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ORIGINAL ARTICLE

Prognostic model for brain metastases from lung adenocarcinoma identified with epidermal growth factor receptor mutation status

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Abstract

Background: Several indices have been developed to predict survival of brain metastases (BM) based on prognostic factors. However, such models were designed for general brain metastases from different kinds of cancers, and prognostic factors vary between cancers and histological subtypes. Recently, studies have indicated that epidermal growth factor receptor (EGFR) mutation status may be a potential prognostic biological factor in BM from lung adenocarcinoma. Thus, we sought to define the role of EGFR mutation in prognoses and introduce a prognostic model specific for BM from lung adenocarcinoma.

Methods: Data of 256 patients with BM from lung adenocarcinoma identified with EGFR mutations were collected. Independent prognostic factors were confirmed using a Cox regression model. The new prognostic model was developed based on the results of multivariable analyses. The score of each factor was calculated by six-month survival. Prognostic groups were divided into low, medium, and high risk based on the total scores. The prediction ability of the new model was compared to the three existing models.

Results: EGFR mutation and Karnofsky performance status were independent prognostic factors and were thus integrated into the new prognostic model. The new model was superior to the three other scoring systems regarding the prediction of three, six, and 12-month survival by pairwise comparison of the area under the curve.

Conclusion: Our proposed prognostic model specific for BM from lung adenocarcinoma incorporating EGFR mutation status was valid in predicting patient survival. Further verification is warranted, with prospective testing using large sample sizes.

Introduction

Brain metastases (BM) are one of the leading causes of morbidity and mortality in patients with non-small cell lung cancer (NSCLC).[1] The risk of developing BM in lung adenocarcinoma has been reported at 45%.[2,3] Generally, prognosis of BM is poor, with median survival reported at one to two months in untreated BM patients. Whole brain radiotherapy (WBRT), the standard treatment method for BM, has improved median survival to four to six months, irrespective of histological subtype.[4] To analyze the contributions of pretreatment variables to survival with BM and to select the appropriate treatment recommendations for individual patients, several scoring systems have been developed based on independent prognostic factors. The

widely accepted prognostic systems include recursive partitioning analysis (RPA), basic score for brain metastases (BS-BM), and the graded prognostic assessment index (GPA).[5–7] However, prognostic factors vary between different cancers and their histological subtypes. For example, BM develops more commonly in NSCLC, small-cell lung cancer (SCLC), breast cancer, melanoma, and renal carcinoma, which all have different prognostic factors. Although a diagnosis-specific prognostic factors index (DS-GPA) was developed by Paul *et al.* it does not meet the needs of daily clinic practice.[8]

In recent decades, epidermal growth factor receptor (EGFR) mutations have been shown to be an important biologic marker for NSCLC. EGFR mutations are more common in adenocarcinoma than squamous cell carcinoma, identified in 40–60% of Asian patients with adenocarcinoma.[9] EGFR mutation status is significantly associated with therapeutic efficacy and progression-free survival (PFS) using EGFR-tyrosine kinase inhibitors (TKIs). Several studies have demonstrated that EGFR mutation status is an independent prognostic factor in BM from NSCLC, especially in patients with adenocarcinoma.[10–12] This may suggest that these genotypes should be integrated into the prognostic scoring classification system in lung adenocarcinoma with BMs. We identified the specific prognostic factors in lung adenocarcinoma and designed a valid prognostic model integrated with genotypes suitable for patients with BM from lung adenocarcinoma.

Methods

Data of 1063 patients with BM from lung adenocarcinoma identified with EGFR mutations between August 2010 and May 2015 from the lung cancer medical database in our institute were reviewed. All patients were identified with EGFR mutation status by DNA direct sequencing or the amplification refractory mutation system. Patients who had BM since their diagnosis of NSCLC were included. Inclusion criteria were: patients diagnosed with pathologic types of lung adenocarcinoma; BM confirmed by enforced computed tomography or magnetic resonance imaging; detailed clinical and treatment data, and date of death or follow-up examination. Two hundred and fifty-six BM patients met the selection criteria. Patient-related variables were collected, including age, gender, Karnofsky performance status (KPS), status of primary lesion (controlled vs. uncontrolled), presence of extracranial systemic metastases (present vs. absent), number of brain metastases (single vs. multiple), and status of EGFR mutations. Treatment options included WBRT with 30–40 Gy in 10–20 fractions, management with EGFR-TKIs (gefitinib or erlotinib at a daily dose of 150 mg or 250 mg), or a combination of these two treatments.

