Brain Metastases in Lung Cancer Patients: Clinical Potential Risk Factors of CYFRA21-1 and CEA

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Research

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Abstract

Background

At present, little is known about the specific risk factors of brain metastasis in patients with lung cancer. This study aims to explore the risk factors of brain metastasis.

Methods

From April 1999 to July 2017, a total of 1,615 lung cancer patients were included in this retrospective study. The patients were divided into two groups, namely brain metastasis group and non-brain metastasis group. Student's t test, non-parametric rank sum test and chi-square test were used to describe whether there is a significant difference between the two groups. We compared the serum biomarkers of the two groups of patients, including alkaline phosphatase (ALP), Calcium, calcium hemoglobin (HB), alpha fetoprotein (AFP), cancer embryonic antigen (CEA), CA-125, CA-199, CA- 153, CA-724, cytokeratin fragment 19 (CYFRA 21 – 1), total prostate specific antigen (TPSA), squamous cell carcinoma antigen (SCC-Ag) ,and neuron specific enolase (NSE). Binary logistic regression analysis was used to determine its risk factors, and receiver operating curve (ROC) analysis was used to evaluate its diagnostic value for brain metastases in patients with lung cancer.

Results

In the analysis of brain metastases in patients with lung cancer, binary logistic regression analysis showed that CYFRA21-1 and CEA are independent risk factors for brain metastases in patients with lung cancer (both $P < 0.001$). The sensitivity and specificity of diagnosing brain metastasis were CYFRA21-1, 38.0% and 87.4%, respectively; CEA was 39.7% and 79.3%, respectively.

Conclusion

Serum CYFRA21-1 and CEA have predictive value in the diagnosis of brain metastases in patients with lung cancer.

Background

Lung cancer is a malignant tumor disease associated with the highest morbidity and mortality worldwide, posing a great threat to human life. With the improvement in the treatment of primary lung lesions, the treatment of brain metastases has attracted considerable attention in clinical research. At present, there is controversy regarding the treatment of brain metastatic tumors, and there are no standard diagnostic and treatment norms. This is mainly attributed to the lack of comparability of several key factors, such as the course of systemic disease, the degree of nerve damage symptoms, the number and location of

metastases, the sensitivity of the tumor cell type or primary lesion to radiotherapy, and the difficulty in selecting the combination of different treatment methods in clinical practice. Primary lung cancer is one of the most common malignant tumors in China, with non-small cell lung cancer and lung adenocarcinoma accounting for approximately 80% of lung cancer cases. One of the most common distant metastatic sites of lung cancer is the brain. Studies have shown that approximately one-third of patients with lung cancer have metastasis or local advanced disease at the time of diagnosis, missing the optimal time for treatment. The prognosis of patients with brain metastasis of lung cancer is poor, and the usual average survival time is only 1–2 months. The progress of radiotherapy technology and the rapid development of new therapies (i.e., molecular targeted therapy) have provided more treatment options and greater expectations for patients with brain metastasis of advanced lung cancer. The comprehensive application of surgery, radiotherapy, and chemotherapy has extended the survival period, and improved the quality of life of patients with brain metastasis of lung cancer to a certain extent. In recent years, studies [1]have shown that exposure of the whole brain to radiation can reduce or delay the occurrence of brain metastasis in lung cancer patients and improve the survival rate. However, the overall survival rate has not been significantly improved, which may be attributed to the lack of irradiation in high-risk cases. At present, clinical diagnosis of brain metastasis of lung cancer is usually reached by combining pathology and imaging. Therefore, the detection of tumor markers is gradually attracting clinical attention due to the advantages of a non-invasive operation, high safety, and strong feasibility. We identified high-risk cases of lung cancer prone to brain metastasis, which is of great importance in determining prognosis and guiding individualized treatment. The detection of tumor markers is of great value in the diagnosis and prognosis of lung cancer. In this study, combined detection of multiple tumor markers in the serum of patients was also performed to assess the relationship between brain metastasis of lung cancer and clinical and pathological characteristics. Such data may provide reference for the clinical diagnosis and treatment.

Materials And Methods

Ethics statement

Patients diagnosed with lung cancer between September 1999 and July 2017 were included in this study. Patients with brain metastasis were identified, and their medical records and serological examination data were analyzed. In addition, these data were compared with those of patients without brain metastasis. All patients in this study provided written informed consent. This study was approved by the medical research ethics committee of the First Affiliated Hospital of Nanchang University, Nanchang, China. The definitive diagnosis of lung cancer was reached using pathological sections obtained from surgical resection or biopsy. Computed tomography and magnetic resonance imaging were used to diagnose brain metastasis of lung cancer, and the data of serum tumor markers were recorded.

