26.9)	67 (26.9)	
Left lower	1057 (11.6)	1028 (11.6)	29 (11.6)		Left lower	58 (11.6)	29 (11.6)	29 (11.6)	
left main bronchus	140 (1.5)	138 (1.6)	2 (0.8)		Left main bronchus	2 (0.4)	0 (0.0)	2 (0.8)	
Right upper	2564 (28.2)	2491 (28.2)	73 (29.3)		Right upper	151 (30.3)	78 (31.3)	73 (29.3)	
Right middle	371 (4.1)	358 (4.0)	13 (5.2)		Right middle	28 (5.6)	15 (6.0)	13 (5.2)	
Right lower	1220 (13.4)	1178 (13.3)	42 (16.9)		Right lower	75 (15.1)	33 (13.3)	42 (16.9)	
Right main bronchus	216 (2.4)	213 (2.4)	3 (1.2)		Right main bronchus	6 (1.2)	3 (1.2)	3 (1.2)	
Other	1500 (16.5)	1480 (16.7)	20 (8.0)		Other	44 (8.8)	24 (9.6)	20 (8.0)	
Bone metastases				<0.001	Bone metastases				0.801
No	5557 (61.1)	5347 (60.5)	210 (84.3)		No	425 (85.3)	215 (86.3)	210 (84.3)	
Yes	3303 (36.3)	3268 (37.0)	35 (14.1)		Yes	66 (13.3)	31 (12.4)	35 (14.1)	
Unknown	230 (2.5)	226 (2.6)	4 (1.6)		Unknown	7 (1.4)	3 (1.2)	4 (1.6)	
Liver metastases				<0.001	Liver metastases				0.721
No	7112 (78.2)	6880 (77.8)	232 (93.2)		No	464 (93.2)	232 (93.2)	232 (93.2)	
Yes	1642 (18.1)	1630 (18.4)	12 (4.8)		Yes	26 (5.2)	14 (5.6)	12 (4.8)	
Unknown	336 (3.7)	331 (3.7)	5 (2.0)		Unknown	8 (1.6)	3 (1.2)	5 (2.0)	
Distant lymph node metastases				0.215	Distant lymph node metastases				0.886
No	1944 (21.4)	1893 (21.4)	51 (20.5)		No	99 (19.9)	48 (19.3)	51 (20.5)	
Yes	370 (4.1)	365 (4.1)	5 (2.0)		Yes	9 (1.8)	4 (1.6)	5 (2.0)	
Unknown	6776 (74.5)	6583 (74.5)	193 (77.5)		Unknown	390 (78.3)	197 (79.1)	193 (77.5)	
T				<0.001	*T*				0.883
T1	700 (7.7)	668 (7.6)	32 (12.9)		T1	67 (13.5)	35 (14.1)	32 (12.9)	
T2	1655 (18.2)	1585 (17.9)	70 (28.1)		T2	131 (26.3)	61 (24.5)	70 (28.1)	
T3	1490 (16.4)	1446 (16.4)	44 (17.7)		T3	93 (18.7)	49 (19.7)	44 (17.7)	
T4	1838 (20.2)	1802 (20.4)	36 (14.5)		T4	75 (15.1)	39 (15.7)	36 (14.5)	
Other	3407 (37.5)	3340 (37.8)	67 (26.9)		Other	132 (26.5)	65 (26.1)	67 (26.9)	
N				<0.001	*N*				0.896
N0	1376 (15.1)	1283 (14.5)	93 (37.3)		N0	189 (38.0)	96 (38.6)	93 (37.3)	
N1	575 (6.3)	546 (6.2)	29 (11.6)		N1	60 (12.0)	31 (12.4)	29 (11.6)	
N2	2827 (31.1)	2771 (31.3)	56 (22.5)		N2	116 (23.3)	60 (24.1)	56 (22.5)	
N3	1429 (15.7)	1419 (16.1)	10 (4.0)		N3	17 (3.4)	7 (2.8)	10 (4.0)	
Other	2883 (31.7)	2822 (31.9)	61 (24.5)		Other	116 (23.3)	55 (22.1)	61 (24.5)	
Radiotherapy				0.006	Radiotherapy				0.179
No	109 (1.2)	109 (1.2)	0 (0.0)		No	80 (16.1)	34 (13.7)	46 (18.5)	
Yes	6663 (73.3)	6460 (73.1)	203 (81.5)		Yes	418 (83.9)	215 (86.3)	203 (81.5)	
None/unknown	2318 (25.5)	2272 (25.7)	46 (18.5)						
Chemotherapy				<0.001	Chemotherapy				0.499
No	4281 (47.1)	4199 (47.5)	82 (32.9)		No	156 (31.3)	74 (29.7)	82 (32.9)	
Yes	4809 (52.9)	4642 (52.5)	167 (67.1)		Yes	342 (68.7)	175 (70.3)	167 (67.1)	

