Risk Factors, Prognosis and A New Nomogram for Predicting Cancer-Specific Survival Among Lung Cancer Patients with Brain Metastasis: A Retrospective Study Based on SEER

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Abstract

Purpose: A comprehensive population-based study on risk and prognostic factors of lung cancer with brain metastasis is lacking.

Methods: 95191 patients diagnosed with lung cancer between 2010 and 2017 were collected from the Surveillance, Epidemiology and End Results (SEER) database. Patients were stratified by different variables. Multivariable logistic and Cox regression were applied to analyze the risk and prognostic factors of brain metastasis among lung cancer patients, respectively. The Fine and Gray's competing risk regression model was performed to obtain prognostic factors associated with cancer-specific mortality.

Results: Among the 95191 patients diagnosed with lung cancer, 10765 patients have brain metastasis, with a metastatic incidence of 11.31%. The primary site of tumor, residence type, age, histological type, race and extracranial metastasis were all independent risk factors of brain metastasis. Compared with other histological types, small cell lung cancer displayed a highest incidence of brain metastasis (16.62%). The median overall survival (OS) among lung cancer patients with brain metastasis was only 6.05 months. The primary site of tumor, median household income, age, histological type, race, gender and extracranial metastasis were all associated with the prognosis of brain metastasis. Patients with squamous cell carcinoma had the worst prognosis, the median OS was only 3.68 months. And our established new nomogram showed a good discriminative ability on predicting the probability of cancer-specific survival among patients with brain metastasis, the C-index was 0.61.

Conclusion: Our study provided a deeper insight into the risk factors and prognosis of brain metastasis among lung cancer patients.

Introduction

Lung cancer is the main contributor of cancer mortality among both men and women in the United States (1). Clinically, most lung cancers eventually develop into advanced diseases with distant metastasis, among which the intracranial metastasis is the most common (2). It has been reported that lung cancer had the higher incidence of brain metastasis compared with other cancers, which also leads to a significantly shorter survival of patients (3). The high morbidity and mortality of intracranial metastasis among lung cancer patients pose a great challenge to clinicians.

At present, the risk and prognostic factors of brain metastasis among lung cancer patients have been analyzed in a large number of studies. Previous articles have shown that elevated serum CEA and NSE levels were positively associated with the risk of brain metastasis among non-small cell lung cancer (NSCLC). In addition, the non-squamous cell carcinoma was more likely to develop brain metastasis compared with other histological type, younger age and the metastasis of lymph node were also the independent risk factors of brain metastasis among NSCLC (4, 5). In order to estimate the prognosis of intracranial metastasis among lung cancer, Sperduto PW et al. updated the graded prognostic assessment of lung cancer with brain metastasis using the molecular markers (Lung-molGPA) (6). In

addition, a retrospective study investigated the influence of extracranial metastasis on prognosis of NSCLC with intracranial metastasis based on Surveillance, Epidemiology, and End results (SEER) database (7). Although there are many studies on the risk factors and prognosis of brain metastasis among lung cancer patients, these studies mainly focused on NSCLC, or only limited to the impacts of some specific factors on the prognosis of lung cancer patients with brain metastasis. A comprehensive retrospective study on the risk factors and prognosis of brain metastasis among lung cancer patients is lacking.

Our study aimed to investigate the risk and prognostic factors of brain metastasis among lung cancer patients based on the SEER database. Besides, we intended to establish a new practical nomogram, which was suitable for squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine carcinoma and small cell lung cancer (SCLC).

Methods

Study subjects

In this study, 140463 lung cancer patients diagnosed between 2010 and 2017 were enrolled as the study population through the SEER database. This database consists of 18 cancer registries from the United States and provides the incidence of cancer, treatment information and follow-up survival data of cancer patients for approximately 30% of the United States population. Median household income, residence type, age at diagnosis, race and gender were included into the demographic variables, cancer-related variables included primary sites of tumor, histologic types, extracranial metastatic sites to bone and liver, survival time (month) and vital status.