Study design

We collected clinical data (i.e., age, sex, time of diagnosis, metastasis, and treatment) from the medical records of patients with brain metastasis of lung cancer. The levels of tumor markers in the serum, including alkaline phosphatase, calcium, HB, alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratin fragment 19 (CYFRA 21-1), CA-125、CA-199、CA-153, and free prostate-specific antigen were determined.

Statistical analyses

We analyzed the differences in the levels of tumor markers between the brain metastasis group and the other metastases group through an independent t-test. Subsequently, the binary logistic regression model was used to identify the independent risk factors of brain metastasis. The receiver operating characteristic (ROC) curve was constructed, and the area under the curve (AUC) was calculated. In addition, we calculated the cut-off values, sensitivity, and specificity of the risk factors. A $P<0.05$ denoted statistical significance. All statistical analyses were performed using the SPSS 20.0 software (SPSS, IBM, USA) and Excel 2010 software (Excel, Microsoft, USA) .

Results

Relationship between tumor markers and brain metastasis of lung cancer

In this study, 234 cases of lung cancer with brain metastasis and 2,809 cases of lung cancer with other metastases were collected. The mean age was 60.2 ± 3.6 and 61.0 ± 4.1 years, respectively. According to the chi-squared test and Student's t-test, there was no significant difference between the two groups in terms of gender and age ($P > 0.05$). However, there was a statistically significant difference between the two groups in the histopathological types ($P < 0.05$). Moreover, there was a statistical difference in the proportion of pathological types between the brain metastasis group and other metastases group ($P = 0.003$). The proportion of adenocarcinoma and small cell carcinoma in the brain metastasis group was higher than that observed in the other metastases group. Since the onset of the disease, the majority of patients selected chemotherapy for their treatment. The detailed clinical data of all patients involved in the study are listed in Table 1 and Figs. 1–3.

Table 1
clinical data of patients with and without brain metastasis from lung cancer

Patient characteristics	Lung cancer brain metastasis group (%)	Without lung cancer brain metastasis group (%)	P value
	(n = 234)	(n = 2809)	
Gender [b]			
Male	152(65.0)	1927(68.6)	0.335
Female	82(35.0)	1843(31.4)	
Age [c]			
Mean	60.2 ± 3.6	61.0 ± 4.1	0.223
Histopathological type [b]			
Adenocarcinoma	116(49.6)	1138(40.5)	0.001
Squamous cell carcinoma	64(27.4)	1038(27.0)	
Small cell carcinoma	36 (15.4)	336 (12.0)	
Other	18(7.7)	297(10.6)	

The left side shows patients with brain metastasis of lung cancer, while the right side shows patients with other metastases. (A) Gender data of patients with brain metastasis of lung cancer and lung cancer with other metastases (B) Age data of patients with brain metastasis of lung cancer and lung cancer with other metastases (C) Differences in the pathological features between patients with brain metastasis of lung cancer and lung cancer with other metastases.

Differences in clinical data and risk factors of brain metastasis of lung cancer

Comparison of tumor biomarker data between the two groups showed that AFP, CEA, ca-125, ca-153, TPSA and cyfra21-1 levels were significantly higher in patients with lung cancer brain metastases than in other patients. Transfer ($P < 0.05$). However, NSE levels in patients with lung cancer brain metastases are lower than those in other lung cancer patients. Moreover, there was no statistically significant difference between the two groups in the levels of calcium, ca-199, HB, ca-724, and ALP in the serum ($P > 0.05$). These results are shown in Table 2. Using binary logistic regression analysis, CEA and cyfra21-1 were identified as independent risk factors of brain metastasis of lung cancer. These results are shown in more detail in Table 3.

Table 2
difference of tumor biomarkers between brain metastasis of lung cancer and brain metastasis without lung cancer

Tumor biomarkers	Lung cancer brain metastasis group	Without lung cancer brain metastasis group	t	P value
ALP(U/L)	94.4 ± 57.2	93.0 ± 81.8	0.25	0.442
Calcium(mmol/L)	2.3 ± 0.22	2.3 ± 1.5	0.22	0.74
AFP (ng/ml)	2.5 ± 1.2	1.74 ± 1.58	7.47	<0.001
CEA (ng/ml)	100.2 ± 16.57	42.33 ± 4.90	3.46	0.0005
CA-125 (U/ml)	156.1 ± 358.1	64.85 ± 4.96	7.18	<0.001
CA-199 (U/ml)	67.7 ± 57.7	44.36 ± 8.98	0.82	0.4151
CA-153 (U/ml)	44.8 ± 9.72	18.67 ± 6.67	11.4	<0.001
CA-724 (U/ml)	23.7 ± 7.48	8.30 ± 4.13	0.77	0.53
CYFRA21-1(ng/ml)	23.8 ± 5.83	8.54 ± 0.023	7.41	<0.001
TPSA (ng/L)	2.78 ± 0.79	1.58 ± 0.38	4.66	<0.001
NSE (μg/L)	33.3 ± 5.0	42.06 ± 0.79	2.85	0.0044
HB (g/L)	119.8 ± 1.94	119.04 ± 9.09	0.59	0.55