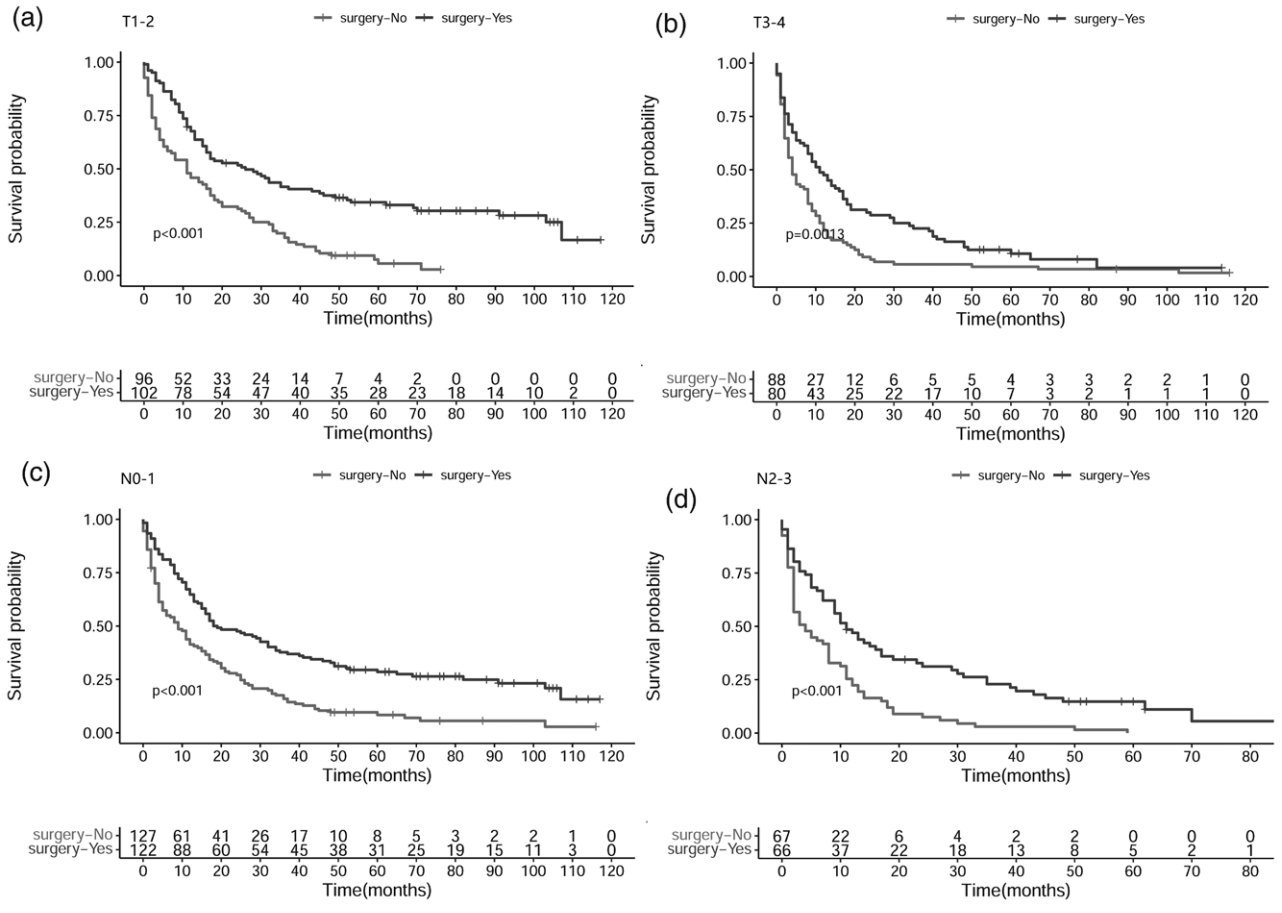
PSM, Propensity score matching.

