Prognostic factors analysis in EGFR mutation-positive non-small cell lung cancer with brain metastases treated with whole brain-radiotherapy and EGFR-tyrosine kinase inhibitors

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Abstract. The survival time of non-small cell lung cancer (NSCLC) patients with brain metastases has been previously reported to be 6.5-10.0 months, even with systematic treatment. Patients that possess a certain epidermal growth factor receptor (EGFR) mutation alongside NSCLC with brain metastases also have a short survival rate, and a reliable prognostic model for these patients demonstrates a strong correlation between the outcome and treatment recommendations. The Cox proportional hazards regression and classification tree models were used to explore the prognostic factors in EGFR mutation-positive NSCLC patients with brain metastases following whole-brain radiation therapy (WBRT) and EGFR-tyrosine kinase inhibitor (EGFR-TKI) treatment. A total of 66 EGFR mutation-positive NSCLC patients with brain metastases were retrospectively reviewed. Univariate and multivariate analyses by Cox proportional hazards regression were then performed. The classification tree model was applied in order to identify prognostic groups of the patients. In the survival analysis, age, carcinoembryonic antigen (CEA) and status of the primary tumor were prognostic factors for progression free survival (P=0.006, 0.014 and 0.005, respectively) and overall survival (P=0.009, 0.013 and 0.009, respectively). The classification tree model was subsequently applied, which revealed 3 patient groups with significantly different survival times: Group I, age <65 years and CEA ≤10 μg/ml; Group II, age <65 years and CEA >10 μg/ml or age ≥65 years and CEA ≤10 μg/ml; and Group III, age ≥65 years and CEA >10 μg/ml. The major prognostic predictors for EGFR mutation-positive NSCLC patients with brain metastases following WBRT and EGFR-TKI were age and CEA. In addition, primary tumor control may be important for predicting survival.

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Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; WBRT, whole-brain radiation therapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors

Key words: non-small cell lung cancer, brain metastases, epidermal growth factor receptor mutation-positive, classification tree model, prognostic factors

Introduction

Patients with non-small cell lung cancer (NSCLC) possess a high risk of developing brain metastases. The incidence rate of brain metastases for patients with lung cancer is 23-65% (1). Once intracerebral metastases develop, the prognosis is poor. The median survival time for patients with untreated brain metastases is only ~1 month (2,3). The principle therapeutic modality for brain metastases is whole-brain radiation therapy (WBRT), and the median survival time following this treatment may increase to 4-6 months. Although therapies, including surgery, WBRT, stereotactic radiotherapy and systematic chemotherapy, are rapidly improving, the prognosis of patients with brain metastases from lung cancer remains poor, and the median survival time for patients remains at ~6.5-10 months (4-7).

In 2004, the genes encoding the read code box of epidermal growth factor receptor (EGFR) were sequenced (8). In addition, the gene mutation status has been elucidated and is now widely used in clinical practice. As a result, the identification of the EGFR mutation and the introduction of treatment with EGFR-tyrosine kinase inhibitors (EGFR-TKI) has improved clinical outcomes (9). EGFR-TKI regimens have a good efficacy against brain metastases in NSCLC. In previous years, increasing efforts have been made to understand and use prognostic indicators in patients with brain metastases from NSCLC (9,10). However, the prognostic factors of EGFR mutation-positive NSCLC patients with brain metastases following WBRT have not been studied extensively.

Based on the aforementioned considerations, the purpose of the present study was to analyze and assess the prognostic factors in EGFR mutation-positive NSCLC patients with brain metastases following WBRT and EGFR-TKI treatment, using

the classification tree and Cox proportional hazards regression models.

