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Original Article

Risk factor of brain metastases and its influence on patient prognosis after complete resection of non-small cell lung cancer

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Abstract: Objective: To investigate the risk factors of brain metastases and its influence on the prognosis of patients with complete resected non-small cell lung cancer (NSCLC). Methods: The clinical data of 190 patients with completely resected NSCLC were retrospectively analyzed. The effect of brain metastasis on prognosis in patients with NSCLC after complete resection was investigated. The identification of risk factors for brain metastases was conducted by single-factor and Cox multivariate regression analysis. Results: Among 190 patients, 9 patients were lost to follow up. Finally, 181 patients were included in this study. The median survival time of brain metastases patients (64 cases) was 700 days. At 1 year, 3 years, and 5 years after surgery, the survival rates of patients with brain metastases were 62.5%, 28.13% and 7.81% respectively. Compared with those in patients without brain metastases, significant differences were found for median survival time and survival rates ($P < 0.05$). The Single-factor and multivariate Cox regression analysis indicated that the level of preoperative carcinoembryonic antigen (CEA), the lymph node ratio (≥ 30%) and non-squamous carcinoma type were risk factors for brain metastasis ($P < 0.05$). Conclusions: Brain metastasis is a risk factor for mortality in NSCLC patients after complete resection. Preoperative CEA levels, lymph node ratio (≥ 30%), and type of non-squamous cell carcinoma were risk factors for brain metastases.

Keywords: Non-small cell lung cancer, complete resection, brain metastases, risk factor

Introduction

In recent years, both the incidence and mortality of lung cancer have been on the rise, and NSCLC is the most common type [1]. The current treatment methods of local non-small cell lung cancer include surgery, chemotherapy, radiotherapy and other comprehensive treatment [2]. An operation with complete resection of the tumor is considered as a significantly effective method. It is reported that the median survival time of completely resected NSCLC in patients is up to 25 months and the 2-year survival rate is up to 66% [3]. However, patients with NSCLC after comprehensive treatment still face local recurrence and distant metastasis [4]. Several clinical studies have confirmed that the brain has become one of the most common metastatic sites in NSCLC patients with postoperative treatment failure [5, 6]. Long-term follow-up studies for patients with completely resected NSCLC have found that the incidence rate of brain metastases is as high as 54%, and it is generally more than 15% [7]. Brain metastasis has an obvious impact on survival and prognosis of completely resected NSCLC patients. It is necessary to strengthen research on brain metastases [8]. So far, it is not clear regarding the risk factors for brain metastases and the relationship between brain metastasis and mortality in patients with completely resected NSCLC. Therefore, the purpose of this study was to analyze the risk factors for brain metastases and investigate its influence on prognosis in patients with completely resected NSCLC.

Materials and methods

Subjects

The clinical data of 190 patients with NSCLC who received complete resection of lung tumors

in our hospital from January 2011 to December 2012 were retrospectively analyzed. The inclusion criteria was as follows: the pathological diagnosis was non-small cell lung cancer; patients received surgery for complete resection for the first time, preoperative brain, chest, abdomen CT or MRI examinations and bone scan were performed to exclude extrapulmonary metastasis; the hilar and mediastinal lymph nodes during operation were cleared away; the postoperative follow up continued for more than 5 years; postoperative adjuvant chemotherapy were performed using cisplatin if needed; postoperative Radiotherapy was performed as follows: 6MVX rays were applied, each time was 2 Gy, there was 5 application times in each week, the total dose was 40~50 Gy if needed. The exclusion criteria were: history of other cancer; severe liver and kidney dysfunction; history of psychiatric illness; patients receiving radiotherapy and chemotherapy before operation; patients who died of surgical complications early after operation. This study was approved by the Ethics Committee of our hospital and all the selected patients and their families signed the informed consent.

Follow-up

After surgery, the patients were examined by chest X-ray, abdominal ultrasound brain CT or MRI every year, the time of follow-up was at least five years or until death. The patient's clinical data, telephone follow-up, previous medical records and other information were collected. Brain metastasis was confirmed by imaging examinations [9].

Outcome measures

The effect of postoperative radiotherapy or chemotherapy on the 5-year survival rate in advanced NSCLC patients after complete resection was observed. The comparison of median survival time and survival rate between completely resected NSCLC patients with brain metastases and those without brain metastases was performed. The single factors and multivariate Cox regression analysis were performed for risk factors of brain metastases in patients with completely resected NSCLC.