Abbreviation: alkaline phosphatase(ALP), calcium hemoglobin(HB), alpha fetoprotein(AFP), Cancer embryonic antigen (CEA), cytokeratin fragment 19 (CYFRA 21 − 1), total prostate specific antigen(TPSA), and neuron-specific enolase (NSE)

Table 3
risk factors of brain metastasis in patients with lung cancer

Factors	B	Exp(B)	OR (95% CI)	P
AFP	0.189	1.21	1.113–1.308	0.215
CEA	0.000	1.000	1.000-1.001	< 0.001
CA-125	0.000	1.000	1.000-1.001	0.114
CA-153	0.009	1.009	1.006–1.012	0.44
CYFRA21-1	0.007	1.007	1.004–1.010	< 0.001
TPSA	0.03	1.03	1.009–1.052	0.075
NSE	0.002	1.002	1.000-1.005	0.34

Abbreviation: alpha fetoprotein(AFP), Cancer embryonic antigen (CEA), cytokeratin fragment 19 (CYFRA 21 − 1), total prostate specific antigen(TPSA), and neuron-specific enolase (NSE)

The diagnostic thresholds, sensitivity, specificity, and AUC of CEA and cyfra21-1 for brain metastasis of lung cancer

Table 4 shows that the cut-off values for CEA and cyfra21-1 were 26.98 U/ml and 10.72 ng/ml, respectively. Notably, cyfra21-1 yielded the greatest AUC. Figure 4A shows the ROC curves of CEA and cyfra21-1 as independent factors. Subsequently, we investigated the combination of these two risk factors. Figure 4B shows the ROC curve of CEA + cyfra21-1. We found that the combination of CEA + cyfra21-1 yielded a similar AUC value, reaching 0.661. The sensitivity and specificity of CEA + cyfra21-1 are shown in Table 4, and all the data were statistically significant (P < 0.05).

Table 4
critical values, sensitivity and specificity, AUC of CEA and cyfra21-1 in patients with lung cancer with brain metastasis

Factor	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	P
CYFRA21-1 (U/ml)	10.72	38.0	87.4	0.643	< 0.001
CEA (ng/ml)	26.98	39.7	79.3	0.593	< 0.001
CEA + CYFRA21-1	33.48	51.3	76.7	0.661	< 0.001
Abbreviation: Cancer embryonic antigen (CEA), cytokeratin fragment 19 (CYFRA 21 − 1)					

Discussion

The incidence of brain metastasis in patients with lung adenocarcinoma is high, accounting for 43–62% of brain metastases. Mujoomdar et al. [1]found that, compared with squamous cell carcinoma, the risk of brain metastasis of adenocarcinoma and undifferentiated cell type was significantly higher. In addition, the rate of brain metastasis of squamous cell carcinoma, adenocarcinoma, and undifferentiated cell type was 13%, 41%, and 43%, respectively (P = 0.003). In a multivariate analysis, Bajard et al. [2]found that the rate of brain metastasis of adenocarcinoma in patients with non-small cell carcinoma was higher than that of squamous cell carcinoma and large cell carcinoma. This finding was consistent with those reported by previous studies.

Hematogenous metastasis is the most common metastatic mode of lung cancer, and brain metastasis is the most common metastatic site of advanced lung cancer. Approximately 80% of patients are at the advanced stage of the disease at the time of diagnosis. Moreover, 10–25% and 30–45% of patients have brain metastasis at the time of initial diagnosis or develop brain metastasis during treatment, respectively[3]. The limitations of computed tomography, magnetic resonance imaging, and other imaging examinations, as well as and the high cost of PET examination, hinder the early clinical qualitative diagnosis of tumors. Therefore, the combined detection of tumor markers and imaging examination has become an important method for the diagnosis of lung tumors. Tumor markers are produced during the process of occurrence and development of tumor tissues, and can reflect the presence of the tumor. Certain active chemical substances are present in carcinoma tissue and body

fluids, the same kind of tumor can contain a variety of tumor markers, the same tumor different tissue types can express the same as well as different tumor markers. Therefore, the combined detection of multiple tumor markers may improve the diagnostic sensitivity for lung cancer, and provide a reference for the differential diagnosis and prognosis of this disease.