Materials and methods

Patients. Between January 2005 and July 2014, 66 EGFR mutation-positive patients diagnosed with NSCLC were identified with brain metastases and treated at the Department of Radiation Oncology and Chemotherapy at The First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China). The criteria for inclusion in the present retrospective study were as follows: i) All patients possessed a histopathological diagnosis of NSCLC, acquired by bronchial biopsy, fine needle aspiration biopsy or a surgical excision specimen; ii) all brain metastasis diagnoses were confirmed by head magnetic resonance imaging (MRI), contrast-enhanced computed tomography (CT) or positron emission tomography (PET)/CT scans; iii) the EGFR gene mutation was detected; iv) all patients were treated with EGFR-TKI until the disease progressed or the toxicity was intolerable; v) all patients were treated with WBRT (typically 30 gray units per 10 fractions); vi) all survival data were up to date on July 31, 2014; and vii) the clinical data of all patients were complete. In total, 66 patients were available for the present analysis, 34 of which were males and 32 were females. The median age at the diagnosis of brain metastasis was 61 years old (range, 38-82 years). A total of 11 (16.7%) patients possessed squamous cell lung carcinoma, while 55 (83.3%) patients possessed adenocarcinoma.

Study design. The first section of the present study was a retrospective description regarding the recent therapeutic effects and long-term treatment effects observed in the patients. The second section of the study was a multivariate analysis that followed a univariate analysis, including 14 prognostic factors, using Cox proportional hazards regression. The final section of the study was a classification tree model.

The following variables were examined to determine the prognostic value for EGFR mutation-positive NSCLC patients with brain metastases following WBRT and EGFR-TKI treatment: i) Age at diagnosis of brain metastasis (for statistical purposes, the patients were classified into two age groups, <65 vs. ≥65 years); ii) gender (male vs. female); iii) Eastern Cooperative Oncology Group performance status (ECOG PS; PS ≤2 vs. >2 points); iv) histopathology (adenocarcinoma vs. squamous cell carcinoma); v) primary tumor node metastasis (TNM) stage (I-III vs. IV stage); vi) smoking (heavy vs. no/little); vii) history of pulmonary lesions radiotherapy (with vs. without); viii) history of pulmonary lesions surgical resection (with vs. without); ix) cisplatin-based chemotherapy (with vs. without); x) number of brain metastases (single vs. multiple); xi) extracranial metastases (with vs. without); xii) carcinoembryonic antigen (CEA) levels at brain metastases diagnosis (for statistical purposes, the patients were classified into two groups, ≤10 μg/ml vs. >10 μg/ml); xiii) the status of the primary tumor (controlled vs. uncontrolled); and xiv) supportive chemotherapy (yes vs. no). No/little smoking was defined as a smoking index (SI) of <200 (11). SI was defined as the number of cigarettes smoked per day multiplied by the number of years smoked.

Evaluation. The therapeutic effects were evaluated using the RECIST 1.1 criteria (12). The therapeutic effects may be divided into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR) refers to the percentage of CR+PR patients out of the total number of patients, and the disease control rate (DCR) refers to the percentage of CR+PR+SD patients out of the total number of patients. The long-term treatment effects were evaluated by recording the progression free survival (PFS) and overall survival (OS) rates. PFS was defined as the interval between the diagnosis of brain metastasis and the initial observation of PD or mortality from any cause. The OS was measured between the date of the diagnosis of brain metastasis and the time of the mortality of the patient or the deadline for the study (July 31, 2014).

Statistical analysis. The clinical data were described by median, frequency and percentage. Survival analyses for each prognostic factor were performed using the Kaplan-Meier method, using SPSS software version 19.0 (IBM SPSS; Armonk, NY, USA). The log rank test was used in statistical comparisons. The multivariate analysis was conducted using the Cox proportional hazard regression model. The classification tree model was subsequently applied. A P-value of <0.05 was considered to indicate a statistically significant difference.

Results

Statistical description. A total of 66 patients were analyzed. Of these, 3 patients achieved CR, 27 patients demonstrated a PR, 25 patients remained to possess SD and 11 patients developed a PD; therefore, the patients demonstrated an ORR of 45.5% (30/66) and a DCR of 83.3% (55/66). At the time of analysis, 5 patients (7.58%) were alive, while 61 patients (92.42%) had succumbed. The median PFS was 5.9 months (95% CI, 4.2-8.8 months) and the median survival time of the entire cohort was 10.9 months (95% CI, 8.7-14.1 months). The survival curve for EGFR mutation-positive NSCLC patients with brain metastases is shown in Fig. 1.