Fig. 2



Result of Kaplan–Meier analysis. (a) Kaplan–Meier analysis including 9090 patients. (b) After PSM, a similar result was obtained. PSM, Propensity score matching.

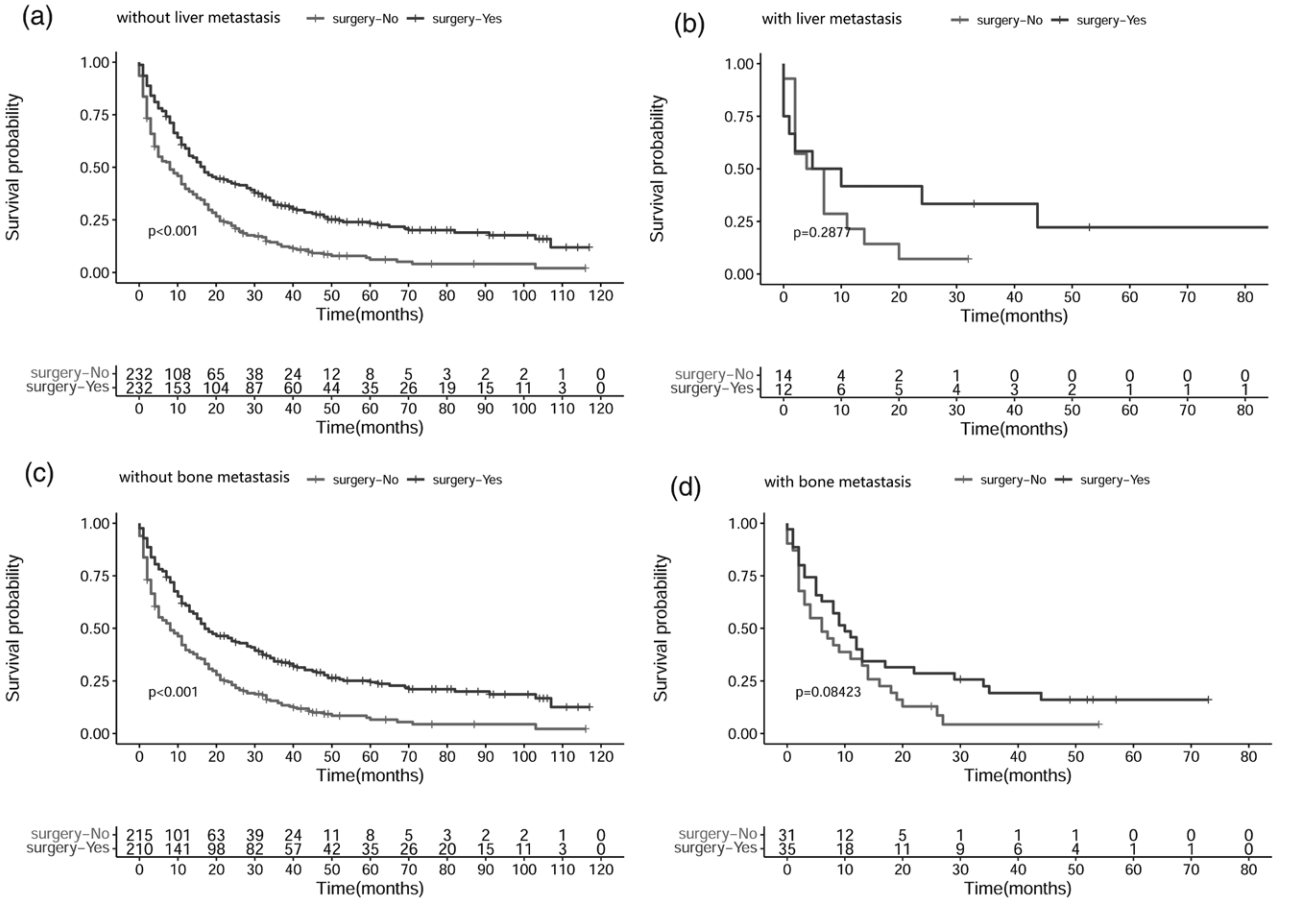
Fig. 3



Kaplan–Meier analysis of the effect of primary lesion surgery in T1-2 patients (a), T3-4 patients (b), N0-1 patients (c), and N2-3 patients (d).