Data collection

Inclusion criteria for this study were as follows: (a) patients were older than 18 years at the time of diagnosis; (b) histological types were adenocarcinoma, squamous cell carcinomas, adenosquamous carcinoma, neuroendocrine carcinoma and SCLC. the corresponding ICD-O-3 codes were showed in **supplementary table 1**. The exclusion criteria of this study were as follows: (a) whether there is brain metastasis at the time of diagnosis is not known; (b) the information of demographic variables and cancer-related variables was unknown. We finally identified 95191 lung cancer patients for incidence analysis of brain metastasis, of these, 10765 patients had brain metastasis. Of these patients, we excluded those with incomplete follow-up and those diagnosed by death certificates or autopsy, leaving 8655 patients with brain metastasis for survival analysis.

Statistical methods

Patients were grouped according to the primary site of tumor, median household income, residence type, age, histological type, race, gender and extracranial metastasis to bone or liver. The number and proportion of patients with brain metastasis from lung cancer were calculated. The incidence of brain

metastasis among lung cancer patients was obtained by calculating the ratio of the number of lung cancer patients with brain metastases to the total number of lung cancer patients (8).

Multivariable logistic regression was used to analyze whether the primary site of tumor, median household income, residence type, age, histological type, race, gender and extracranial metastatic sites to bone and liver were independent risk factors of brain metastasis among lung cancer patients.

The Kaplan-Meier method was used to obtain the cumulative overall survival curve and median overall survival (OS) time, the difference of survival time among subgroups was compared using the Log-Rank test. The all-cause mortality-related prognostic factors of lung cancer with brain metastasis were identified through multivariable Cox regression analysis using the variables identified in the Log-Rank test.

The Fine and Gray's competing risk regression analysis was applied to investigate the prognostic factors associated with increased cancer-specific mortality. Prognostic nomogram for predicting cancer-specific survival of brain metastasis patients among lung cancer were established based on the independent prognostic factors identified in the Fine and Gray's competing risk regression model (9).

Statistical analysis was completed in the SPSS statistics software (IBM SPSS Statistics, version 21.0) and R software (version 4.0.4.).

Results

Incidence

Among the 95191 patients with lung cancer, 10765 patients developed brain metastasis, with a rate of 11.31%. Patients were stratified by the primary site of tumor, median household income, residence type, age, histological type, race, gender and extracranial metastatic sites to bone or liver, the number and proportion of patients with brain metastasis from lung cancer were provided in **Table 1**. We found the rate of brain metastasis is highest when the primary site of tumor is main bronchus, up to 14.60%. In addition, younger patients were more likely to develop brain metastasis, the metastatic rate among patients aged 18-41 years and 41-60 years were 16.22% and 17.65%, respectively. SCLC and adenocarcinoma had higher rates of brain metastasis (16.62% and 13.37%, respectively) compared with other histological types. The incidence of brain metastasis among Asian population was 14.83%, which was higher than that in other ethnic groups. In addition, when patients had extracranial metastasis to bone and liver, the incidence of brain metastasis was as high as 28.65%.

Table 1. Incidence proportion and median overall survival of lung cancer patients with brain metastasis

Variables	Patients, No		Incidence	Median Overall Survival Among Patients with Brain Metastasis, month (IQR)
	With Lung Cancer (n=95191)	With Brain Metastasis (n=10765)	Proportion of Brain Metastasis, %	
Primary site				
Upper lobe	55082	6368	11.56	6.22 (2-12)
Middle lobe	5072	520	10.25	5.43 (2-10)
Lower lobe	29861	3144	10.53	6.16 (2-12)
Overlapping	1046	130	12.43	5.61 (1-9)
Main bronchus	4130	603	14.60	4.59 (1-9)
Median household income	313	34	10.86	NA
<¥35000	20882	2391	11.45	5.17 (2-11)
¥35000-¥54999	43759	4742	10.84	5.55 (2-11)
¥55000-¥74999	30237	3598	11.90	7.13 (2-13)
¥75000+				
Residence				
Urban	83715	9410	11.24	6.03 (2-12)
Rural	11476	1355	11.81	6.51 (2-11)
Age				
18-40	592	96	16.22	15.08 (3-19)
41-60	18751	3310	17.65	8.52 (2-15)
61-80	61352	6474	10.55	5.42 (1-11)
>80	14496	885	6.11	2.86 (1-6)
Histological type				
Squamous cell carcinomas	25071	1282	5.11	3.68 (1-7)
Adenocarcinoma	52783	7056	13.37	6.72 (2-13)
Adenosquamous carcinoma	1196	108	9.03	6.46 (2-13)
Neuroendocrine carcinoma	3514	221	6.29	6.44 (1-11)
	12627	2098	16.62	6.02 (1-10)