CEA is an acidic glycoprotein. It has been reported that the positive rate of CEA in patients with lung adenocarcinoma is > 70% higher than that observed in patients with small cell lung cancer. In addition, high levels of CEA in the serum are linked to higher TNM stages. A number of studies have found that the preoperative level of CEA is an important independent factor related to the survival of patients with non-small cell lung cancer[4, 5]. Consistent with previous findings, the results of this study showed that the level of CEA in the serum was positively correlated with brain metastasis, and was an independent factor of lung cancer brain metastasis. In addition, the level of CEA was higher in the serum of patients with lung adenocarcinoma, suggesting that CEA may be helpful for the differential diagnosis of lung cancer.

CA-125 is a mucus-like glycoprotein complex. In recent years, it has been demonstrated that the content of CA-125 in the serum of patients with lung cancer is significantly different from that measured in healthy individuals[6]. The results of this study are consistent with these reports.

Cyfra21-1 is a 19 fragment of the cytokeratin family, which is expressed by multiple epithelial cells. It is mainly distributed in the cytoplasm of the laminated tumor epithelium. Following the death of cells, it is released into the bloodstream in the form of dissolved fragments to increase its content in the serum. It has been reported that cyfra21-1 is an independent prognostic factor of lung cancer[7]. The results of this study showed that the level of cyfra21-1 in the serum was positively correlated with and was an independent factor of brain metastasis of lung cancer. It was the most sensitive marker of lung cancer, and may be used for the differential diagnosis of lung cancer in combination with the level of CEA. According to the literature[8, 9], CYFRA21 -1 is an independent risk factor for brain metastases in lung cancer, and it is found to be negatively correlated by comparing CYFRA21-1 levels and survival time.

NSE is an acid protease, which is involved in glycolysis. Studies have shown that the level of NSE in the serum of patients with small cell lung cancer is significantly higher than that measured in patients with other types of lung cancer[10]. This finding has prognostic value for small cell lung cancer. The results of this study showed that NSE was not correlated with brain metastasis of lung cancer, which may be related to the low number of lung cancer cases included in previous study. More reports [11, 12] claim that CA-125, AFP and NSE are not specific for lung cancer metastasis.

It has been reported in the literature that the positive rate of CEA in patients with lung adenocarcinoma is as high as 70%, which is significantly higher than that of small cell lung cancer, and the higher the TNM stage, the higher the serum CEA level. Some studies have found that the preoperative CEA level has nothing to do with the survival rate of NSCLC, but it can be used as an index to predict brain metastasis in NSCLC patients[8, 13]. Differentiation degree and lymph node metastasis have been independent risk factors for brain metastasis of lung cancer. Basic medicine confirmed that the lower the degree of differentiation, the higher the degree of malignancy, the rapid growth of tumor, easy to metastasize[9],

and the survival of patients with lymph node metastasis was significantly lower than that of no. Lymph node metastasis and the number of lymph node metastases are negatively correlated with survival, which to some extent proves that there are many factors that affect lung cancer brain metastasis.

In Table 5, we reviewed some risk factors of metastases of lung cancer. However, the distribution of brain metastases of lung cancer has rarely been comprehensively analyzed. In our study, we collected serum and determined the levels of ALP, calcium, HB, AFP, CEA, ca-125, ca-199, ca-153, cyfra21-1, TPSA, and NSE. High levels of AFP, CEA, ca-125, ca-153, TPSA, SCC-ag, and cyfra21-1 were found in patients with brain metastasis of lung cancer. Note that the levels of NSE were lower in patients with other metastases ($P < 0.05$). Based on the analysis of large amounts of data in previous studies[14], CEA and cyfra21-1 were selected as independent risk factors of brain metastasis of lung cancer ($P = 0.0005$ and $P < 0.0001$, respectively). In addition to the levels of CEA and cyfra21-1, we also determined their threshold, sensitivity, specificity and AUC. The results of this analysis also show that CEA + cyfra21-1 are risk factors for specifically promoting brain metastases in lung cancer.