The primary endpoint of this study was the overall survival (OS) rate, defined as the date of BM diagnosis to death or the last follow-up. Differences in survival rates by patients and treatment variables were analyzed in univariable and multivariable tests. The new prognostic classification model was developed based on the results of multivariable analyses (Table 1). Following Rades *et al.*, the score of each factor was determined by six-month survival rates (Table 2). The total prognostic scores were obtained from the sum of the scores for each factor.[13] Prognostic groups were divided into high (A), medium (B), and low risk (C) groups based on the total scores. Patients were also grouped by the previous common scoring systems of RPA, GPA, and BS-BM. The prediction ability of the different models in this group of patients was compared.

The Kaplan–Meier method was used to calculate the OS rate. A log-rank test was performed to explore the impact of variables on survival rates and survival difference of groups in different prognostic models. Multivariable analysis was performed using a Cox proportional hazards model to define the independent prognostic factors. The area under the receiver operating characteristic curve was used to define predictive ability. The area under the curve (AUC) of the new prognostic model and the other three scoring systems were compared regarding the prediction of three, six, and 12 month survival. A P value of <0.05 was considered statistically significant. An AUC value of 0.5 indicated no diagnostic value of the models. The low, medium, and high values refer to 0.5–0.7, 0.7–0.9 and 0.9 or more, respectively. All analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 15 (MedCalc Software, Ostend, Belgium).

Results

Patient characteristics

Patient age ranged from 28 to 79 years old (median 57 years) and 0.138 (53.9%) patients were male. The sample included 142 (55.5%) cases of primary lung cancer with synchronous BM and 114 (44.5%) of metachronous BM. In 187 cases (73.05%), the brain was the first site of distant metastases, while 77 patients (30.1%) presented with BM as the solitary metastases site at the time of BM diagnosis. One hundred and five (41%) BM patients had single metastases, 81 (31.6%) had two to three lesions, and 70 (27.3%) had four or more lesions. At the time of BM diagnosis, 61 patients (23.8%) were confirmed with controlled primary tumors and 179 (69.9%) had extracranial metastases. KPS scores were 72 (28.1%) <70, 154 (60.2%) 70–80, and 30 (11.7%) 90–100. In the entire sample,

Table 1 Patient characteristics and univariate and multivariate analysis of survival

Variables	N (%)	Univariate	Multivariate analysis		
		P	HR	95% CI	*P*
Gender					
Male	138 (53.9%)	0.006	—	—	—
Female	118 (46.1%)	—	—	—	—
Age					
≤65	210 (82.0%)	0.524	—	—	—
>65	46 (18.0%)				
KPS					
<70	72 (27.7%)	<0.001	0.226	0.171–0.298	<0.001
70–80	154 (60.2%)	—	—	—	—
90–100	30 (12.1%)	—	—	—	—
Number of BM					
Single	105 (41.0%)	0.068	—	—	—
Two or more	151 (59.0%)	—	—	—	—
EGFR status					
Mutation	108 (42.2%)	<0.001	0.663	0.485–0.907	0.01
Wild type	148 (58.2%)	—	—	—	—
BM					
Synchronous	142 (55.5%)	0.1	—	—	—
Metachronous	114 (44.5%)	—	—	—	—
ECM					
Yes	179 (69.9%)	0.304	—	—	—
No	77 (30.1%)	—	—	—	—
Control of primary tumor					
Yes	61 (23.8%)	0.274	—	—	—
No	195 (76.2%)	—	—	—	—
Chemotherapy and supportive treatment					
Yes	139 (54.3%)	0.093	—	—	—
No	117 (45.7%)	—	—	—	—
WBRT					
Yes	127 (49.6%)	0.234	—	—	—
No	129 (50.4%)	—	—	—	—
EGFR-TKI					
Yes	85 (33.2%)	0.003	—	—	—
No	171 (66.8%)	—	—	—	—

CI, confidence interval; BM, brain metastasis; ECM, extracranial metastases; EGFR, epidermal growth factor receptor; HR, hazard ratio; KPS, Karnofsky performance status; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiation therapy.

Table 2 Survival rates six months after brain metastases and corresponding scores

	Survival at six months (%)	Score
EGFR		
Mutation	79.3	8
Wild type	60	6
KPS		
<70	26.65	2.5
70–80	81	8
90–100	100	10

EGFR, epidermal growth factor receptor; KPS, Karnofsky performance status.