Small cell lung carcinoma				
Race				
White	76211	8210	10.77	5.65 (2-11)
Black	10647	1345	12.63	5.93 (2-11)
Asian	7816	1159	14.83	9.39 (2-16)
American Indian	517	51	9.86	6.77 (2-12)
Gender				
Female	47301	5342	11.29	6.73 (2-13)
Male	47890	5423	11.32	5.40 (1-10)
Extracranial metastatic sites				
to bone and liver				
None	74709	5963	7.98	7.48 (2-14)
Liver	11015	2536	23.02	5.37 (2-11)
Bone	4601	872	18.95	3.51 (1-7)
Liver and Bone	4866	1394	28.65	3.81 (1-8)

In the multivariable logistic regression model for the incidence analysis of brain metastasis, the primary site: main bronchus (vs upper lobe; odds ratio [OR], 1.12; 95%CI, 1.01-1.23; $P=0.024$), the residence type: rural (vs urban; OR, 1.10; 95%CI, 1.02-1.18; $P=0.008$), the histological type: adenocarcinoma (vs squamous cell carcinomas; OR, 2.41; 95%CI, 2.27-2.57; $P<0.001$), adenosquamous carcinoma (vs squamous cell carcinomas; OR, 1.62; 95%CI, 1.31-1.99; $P<0.001$) and small cell lung carcinoma (vs squamous cell carcinomas; OR, 2.48; 95%CI, 2.29-2.68; $P<0.001$), the race: Black (vs White; OR, 1.13; 95%CI, 1.06-1.21; $P<0.001$) and Asian (vs White; OR, 1.29; 95%CI, 1.20-1.39; $P<0.001$), and extracranial metastasis to liver (vs no extracranial metastasis to liver and bone; OR, 3.03; 95%CI, 2.87-3.19; $P<0.001$), extracranial metastasis to bone (vs no extracranial metastasis to liver and bone; OR, 2.46; 95%CI, 2.26-2.67; $P<0.001$) and extracranial metastasis to liver and bone (vs no extracranial metastasis to liver and bone; OR, 3.92; 95%CI, 3.66-4.21; $P<0.001$) were significantly more likely to have brain metastasis at diagnosis. When the primary site of lung cancer was the middle lobe (vs upper lobe; OR, 0.88; 95%CI, 0.80-0.97; $P=0.009$) and lower lobe (vs upper lobe; OR, 0.94; OR, 0.90-0.99; $P=0.013$), the risk of developing brain metastasis is significantly reduced. Furthermore, patients aged 61-80 (vs aged 18-40; OR, 0.62; 95%CI, 0.50-0.79; $P<0.001$) and older than 80 (vs aged 18-40; OR, 0.36; 95%CI, 0.28-0.46; $P<0.001$) were also associated with significantly lower odds of having brain metastasis. The median household income

and gender were not associated with a risk of brain metastasis. The forest plot makes these results more intuitive (**Figure 1**).