Table 5
The Risk Factors of Metastases of Lung Cancer

Author	Year	Histopathological Type	Metastatic Sites	Risk Factor
Morita et al [21]	2019	NSCLC	Intertrabecular Vertebral	CEA
Zhou et al [22]	2017	NS	Bone	CA-125, ALP
Zhang et al [23]	2017	Adenocarcinoma	Brain, Lymph node	CYFRA21-1
Wu et al [24]	2017	NSCLC	Lymph node	MicroRNA-422a
Chu et al [25]	2017	Adenocarcinoma	Lymph node	CLSTNI, CLU, NGAL
Chen et al [26]	2015	NSCLC	Brain	NSE
Chen et al [27]	2015	NS	Lymph node	CYFRA21-1, CEA
Lee et al [28]	2012	NSCLC	Brain	CEA
Cabrera-Alarcon et al [29]	2011	NS	NS	CYFRA21-1
Cedrés et al [14]	2011	NSCLC	Brain	CEA, CYFRA21-1, CA-125
Oshiro et al [30]	2004	Adenocarcinoma	Liver	AFP
Pollán et al [31]	2003	NSCLC	NS	CA-125
Niklinskij et al [32]	1992	NSCLC	Lymph node	SCC

We concluded that the cut-off values of CEA and cyfra21-1 were 26.98 U/ml and 10.72 ng/ml, respectively. These values are the key indicators of brain metastasis in patients with lung cancer. Cyfra21-1 yielded the highest AUC, and showed the highest accuracy in differentiating lung cancer brain metastasis patients. On this basis, we performed additional detailed diagnostic techniques, to confirm or exclude the diagnosis of brain metastasis. Unlike previous studies, this study showed that the optimal diagnostic value of the CEA + cyfra21-1 combination was 33.48 U/ml. We found that the combination of CEA + cyfra21-1 yielded a similarly high AUC value (≤ 0.661) and a high sensitivity. Notably, cyfra21-1 exhibited the highest specificity. These findings indicate that higher levels of CEA and cyfra21-1 are associated with a higher risk of brain metastasis of lung cancer. Therefore, the combination of CEA + cyfra21-1 may also be used as an indicator of brain metastasis of lung cancer.

Studies have found that the level of SCC-ag in the serum is related to brain metastasis of lung cancer. This is a tumor-related antigen, which is widely distributed in tumor tissues of the esophagus, pharynx, lung, cervix, and other parts, especially in patients with squamous cell carcinoma. Studies conducted by Jingxuan Fu et al.[15] have shown that SCC-ag is abundant in highly differentiated tumor cells with high sensitivity, and can be used as a diagnostic marker of squamous cell carcinoma. Studies have shown that the levels of SCC-ag are high in lung cancer tissues, and are associated with brain metastasis of lung cancer. SCC-ag is a tumor marker in the serum derived from squamous epithelial cells, and its content is significantly increased in patients with squamous cell carcinoma. Hence, it is the main marker for the diagnosis of squamous cell carcinoma, and its level can be used to evaluate the prognosis of lung cancer. Moreover, the level of SCC-ag in the serum is positively correlated with brain metastasis of lung cancer. Barak et al. [12]found that high levels of SCC-ag in patients with lung cancer were linked to poor prognosis. SCC-ag has been widely found in many parts of the lung, pharynx, esophagus and other tumors in recent years, especially in squamous cell carcinoma[16]. According to the study[17, 18], this index is widely distributed in well-differentiated large cells with strong sensitivity and can be used as a tumor marker for squamous cell carcinoma.

The size of the primary tumor is the main risk factor of brain metastasis. Jessica et al. [19]found that in patients with early-stage lung cancer, the size of the primary tumor was positively correlated with the incidence of brain metastasis. Bajard et al. [2] reported that, among 305 patients with stage I–IIIB disease, the risk of brain metastasis in T4 patients was higher than that observed in T1–3 patients (P = 0.0009). Mediastinal lymphadenopathy is also associated with an increased risk of brain metastasis, with an incidence rate of about 34%[20]. However, this study did not include a follow-up investigation of the levels of SCC-ag or the size of the primary tumor.

Conclusion

the high expression levels of CEA and cyfra21-1 in the serum may be related to the occurrence of brain metastasis of lung cancer. Meanwhile, the combination of CEA + cyfra21-1 may also be helpful for the diagnosis of brain metastasis of lung cancer. The positive expression of CEA and cyfra21-1 in the serum is a prognostic factor for lung cancer patients with brain metastasis. However, currently, there are few

studies investigating the relationship between tumor markers in the serum and the occurrence and prognosis of brain metastasis of lung cancer. Additional prospective studies, involving larger numbers of patients, are warranted to further explore the relationship between tumor markers in the serum and the occurrence and prognosis of brain metastasis of lung cancer. Such studies, may also reveal the mechanisms involved in these processes.