108 patients (42.2%) had EGFR mutations, including 45 (17.6%) with exon 19 deletions, 51 (19.9%) with 21 point mutations (L858R, L861Q etc.), and nine (3.5%) with other rare mutations (20 or 18).The remaining three (1.2%) patients had two or more EGFR mutations. Of the 256 cases, 173 patients received treatment for BM: 127 received WBRT with 30–40 Gy in 10–20 fractions, 85 received EGFR-TKIs, and 39 received a combination of the two treatments (Table 1).

Prognostic model from lung adenocarcinoma integrated with genotypes

At the end of follow-up, 78 (30.5%) patients were still alive. The median survival of whole group was 10.13 months (95% confidence interval 8.176–12.084). Univariate and multivariate analyses of prognostic factors is shown in Table 1. The log-rank test identified gender, KPS, EGFR, and treatment with

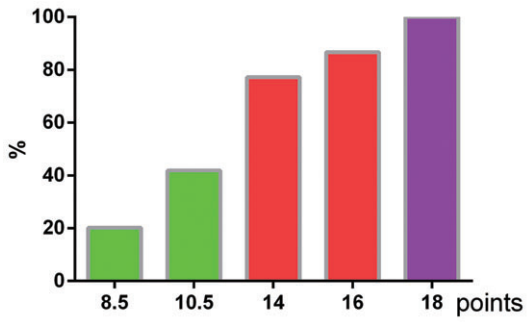

Figure 1 Six-month survival rates related to the corresponding scores.

EGFR-TKIs as significant factors associated with survival. In the Cox regression model, only KPS and EGFR mutation status were independently associated with survival. These two independent factors were integrated into the new prognostic system. The scores of each factor are shown in Table 2. The total scores ranged from 8.5 to 18 (Fig 1). The patients were divided into three groups: A, with scores of 8.5–10.5 presenting high risk; B, with 14–16 presenting medium risk; and C group had the lowest risk with scores of 16–18.

Evaluation of the predictive ability of different models

The results of Kaplan–Meier curves are presented in Figure 2. Differences in treatment methods between the models were tested using log-rank analysis; the results showed $P < 0.001$ in all groups (Fig 3). The area under the receiver operating characteristic curve was used to show the prediction results in three, six, and 12-month survival in the four prognostic scoring systems (Table 3) and pairwise comparison was carried out. The new prognostic model was superior to the three other scoring systems regarding the prediction of three, six, and 12-month survival (Table 4). The AUCs in the new prognostic model were 0.802, 0.775, and 0.752 respectively. The new prognostic model showed the most powerful predictive ability.

Discussion

The most common prognostic classification systems in BM include GPA, BSBM, and RPA,[5–7] and their efficacy has been validated in previous studies.[14–17] However, these prognostic models were designed for a heterogeneous population and prognostic factors vary between different cancers and their histological subtypes. The optimal treatment for BM patients is also different in various patient subsets. The previous prognostic indices might not meet the current needs in clinical assessment specific to BM in different cancers. In recent years, EGFR mutation has been recognized as an important biologic marker in lung adenocarcinoma for therapeutic efficacy and PFS of EGFR-TKI treatment.[17–21] We have integrated EGFR mutation status into a new prognostic model for BM from