Statistical treatment

SPSS 22.0 software was used to analyze all the data. The measurement data was expressed as Mean ± Standard Deviation (SD). Comparison between the two groups was performed with independent t-test. The χ^2 test was used for comparison of the count data between the two groups. The risk factors for brain metastases of patients were analyzed by methods of single factor and Cox multivariate regression analysis. The risk factors that showed marked differences between groups by means of single factor analysis were included in Cox multivariate regression analysis. $P < 0.05$ represented statistical significance.

Results

The baseline information of patients

Among 190 patients, 9 were lost to follow up. The successful follow-up rate was 95.3%. At last, 181 patients were included in this study. The basic information of these patients was shown in **Table 1**.

The effect of postoperative chemotherapy on the 5-year survival rate in patients

The results showed that the 5-year survival rate of patients with and without postoperative adjuvant chemotherapy was 28.24% (37/131) and 12% (6/50), respectively. There was a significant statistical difference between the groups ($\chi^2 = 5.272$, $P = 0.022$), as seen in **Figure 1**.

The effect of postoperative radiotherapy on the 5-year survival rate in patients

The 5-year survival rate of patients with and without postoperative radiotherapy was 26.32% (20/76) and 20.95% (22/105), respectively. A statistical difference was not found between groups ($\chi^2 = 0.712$, $P = 0.399$), as seen in **Figure 2**.

Comparison of survival rate between patients with brain metastases and without brain metastases

At 1 year, 3 years, and 5 years after surgery, the survival rate of patients was 72.93% (132/181), 38.67% (70/181) and 23.20% (42/181) respectively. Sixty-four patients (35.36%) had brain metastases with a median survival time of 700 days. At 1 year, 3 years, and 5-years after surgery, the survival rate of patients with brain metastases were 62.5%

Table 1. Comparison of general information between patients with brain metastases and without brain metastases (cases)

Characteristics	Brain metastases group	Non-brain metastases group	χ^2 value	*P* value
Sex			1.442	0.230
Male	41	85		
Female	23	32		
Age (years)			0.196	0.658
< 60	36	65		
≥ 60	26	54		
Smoking history			0.740	0.390
Smoking	38	77		
Non-smoking	26	40		
Preoperative serum CEA levels			5.164	0.023
Normal	20	57		
Increased	44	60		
Preoperative serum LDA levels			0.640	0.424
Normal	58	96		
Increased	8	19		
Surgery			0.722	0.396
Lobectomy	56	107		
Pneumonectomy	8	10		
T stage			0.001	0.975
T1-T2 stage	48	88		
T3 stage	16	29		
Pathological pattern			96.760	< 0.001
Squamous carcinoma	13	108		
Non-squamous carcinoma	51	9		
Differentiated degree			0.087	0.769
Poorly differentiated	33	63		
Middle and high differentiated	31	54		
Numbers of Lymphatic metastasis			0.688	0.407
< 3	24	65		
≥ 3	30	62		
Lymph node ratio (%)			5.918	0.015
≥ 30	40	51		
< 30	24	66		
Postoperative chemotherapy			0.651	0.420
Yes	44	87		
No	20	30		
Postoperative radiotherapy			2.356	0.125
Yes	22	54		
No	42	63		

(40/64), 28.13% (18/64) and 7.81% (5/64), respectively. There were 117 patients (64.64%) without brain metastases. The median survival time of these patients was 930 days. At 1 year, 3 years, and 5-years after surgery, the survival rate of patients without brain metastases was 78.63% (92/117), 44.44% (52/117) and 31.62% (37/117), respectively. We showed that there was a significant statistical difference for the median survival time and survival rates

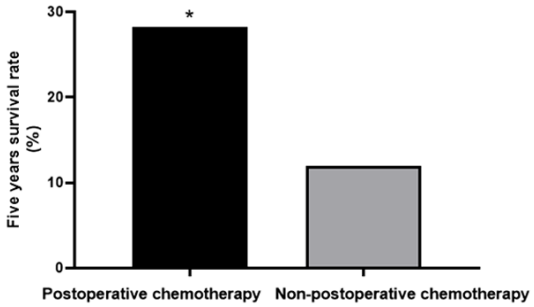

Figure 1. Effect of postoperative chemoradiotherapy on 5-year survival rate of patients, compared with that of patients without chemotherapy after operation, *P < 0.05.