Few articles focused on the site of primary lesion. In our study, primary site is associated with the risk of developing brain metastasis. NSCLC patients whose tumor was present at right middle/lower lobe had a lower risk of developing brain metastasis than at left upper lobe. However, for NSCLC-brain metastasis patients, primary lesion at main bronchus was associated with worse survival. For SCLC, primary lesion site was not related to

Fig. 4



Kaplan–Meier analysis of the effect of primary lesion surgery in patients without liver metastasis (a), with liver metastasis (b), without bone metastasis (c), and with bone metastasis (d).

brain metastasis risk or survival time. Further studies are required to reveal the molecular mechanism of this result.

Surgery, chemotherapy, and radiotherapy are common therapies for cancers. Providing individualized treatment for different patients so as to maximize the personal survival benefits is a research direction (Kang *et al.*, 2020). Previous studies have suggested that surgery could improve the prognosis of IV cancer patients with distant metastases. Mastectomy is associated with better OS among patients with stage IV breast cancer, compared with those who do not undergo surgery (Bilani *et al.*, 2021). For patients with metastatic adrenocortical carcinoma, primary lesion surgery improved OS and cancer-specific survival (Tsilimigras *et al.*, 2021). What is more, the surgical resection of primary gastrointestinal neuroendocrine tumor was correlated with a survival benefit among individuals with unresected metastases (Wang *et al.*, 2017). However, the role of surgical resection of primary lesion has not been discussed among lung cancer patients with brain metastasis. Our results suggested that primary lesion surgery cannot prolong the survival time of SCLC-brain metastasis patients, but could improve the survival of NSCLC-brain metastasis patients with different T and N stages. Radiotherapy and chemotherapy were associated with a better prognosis for patients. We also performed a subgroup analysis of NSCLC-brain metastasis patients to investigate the role of primary lesion surgery. The results suggested that surgery could improve the prognosis of patients with brain metastasis only. However, for NSCLC-brain metastasis patients with liver and bone metastases, there was no significant difference in survival between the surgical and non-surgical groups. Further multicenter prospective studies are still required to validate these outcomes.

This study has some limitations. The accuracy of identifying brain metastasis depends on brain imaging type (including CT and MRI) (Lamba *et al.*, 2021). However, SEER does not provide information relating to the imaging examination for brain metastasis diagnosis. What is more, not all the brain metastasis status of lung cancer

patients in SEER database is sure. Therefore the incidence of brain metastasis may be inaccurate. For many patients, the status of surgery, lymph node metastasis, T stage, N stage, radiotherapy, and chemotherapy were unknown, which reduced the number of patients included in the study cohort. In addition, we do not have specific treatment information such as chemotherapy protocol and radiation planning technique, which may influence the prognosis of brain metastasis patients.

Conclusion

In this study, we found that the incidence of brain metastasis in lung cancer patients was about 14.1%, and the median survival of lung cancer patients with brain metastasis was 5 months. Our study also suggested several homogeneous and heterogeneous risk/prognostic factors associated with brain metastasis, which need to be paid more attention in clinical practice. Using PSM approach, we found that surgery on primary lesion could improve survival in NSCLC patients with brain metastasis, but not SCLC patients with brain metastasis. These results are helpful for clinicians to conduct clinical evaluations and make individualized therapeutic strategies.

Acknowledgements

Y.H.: research design, data collection, interpretation and analysis, article drafting. GL: Research design, critical article revision.

The data used in this study are available from publicly available SEER database. SEER*Stat version 8.4.0 (https://seer.cancer.gov/seerstat/) was used to get data.

SEER database is publicly accessible worldwide. The authors signed the SEER database agreement and got the license to access SEER data.

Conflicts of interest

There are no conflicts of interest.

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