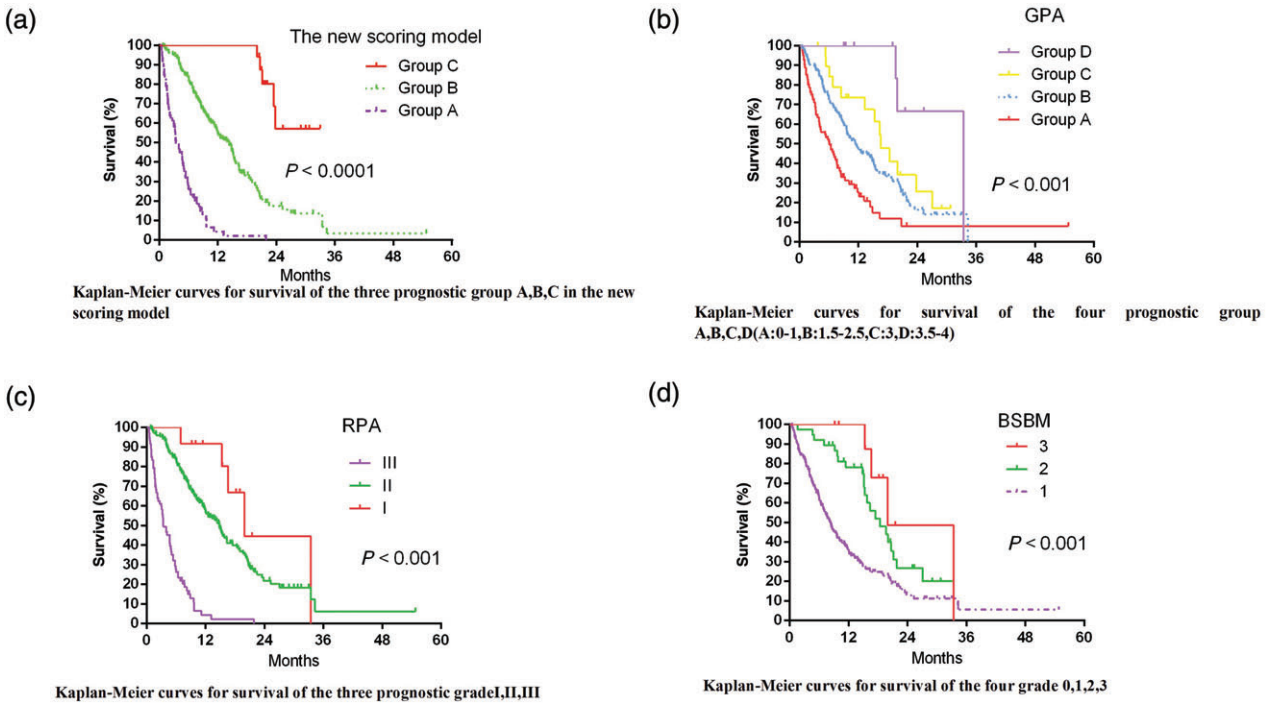

Figure 2 Kaplan–Meier curves for survival of the new and existing prognostic models: (**a,b**) graded prognostic assessment index (GPA), (**c**) recursive partitioning analysis (RPA), and (**d**) basic score for brain metastases (BSBM).

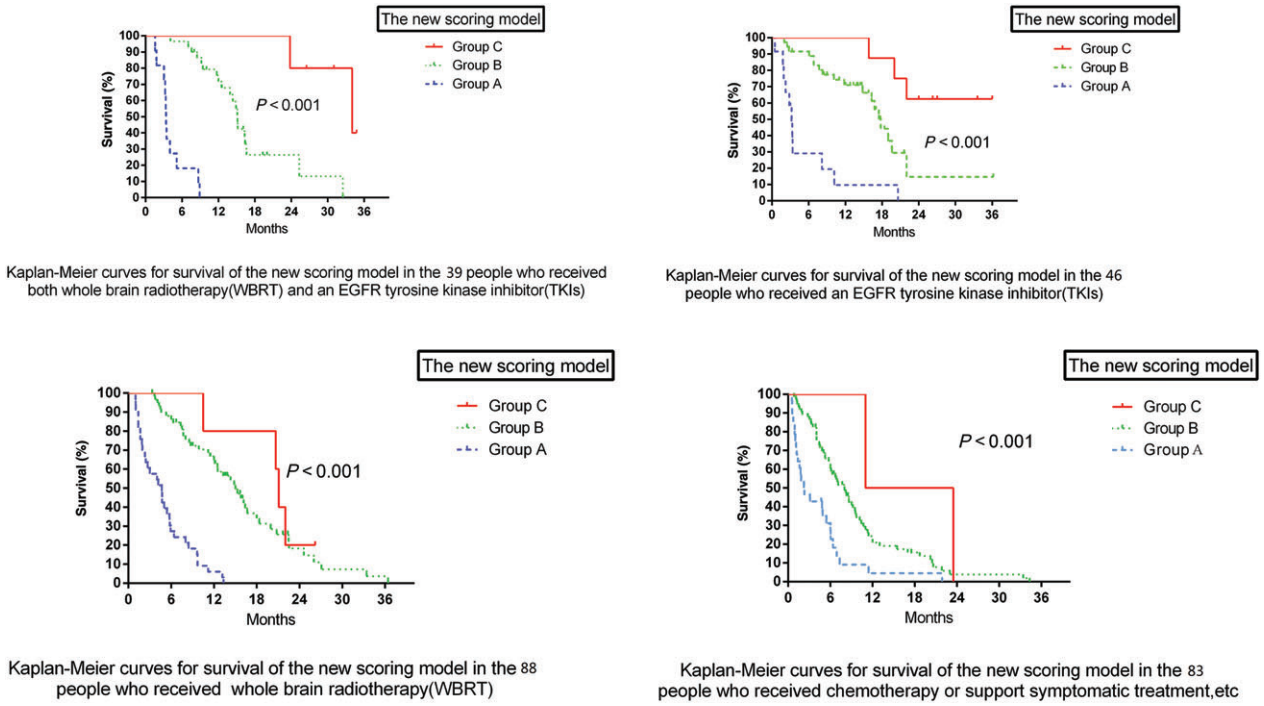

Figure 3 Kaplan–Meier curves for survival of the new prognostic model in different treatment groups. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