Abbreviations

ALP, Alkaline Phosphatase; HB, Hemoglobin; AFP, Alpha Fetoprotein, CEA, Cancer Embryonic Antigen; CYFRA 21 − 1, Cytokeratin Fragment 19; TPSA, Total Prostate Specific Antigen; SCC-Ag, Squamous Cell Carcinoma Antigen, NSE, Neuron Specific Enolase; ROC, Receiver Operating Curve; AUC, Area Under Curve.

Declarations

Ethics approval and consent to participate The present study was approved by the Medical research Ethics Committee of The First Affiliated Hospital of Nanchang university. Written informed consent was obtained from all individuals enrolled in the study.

consent for publication Consent was obtained from all individuals enrolled in the study.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

Authors' contributions: TS, YCP and RBL performed the experiments and collected the data. TS, QMG and LJZ designed the current study. QYL and HYS given final approval of the version to be published. JT wrote the manuscript. All the authors read and approved the final manuscript. The authors report no conflicts of interest in this work. All authors read and approved the final manuscript.

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Figures

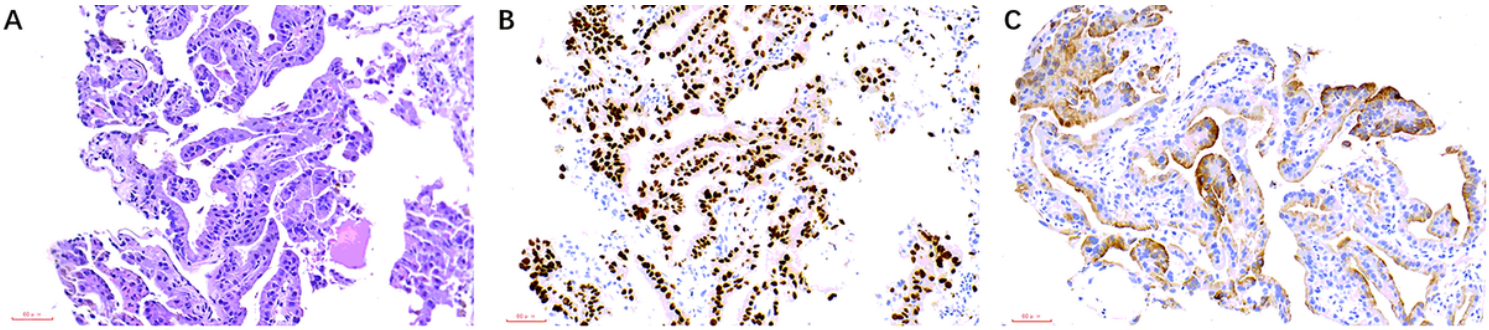

Figure 1

Hematoxylin-eosin staining and immunohistochemical image analysis of patients with lung cancer brain metastases. A. Lung cancer (HE×200). B. TTF-1 (+) (SP×200). C. CK7 (+) (SP×200). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