Survival analysis. In the univariate analysis, the following variables at the diagnosis of brain metastasis were significantly associated with an improved PFS and OS (P-values, respectively): Age (0.008, 0.028); CEA (0.035, 0.031); and the status of primary tumor (0.015, 0.026). The prognostic factors for PFS and OS in the univariate analysis are presented in Table I.

In the multivariate analysis, the prognostic predictors for PFS for EGFR mutation-positive NSCLC patients with brain metastases were age, CEA and status of the primary tumor (P=0.006, 0.014 and 0.005, respectively). Age, CEA and status of the primary tumor were also predictive factors for OS (P=0.009, 0.013 and 0.009, respectively). The results of the prognostic factors for PFS and OS in the multivariate analysis are summarized in Tables II and III.

Classification tree model. Based on the clinical data, a classification and regression tree method (13,14), a non-parametric regression method, was used. In addition, the method selected the automatic depth, which was length of the classification

Table I. Prognostic factors for PFS and OS in univariate analysis.

Prognostic factors	No. of patients	PFS[a]	PFS P-value	OS[a]	OS P-value
Age, years					
<65	40	8.7	0.008	13.2	0.028
≥65	26	3.4		9.0	
Gender					
Male	34	6.9	0.481	10.1	0.929
Female	32	4.6		11.0	
ECOG PS					
≤2	48	6.7	0.424	11.4	0.348
>2	18	3.2		4.1	
Primary TNM stage					
I-III	15	3.3	0.314	6.2	0.125
IV	51	7.1		11.3	
Histopathology					
Adenocarcinoma	55	6.2	0.341	10.9	0.455
Squamous cell carcinoma	11	5.7		7.7	
Smoking					
Heavy	24	8.7	0.478	11.1	0.427
No/little	42	4.6		10.7	
Pulmonary lesions radiotherapy					
With	12	4.6	0.464	9.0	0.514
Without	54	6.1		10.9	
Pulmonary lesions surgical resection					
With	6	7.5	0.189	11.7	0.512
Without	60	5.6		10.9	
Cisplatin-based chemotherapy					
With	37	6.3	0.340	11.3	0.823
Without	29	3.6		9.9	
Brain metastases					
Single	22	6.0	0.538	11.2	0.715
Multiple	44	5.4		10.7	
Extracranial metastases					
With	35	6.2	0.747	11.0	0.441
Without	31	4.4		9.4	
CEA, μg/ml					
≤10	27	9.3	0.035	16.0	0.031
>10	39	4.1		8.7	
Primary tumor status					
Uncontrolled	15	2.7	0.015	6.7	0.026
Controlled	51	7.1		11.3	
Supportive chemotherapy					
Yes	24	5.4	0.450	11.6	0.731
No	42	7.5		10.6	

[a]Data measured in months. PFS, progression free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor node metastasis; CEA, carcinoembryonic antigen.

tree model. The terminal parent and child nodes were defined as 20 and 10, respectively. The adjusted significance level was defined as $P<0.05$ in the splitting and merging of a tree branch. The nodes were combined into the same group where the significance level of the statistical difference between the survival distributions of two terminal nodes was >0.05.

Table II. Multivariate analysis of prognostic factors for progression free survival.

Variable	B	SE	Wald	Exp (B)	P-value
Age, years	-0.721	0.261	7.664	0.486	0.006
CEA, μg/ml	-0.652	0.266	6.003	0.521	0.014
Primary tumor status	0.872	0.312	7.807	2.391	0.005

CEA, carcinoembryonic antigen; B, coefficient for the constant; SE, standard error; Wald, Wald χ^2 test; Exp (B), exponentiation of B.

Table III. Multivariate analysis of prognostic factors for overall survival.

Variable	B	SE	Wald	Exp (B)	P-value
Age, years	-0.706	0.272	6.738	0.494	0.009
CEA, μg/ml	-0.674	0.271	6.178	0.510	0.013
Primary tumor status	0.818	0.313	6.855	2.267	0.009

CEA, carcinoembryonic antigen; B, coefficient for the constant; SE, standard error; Wald, Wald χ^2 test; Exp (B), exponentiation of B.