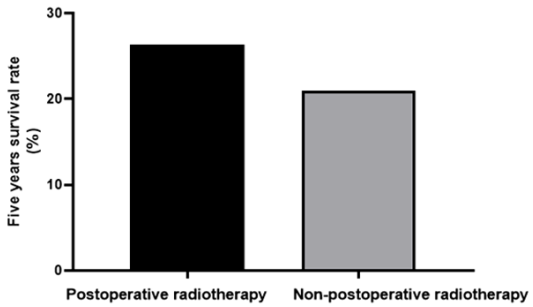

Figure 2. Effect of postoperative radiotherapy on 5-year survival rate of patients.

between the brain metastasis group and the non-brain metastasis group (P < 0.001), as shown in **Tables 2** and **3**. Logistic univariate analysis showed that brain metastases was a risk factor for the prognosis of patients with completely resected non-small cell lung cancer (OR = 1.564, 95% CI: 1.164-2.541, P = 0.041).

Risk factors analysis for brain metastasis

The single factor and Cox prognosis multivariate regression analysis showed that, the preoperative serum CEA levels, a lymph node ratio of more than 30%, and non-squamous cell carcinoma were risk factors for brain metastasis, with statistical significance (P < 0.05); as shown in **Tables 4** and **5**.

Discussion

The retrospective analysis performed in this study showed that in 181 patients with complete resection of NSCLC, the 1, 3 and 5-year survival rates were 72.93%, 38.67% and 23.20% respectively. Some studies have reported that the 5-year survival rate of patients with non-small cell lung cancer was 22.00% [10, 11], which is similar with the results of this study. In recent years, significant progress has been made in the comprehensive treatment of NSCLC [12]. However, in this study 35.26% of patients with non-small cell lung cancer still had brain metastases, and this is basically the same with the results of Ceresoli et al's study [13]. In recent years, with the improvement of local and extracranial control of non-small cell lung cancer, the prevention of brain metastases is becoming more and more important. The median survival time of patients with brain metastases in this study was 700 days and the median survival time in patients without brain metastases was 930 days. The statistical analysis indicated that brain metastases in patients with non-small cell lung cancer after complete resection could be considered as a risk factor for death. Based on these results, finding risk factors and assessing the effects of brain metastases on prognosis in completely resected NSCLC in patients is of great practical significance for taking active and effective treatment and improving patient survival.

At present, most scholars are trying to find the risk factors of brain metastasis in patients with NSCLC after complete resection, such as age, sex, histological type, clinical stage, etc., in order to take effective control of extracranial distance [14, 15]. Among these risk factors, CEA is widely used to assess the prognosis of lung cancer patients and has been confirmed by many studies [16, 17]. It is reported that in NSCLC patients preoperative serum CEA levels were significantly elevated and closely associated with invasion or metastasis of the lymphatic system and peripheral nerves [18]. In this study, univariate and Cox prognostic multivariate regression analysis showed that high levels of preoperative serum CEA increased the risk of brain metastases, compared with patients with normal preoperative CEA levels. These results are similar with the results of Muley et al' study [19].

Ma et al [20] retrospectively analyzed the clinical data of 352 patients with totally resected non-small cell lung cancer and reported that the incidence of brain metastases in two years for patients with adenocarcinoma and squamous cell carcinoma was 25% and 10%,

Table 2. Comparison of median survival time between patients with brain metastases and without brain metastases

Groups	Median survival time (Days)	SE	95% CI	
			Lower limit	Upper limit
Brain metastasis group	700	50.7	597.5	803.4
Non-brain metastasis group	930	64.8	798.6	1061.6

Table 3. The comparison of survival rate between patients with brain metastases and without brain metastases [cases (%)]

Groups	Cases	1-year survival rate	3-year survival rate	5-year survival rate
Brain metastases	64	40 (62.5)	18 (28.13)	5 (7.81)
Non-brain metastases	117	92 (78.63)	52 (44.44)	37 (31.62)
χ^2 value		5.454	4.646	13.165
P value		0.020	0.031	0.000