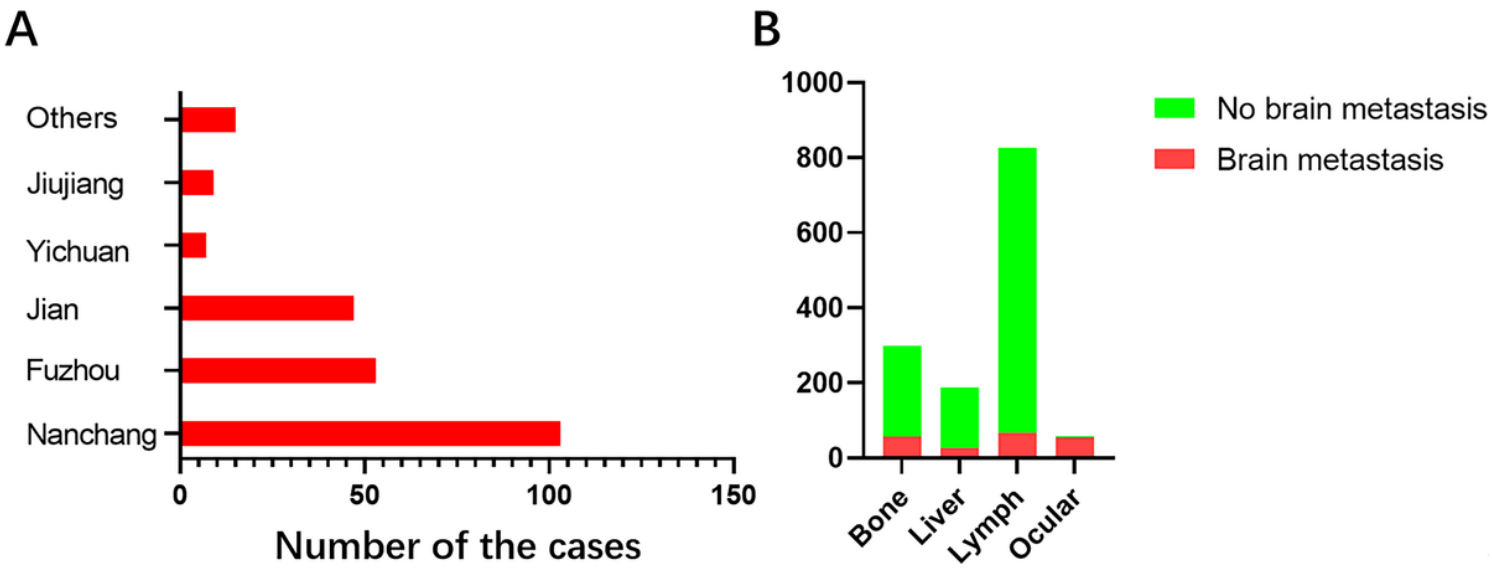

Figure 2

Clinical features of the patients(A) The geographical location of the patients; (B) the other areas of the patients and the corresponding numbers.