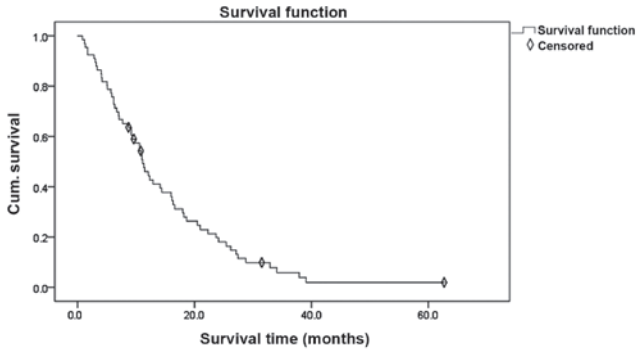

Figure 1. Survival curve of epidermal growth factor receptor mutation-positive non-small cell lung cancer patients with brain metastases. Cum., cumulative.

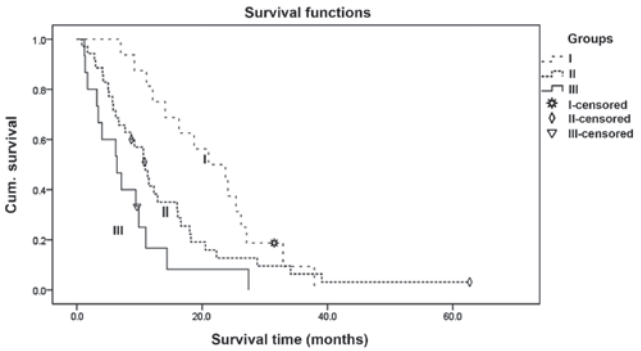

Figure 3. Survival curves of the three groups that were determined by classification tree analysis (log rank test; P=0.004). Cum., cumulative.

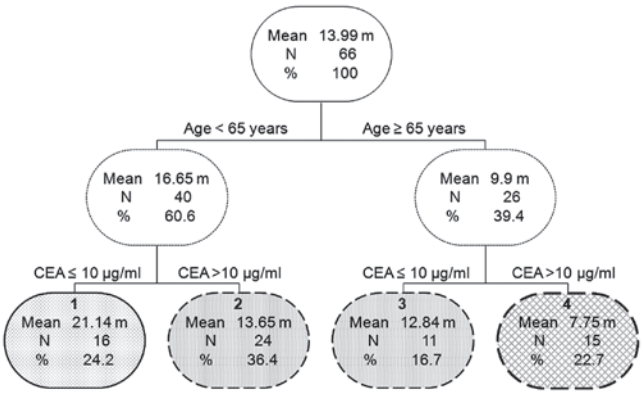

Figure 2. Classification tree model was used for EGFR mutation-positive non-small cell lung cancer patients with brain metastases following whole-brain radiation therapy and EGFR-tyrosine kinase inhibitors. EGFR, epidermal growth factor receptor; N, number of patients; CEA, carcinoembryonic antigen.

Following the application of the classification tree model, a survival tree was generated (Fig. 2), in which the first prognostic split occurred between patients aged <65 years vs. ≥65 years. Within patients aged <65 years or ≥65 years, the CEA level at the diagnosis of brain metastasis (≤10 μg/ml vs. >10 μg/ml) became a dividing factor, finally resulting in four groups. No significant difference in the survival time between groups 2 and 3 was identified (P=0.962; Fig. 2). Therefore, groups 2 and 3 were combined. Finally, the patients were divided into three groups: Group I, age <65 years and CEA ≤0 μg/ml; Group II, age <65 years and CEA >10 μg/ml or age ≥65 years and CEA ≤10 μg/ml; and Group III, age ≥65 years and CEA >10 μg/ml. The survival curves for the three groups that were determined by classification tree analysis are shown in Fig. 3 (P=0.004).