Survival

In this study, 7221 deaths (83.43%) were observed among 8,655 lung cancer patients with brain metastasis, the cumulative overall survival curve showed the median OS among patients with brain metastasis was 6.05 months. Patients were stratified by the primary site of tumor, median household income, residence type, age, histological type, race, gender and extracranial metastatic sites to bone or liver, the median OS of patients with brain metastasis in each subgroup was shown in **Table 1**. The cumulative overall survival curves were plotted through Kaplan-Meier method and the influence of each factor on prognosis of patients with brain metastasis was identified by Log-Rank test. The results indicated that the primary site, median household income, age, histological type, race, gender and extracranial metastatic sites to bone or liver were all independent prognostic factors of brain metastasis among lung cancer patients (**Figure 2**).

In the multivariable Cox regression model for the analysis of all-cause mortality of brain metastasis patients among lung cancer, main bronchus (vs upper lobe; hazard ratio [HR], 1.18; 95%CI, 1.07-1.31; $P=0.001$), age 41-60 years (vs age 18-40 years; HR, 1.45; 95%CI, 1.10-1.91; $P=0.009$), age 61-80 years (vs age 18-40 years; HR,1.91; 95%CI, 1.45-2.51; $P<0.001$) and age older than 80 years (vs aged 18-40 years; HR, 3.24; 95%CI, 2.44-4.29; $P<0.001$), male (vs female; HR, 1.13; 95%CI, 1.08-1.18, $P<0.001$) and extracranial metastasis to liver (vs no extracranial metastasis to liver and bone; HR, 1.34; 95%CI, 1.26-1.42; $P<0.001$), extracranial metastasis to bone (vs no extracranial metastasis to liver and bone; HR, 1.80; 95%CI, 1.65-1.96; $P<0.001$) and extracranial metastasis to liver and bone (vs no extracranial metastasis to liver and bone; HR, 1.75; 95%CI, 1.63-1.87; $P<0.001$) were significantly associated with a higher all-cause mortality. In addition,¥55000-¥74999 (vs¥35000-¥54999; HR, 0.90; 95%CI, 0.84-0.97; $P=0.004$) and¥75000+ (vs¥35000-¥54999; HR, 0.80; 95%CI, 0.75-0.86; $P<0.001$), adenocarcinoma (vs squamous cell carcinomas; HR, 0.66; 95%CI, 0.61-0.71; $P<0.001$), adenosquamous carcinoma (vs squamous cell carcinomas; HR, 0.78; 95%CI, 0.61-0.98; $P<0.001$), neuroendocrine carcinoma (vs squamous cell carcinomas; HR, 0.69; 95%CI, 0.58-0.82; $P<0.001$) and small cell lung carcinoma (vs squamous cell carcinomas; HR, 0.80; 95%CI, 0.74-0.88; $P<0.001$) and Asian (vs White; HR, 0.77; 95%CI, 0.71-0.83; $P<0.001$) were associated with a lower all-cause mortality. The results were showed in **Table 2**.

Table 2 Multivariable Cox regression for all-cause mortality and cancer–specific mortality among patients with brain metastasis

Variables	Patients with brain metastasis (n=8255)	All-Cause Mortality		Cancer-Specific Mortality	
		Hazard Ratio (95CI%)	P value	Hazard Ratio (95CI%)	P value
Primary site					
Upper lobe	5123	Reference	NA	Reference	NA
Middle lobe	418	1.10 (0.99-1.23)	0.078	1.03(0.92-1.16)	0.620
Lower lobe	2544		0.490		0.110
Overlapping	98	0.98 (0.93-1.03)	0.316	0.96(0.91-1.01)	0.880
Main bronchus	472	1.12 (0.90-1.39)	0.001	1.02(0.81-1.28)	0.022
		1.18 (1.07-1.31)		1.14(1.02-1.26)	
Median household income					
	1328	Reference	NA		NA
¥35000-¥54999	3811	0.90(0.84-0.97)	0.004	0.93(0.87-1.00)	0.056
¥55000-¥74999			<0.001		<0.001
¥75000+	3516	0.80(0.75-0.86)		0.85(0.79-0.91)	
Age					
18-40	80	Reference	NA		NA
41-60	2649	1.45(1.10-1.91)	0.009	1.41(1.11-1.79)	0.005
61-80	5181		<0.001		<0.001
>80	745	1.91(1.45-2.51)	<0.001	1.67(1.32-2.11)	<0.001
		3.24(2.44-4.29)		2.40(1.87-3.08)	
Histological type					
Squamous cell carcinomas	970	Reference	NA		NA
	5770	0.66(0.61-0.71)	<0.001	0.74(0.68-0.80)	<0.001
Adenocarcinoma	88		0.033		0.350
Adenosquamous carcinoma	179	0.78(0.61-0.98)	<0.001	0.91(0.74-1.12)	0.002
Neuroendocrine carcinoma	1648	0.69(0.58-0.82)	<0.001	0.75(0.62-0.90)	0.019