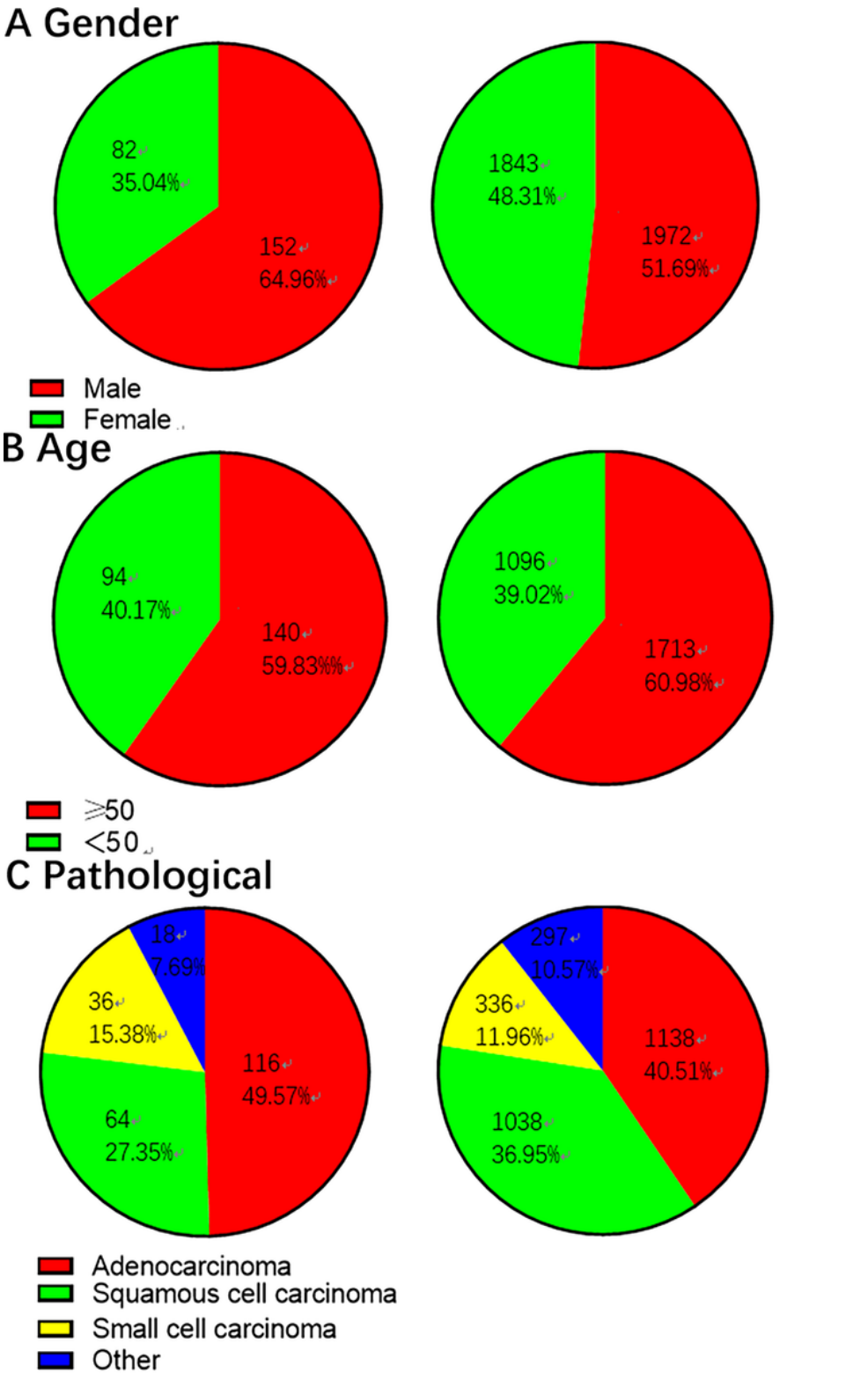

Figure 3

The left side shows lung cancer patients with brain metastases, and the right side shows patients with no lung cancer brain metastases. (A) Gender data of patients with brain metastases from lung cancer and brain metastasis without lung cancer (B) Age data of patients with brain metastases from lung cancer and brain metastases without lung cancer (C) Differences in pathological features between patients with brain metastases from lung cancer and brain metastases without lung cancer.

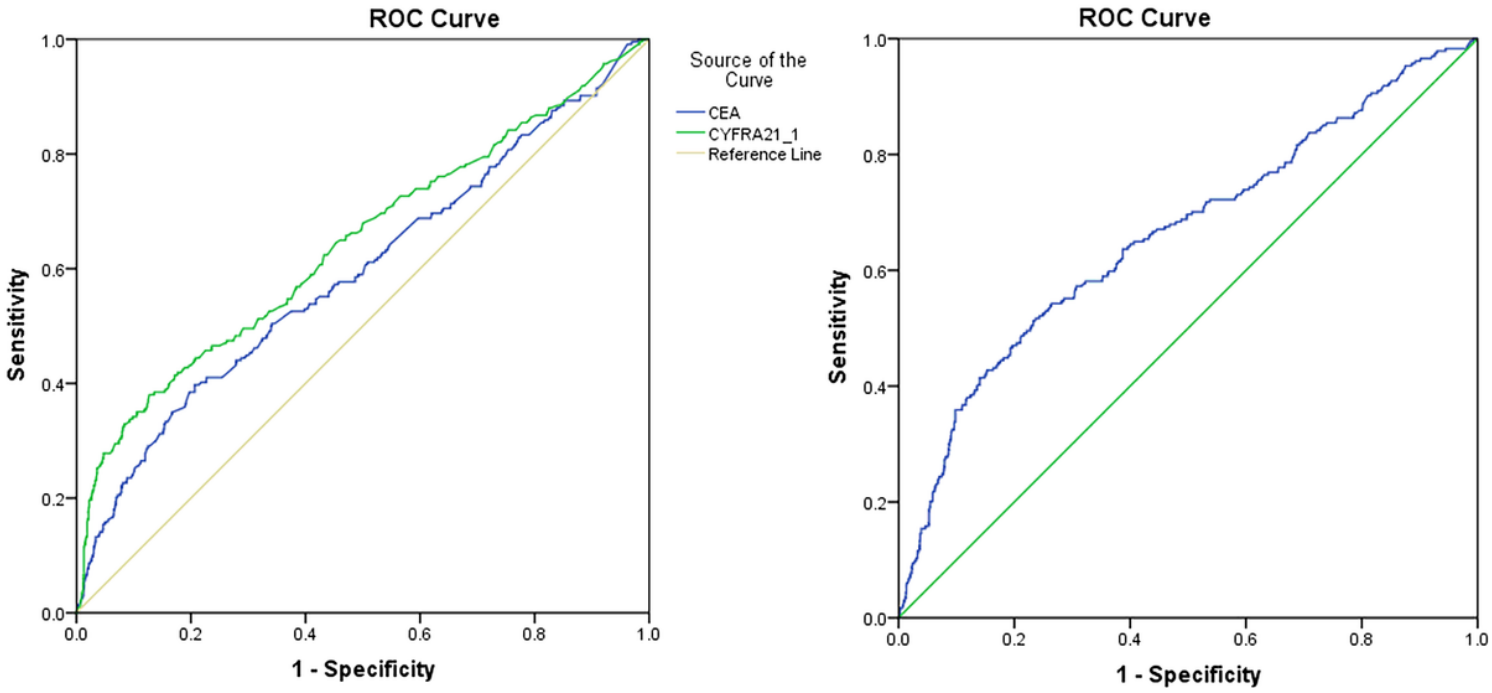

Figure 4

(A)ROC curves of CEA and cyfra21-1 levels in patients with brain metastasis from lung cancer. (B)ROC curve of CEA + cyfra21-1 in patients with lung cancer with brain metastasis