Discussion

The brain is one of the most common sites of metastasis in patients with lung cancer, and lung cancer is the most common intracranial metastatic tumor (15). The incidence of brain metastases in lung cancer is 20% at diagnosis and 40% at autopsy (16). In addition, brain metastases contribute to increased morbidity and mortality and herald a poor prognosis in patients with metastatic lung cancer (16). WBRT continues

to be an important palliative treatment option for patients with brain metastases from NSCLC. In previous studies, WBRT combined with EGFR-TKI treatment was demonstrated to be a safe and effective treatment for EGFR mutation-positive NSCLC patients with brain metastases, with a median survival time of 7.7-13.0 months (9,17,18). The median survival time in the present analysis was 10.9 months, which confirms these expectations. Predicting the survival time of patients is important, and the fact that a significant percentage of patients have a limited survival time suggests that accurate survival prediction models may assist in avoiding overtreatment (19,20).

In 1997, the Radiation Therapy Oncology Group established the prognostic scores recursive partitioning analysis (RPA) classification, which was the first prognostic scoring system for assessing the prognosis of patients with brain metastases (21-23). The detailed parameters of the model contained age, Karnofsky performance status (KPS), with or without extracranial metastases and the status of the primary tumor. Later, other established prognostic scores, including the basic score for brain metastases, systemic inflammatory response and graded prognostic assessment, were developed for the general population of patients with brain metastases.

Previous studies have demonstrated several prognostic factors in NSCLC patients with brain metastases. Gerosa *et al* (23) concluded that the performance status, age, extracranial metastases and primary tumor control caused a potential effect on survival. Zindler *et al* (24) revealed the prognostic value of performance status, age, absence of extracranial metastases, primary tumor site, gender and steroid response for OS. Rotin *et al* (25) indicated that the factors influencing survival were the number of brain metastases and KPS. Rades *et al* (26) revealed that the prior performance status, a younger age and the absence of extracranial metastases were associated with increased survival time. Therefore, in numerous published studies, age was commonly manifested as a prognostic factor. Additionally, patients having no PD in in the lung tumor was commonly mentioned as a prognostic factor.

The present Cox proportional hazards regression analysis of an EGFR mutation-positive NSCLC patient population with brain metastases confirmed that the prognostic implications of age (<65 years), CEA (≤10 μg/ml) and primary tumor control were favorable factors for survival time. Unlike previous studies, the clinical value of CEA in the prognosis of EGFR mutation-positive NSCLC patients with brain metastases was indicated to be extremely important. Recently, Fiala *et al* (27) showed that an increased level of CEA and CYFRA21-1 may be associated with a poor outcome for patients with NSCLC that are treated with erlotinib. These findings indicate that tumor biomarkers may be used for predicting the effect of therapy and the prognosis of patients.

Previous studies that investigated the prognostic factors of patients with brain metastases from NSCLC have indicated that traditional models focus on assessing the relative prognostic factors using the Cox proportional hazards regression model. A previous study indicated that, in combination with Cox proportional hazards regression, the survival tree method may aid prognostic analysis (28). To the best of our knowledge, none of the published prognostic classification models have involved EGFR mutation-positive NSCLC patients with brain metastases.

The present study aimed to use the Cox proportional hazards regression and classification tree models to analyze and explore prognostic factors in EGFR mutation-positive NSCLC patients, following WBRT and EGFR-EKI treatment. Age and CEA were the dominant prognostic factors identified in the classification tree model. Combining the aforementioned results of the Cox proportional hazard regression model, age (≥65 years) and CEA (>10 μg/ml) were considered to be adverse prognostic factors. In particular, the present analysis succeeded in splitting patients with brain metastases from EGFR mutation-positive NSCLC into three groups. The identification of prognostic groups between patients may provide prognostic information and serve as a basis of classification for future trials. In addition, the primary tumor status was indicated to be a prognostic factor in the Cox proportional hazards regression analysis. However, as the third dividing factor of the classification tree model, primary tumor control may be used a good predictor of prognosis, but may not be as reliable as age and CEA.

Regarding the present study, additional prospective studies are recommended to be performed in order to increase the accuracy of the results. Ideally, the sample size would have been larger. In conclusion, the major prognostic predictors of EGFR mutation-positive NSCLC patients with brain metastases following WBRT and EGFR-TKI were age and CEA. Age (≥65 years) and CEA (>10 μg/ml) were considered to be the adverse prognostic factors. In addition, primary tumor control may be important for predicting survival.

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