Small cell lung carcinoma		0.80(0.74-0.88)		0.90(0.82-0.98)	
Race					
White	6209	Reference	NA	NA	NA
Black	1292	0.98(0.91-1.05)	0.512	0.93(0.87-1.00)	0.040
Asian	1112		<0.001		<0.001
American Indian	42	0.77(0.71-0.83)	0.626	0.83(0.77-0.89)	0.990
		1.08(0.78-1.50)		1.00(0.74-1.36)	
Gender					
Female	4352	Reference	NA	NA	NA
Male	4303	1.13(1.08-1.18)	<0.001	1.11(1.06-1.16)	<0.001
Extracranial metastatic sites					
to bone and liver					
None	4766	Reference	NA	NA	NA
Liver	2085	1.34(1.26-1.42)	<0.001	1.30(1.23-1.38)	<0.001
Bone	708		<0.001		<0.001
Liver and Bone	1096	1.80(1.65-1.96)	<0.001	1.60(1.47-1.75)	<0.001
		1.75(1.63-1.87)		1.59(1.48-1.71)	

In the Fine and Gray's competing risk regression model for the analysis of cancer-specific mortality of brain metastasis patients among lung cancer, 55000-74999 (vs 35000-54999; HR, 0.93; 95%CI, 0.87-1.00; $P=0.056$) and adenosquamous carcinoma (vs squamous cell carcinomas; HR, 0.91; 95%CI, 0.74-1.12; $P=0.350$) were not significantly associated with a lower cancer-specific mortality. The results were also showed in **Table 2**. Based on the results of Fine and Gray's competing risk regression, we developed a novel visual nomogram to predict the cancer-specific survival of lung cancer patients with brain metastasis, showed in **Figure 3**. A patient's cancer-specific survival probability can be easily estimated by calculating the scores for each variable. Through internal validation by Heagerty's concordance index, the established nomogram showed a good discriminative ability, the C-index was 0.61.

Discussion

The highlights of our work mainly include three aspects. First, we comprehensively analyzed the incidence and risk factors of brain metastasis among patients with lung cancer based on a population-

based study, and a large number of variables were incorporated. Next, we identified a large number of prognostic factors that influence overall survival and cancer-specific survival of brain metastasis patients among lung cancer based on the multivariable Cox regression and Fine and Gray's competing risk regression analysis. Furthermore, we developed a new practical nomogram for predicting the probability of cancer-specific survival among lung cancer patients with brain metastasis, which was suitable for squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine carcinoma and SCLC.

The high incidence of brain metastasis from lung cancer is a serious threat to lung cancer patients and imposes a great challenge on clinicians. Prophylactic cranial irradiation (PCI) is proposed in both SCLC and non-small-cell lung cancer (NSCLC) in order to improve the survival and quality of life of lung cancer patients with brain metastasis (10). However, many patients refused to undergo PCI in clinical practice because of concerns about the neurotoxicity of craniocerebral irradiation. Identifying lung cancer patients at a high risk of brain metastasis may enhance the benefits of PCI while decreasing the risks of unnecessary craniocerebral irradiation among the patients with lung cancer. Previous studies on the incidence and risk factors of brain metastasis among lung cancer patients mainly focused on the NSCLC, and the clinical implications are limited. In our study, we comprehensively analyzed the risk factors related to the high incidence of brain metastasis among patients with lung cancer based on the SEER database, including SCLC and NSCLC patients.