Table 4. Single-factor analysis for risk factors of brain metastasis

Characteristics		Cases of brain metastasis [n (%)]	*P* value
Sex	Male	41 (32.54)	0.230
	Female	23 (41.82)	
Age (years)	< 60	36 (35.64)	0.658
	≥ 60	26 (32.50)	
Smoking history	Smoking	38 (33.04)	0.390
	Non-smoking	26 (39.39)	
Preoperative serum CEA levels	Normal	20 (25.97)	0.023
	Increased	44 (42.31)	
Preoperative serum LDA levels	Normal	58 (37.66)	0.424
	Increased	8 (29.63)	
Surgery	Lobectomy	56 (34.36)	0.396
	Pneumonectomy	8 (44.44)	
T stage	T1-T2 stage	48 (35.29)	0.975
	T3 stage	16 (35.56)	
Pathological pattern	Squamous carcinoma	13 (21.67)	0.007
	Non-squamous carcinoma	51 (42.15)	
Differentiated degree	Poorly differentiated	33 (34.38)	0.769
	Middle and high differentiated	31 (36.47)	
Numbers of Lymphatic metastasis	≤ 3	24 (26.97)	0.407
	> 3	30 (32.61)	
Lymph node ratio (%)	≥ 30	40 (43.96)	0.015
	< 30	24 (26.67)	
Postoperative chemotherapy	Yes	44 (33.59)	0.420
	NO	20 (40.00)	
Postoperative radiotherapy	Yes	22 (28.95)	0.125
	No	42 (40.00)	

respectively. The incidence of postoperative brain metastases in NSCLC patients was significantly higher than that in patients with squamous cell carcinoma, which may be due to the

Table 5. Multivariate regression analysis for risk factors of brain metastasis

Factors	β	SE	Wald	OR	95% CI	*P* value
Increased levels of preoperative serum CEA levels	0.758	0.309	6.074	2.145	1.165-3.945	0.001
Lymph node ratio more than 30%	-0.912	0.401	5.362	0.401	0.187-0.864	0.000
Non-squamous carcinoma	0.716	0.382	3.845	2.051	0.986-4.046	0.000

invasive growth of adenocarcinoma. Adenocarcinoma is prone to hematogenous metastasis and has a poor prognosis. In this study, the incidence of brain metastases for NSCLC patients was also significantly more than that in patients with squamous cell carcinomas, which is similar with results of previous studies [21].

The lymph node ratio is closely related with the risk of brain metastases. Some studies have reported that the lymph node ratio could be an important indicator of postoperative prognosis in NSCLC patients, and that lymph node ratio could be used as a differentiator for the risk of brain metastases [22]. The results of single-factor and Cox prognosis multivariate regression analysis in this study indicated that a lymph node ratio of more than 30% is a risk factor for patients with complete resection of non-small cell lung cancer.

For patients with completely resected NSCLC, postoperative adjuvant chemotherapy is one of the effective measures that could control and eliminate residual cancer or micrometastasis and significantly reduce the occurrence of extrahepatic metastasis. Because of the blood-brain barrier blocking chemotherapy drugs, it does not significantly reduce brain metastases. Churilla et al [23] reported that increasing local control effects and induction of radiotherapy treatment helped to reduce the incidence of brain metastases. Postoperative brain radiotherapy may help reduce brain metastases in patients with non-small cell lung cancer after complete resection. Clinical scholars tend to apply postoperative brain radiotherapy for patients with non-small cell lung cancer [24, 25]. Enders et al [26] reported that postoperative brain irradiation could significantly reduce or delay brain metastases, and it has an effect on the survival of patients. So it is important that postoperative brain radiotherapy should be performed for patients with high-risk of brain metastases. As chemotherapy drugs are hard to penetrate the blood-brain barrier, it is difficult to effectively control and eliminate micro-metastases in the brain. With the prolongation of survival and the development of micro-metastases in the brain, more and more patients have brain metastases. Based on the above views, the main reason of postoperative adjuvant chemotherapy increasing brain metastasis is to prolong survival. For patients who did not receive postoperative adjuvant chemotherapy, it is more likely for them to have extracerebral metastasis or local recurrence. In this study, the survival of postoperative adjuvant chemotherapy patients was significantly better than that of patients without postoperative adjuvant chemotherapy. These results were in accordance with those reported by Watanabe et al [27]. However, there was no significant difference between patients with and without postoperative radiotherapy. This may be related to a small sample size.

In summary, brain metastasis is a risk factor for the prognosis of patients with completely resected non-small cell lung cancer. Preoperative serum CEA levels, a lymph node ratio of more than 30%, and type of non-squamous cell carcinoma are risk factors for brain metastases. However, there are some limitations in this study such as analysis occurring in a single center, a limited number of patients, need for a longer follow-up intervals, no subgroup analysis stratified by number and size of brain metastases, and so on. In order to provide more scientific results, we will perform a multi-centered, randomized control, and longer-time follow up study.

Disclosure of conflict of interest

None.

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