Recent years, many researches have indicated that patients with non-squamous cell carcinoma or adenocarcinoma had a higher incidence of brain metastasis (4, 11, 12), which is consistent with our results in this study. Our study revealed that SCLC is more easily to have brain metastasis than other histologic types of lung cancer, with a rate of 16.62%, followed by adenocarcinoma with a rate of 13.37%; and squamous cell carcinomas and neuroendocrine carcinoma had a lower rates of brain metastasis, the rate was 5.11% and 6.29%, respectively. Furthermore, we found that lung cancer with a primary site of main bronchus was more likely to have brain metastasis, in addition, the rates of brain metastasis were higher among Asian and Black populations than White populations. The value of gender to predict the rate of brain metastasis among patients with lung cancer is still controversial (13, 14), our results showed that gender were not significantly correlated with the risk of brain metastasis. Many studies have indicated that patients with younger age were more easily to have brain metastasis among NSCLC (15, 16), our findings also suggested that younger age is an independent risk factor of brain metastasis among lung cancer patients. It is also worth noting that extracranial metastasis is also an independent risk factor of brain metastasis among lung cancer patients, when patients presented with liver or bone metastasis, the risk of brain metastasis was significantly increased, and the risk of brain metastasis is highest when patients had both liver and bone metastasis.

The research on the prognosis of brain metastasis patients among lung cancer could provide guidance for clinicians in the treatment and management of patients with lung cancer. Previous epidemiological researches have shown that patients with brain metastasis among lung cancer had a very short survival time (7, 17), and our study also showed a high mortality among patients with brain metastasis from lung

cancer. We found the 1-year overall survival rate was only 28% among patients with brain metastasis, and the median OS time of these patients is 6.05 months, consistent with the results of other studies (18). In the multivariable Cox regression model for the analysis of all-cause mortality of lung cancer patients with brain metastasis, patients with older age and lower income had a higher all-cause mortality. Besides, female and Asian population had a significantly lower all-cause mortality compared with male and White population. And when patients had extracranial metastasis to bone, patients had a worst prognosis, the median OS time was only 3.51 months. Interestingly, we also found that although the brain metastasis rates of lung cancer patients with squamous cell carcinoma was low, the prognosis was very poor once the squamous cell carcinoma developed brain metastasis, with a median OS time of only 3.68 months, which is significantly shorter than other histological types of lung cancer. This may be related to the insensitivity of squamous cell carcinoma to radiotherapy and chemotherapy.

Conclusion

Our study provided a deeper insight into the risk factors and prognosis of brain metastasis among lung cancer patients. And we developed a new practical nomogram, which was suitable for squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, neuroendocrine carcinoma and SCLC, and it greatly expands the scope of clinical applications of nomogram for predicting cancer-specific survival of patients with brain metastasis from lung cancer.

Declarations

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Conflicts of interest: The authors have declared that no competing interests exist.

Availability of data and material: Data in this study are public in the Surveillance, Epidemiology, and End Results (SEER) database (<https://seer.cancer.gov/data/>).

Code availability: Not applicable.

Authors' contributions: The acquisition and analysis of data was completed by Zhang Guihong, the writing of the manuscript was completed by Zhang Guihong and Liu Yuejiao. The design and guidance of this study was performed by Ji Mingde.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Written informed consent for publication was obtained from all participants.

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Figures

Figure 1

Forest plot visualizing the influence of different factors on the risk of brain metastasis based on multivariable logistic regression.

Figure 2

Overall survival curves grouped by patient characteristics: (A) Primary site; (B) Median household income; (C) Residence; (D) Age; (E) Race; (F) Histological type; (G) Gender; (H) Extracranial metastatic sites to bone and liver.

Figure 3

A new Nomogram for predicting cancer-specific survival of brain metastasis patients among lung cancer

Supplementary Files

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