Table 3 Area under ROC curve of each scoring model to predict survival

	Area under ROC curve	*P*	95% CI
Three month survival			
New scoring model	0.788	<0.001	0.717–0.859
GPA	0.71	<0.001	0.634–0.785
RPA	0.785	<0.001	0.712–0.857
BSBM	0.626	0.005	0.550–0.703
Six month survival			
New scoring model	0.757	<0.001	0.698–0.815
GPA	0.652	<0.001	0.589–0.715
RPA	0.749	<0.001	0.689–0.809
BSBM	0.668	<0.001	0.607–0.729
Twelve month survival			
New scoring model	0.721	<0.001	0.663–0.778
GPA	0.651	<0.001	0.584–0.716
RPA	0.682	<0.001	0.622–0.741
BSBM	0.719	<0.001	0.657–0.780

BSBM, basic score for brain metastases; CI, confidence interval; GPA, graded prognostic assessment index; ROC, receiver operating characteristic; RPA, recursive partitioning analysis.

lung adenocarcinoma, which proved superior to the three other scoring systems regarding the prediction of three, six, and 12-month survival.

Many previous studies have confirmed that pretreatment prognostic factors in patients, such as age <65, KPS >70, number of metastases, controlled primary and no extracranial metastases are associated with good prognoses in BM from NSCLC. In this era of personalized treatment, potential oncogenes were also correlated with patient survival. Our results indicate that KPS score and EGFR mutation status are independently associated with survival, consistent with the results of previous studies by Lee *et al.*, Hsiao *et al.*, and Gow *et al.*[10–12] The traditional treatment options for BM include surgery for a single lesion in a non-eloquent region, stereotactic radiosurgery for oligometastases with less than three lesions, and WBRT for multi-metastases. Recently, with the development of molecular biology in lung cancer, it has been reported that EGFR-TKIs could achieve better responses for NSCLC BM patients with EGFR mutations. Wu *et al.* conducted a phase II study in 48 BM patients with EGFR mutations treated with EGFR-TKIs. The median OS and PFS were 18.9 and 9.67 months, respectively.[22] Jamal-Hanjani *et al.* reported that NSCLC BM patients with EGFR mutations treated with EGFR-TKIs achieved a median OS of 12.9–18.8 months.[23] Targeted therapy using EGFR-TKIs is now recognized as an effective treatment option in NSCLC BM patients.[24] To develop an appropriate prognostic model specifically for BM from lung adenocarcinoma and to assist clinicians to select optimal treatment, EGFR mutation status should be integrated into prognostic systems.

Recursive partitioning analysis was the first prognostic index for BM, developed by Gaspar *et al.* in 1997 from 1200

Table 4 Pairwise comparison of ROC curves between the new scoring model and GPA, BSBM, RPA

	GPA			BSBM			RPA		
Group	3 months	6 months	12 months	3 months	6 months	12 months	3 months	6 months	12 months
Z	2.197	3.521	2.341	3.407	2.532	0.0559	1.06	1.615	2.512
P	0.028	0.0004	0.0192	0.0007	0.0114	0.9554	0.2894	0.1062	0.012

BSBM, basic score for brain metastases; GPA, graded prognostic assessment index; ROC, receiver operating characteristic; RPA, recursive partitioning analysis.

cases receiving radiotherapy in Radiation Therapy Oncology Group randomized trials. The system divided BM patients into three groups: level 1 include patients aged <65 years older, KPS >70, with primary tumor lesion control and no extracranial metastases; level 3 included patients with KPS <70; and all other cases were considered as level 2. The reliability of this prognostic system has been demonstrated in many studies since its introduction.[5] To simplify the grouping method, Lorenzoni *et al.* proposed another prognostic index, known as the BS-BM, which assigns a value of 1 to each of three prognostic factors: KPS, primary lesion control, and the existence of extracranial metastases. The total scores of each factor are categorized into three levels. Another widely accepted prognostic index is the GPA system. However, primary tumor control cannot be defined objectively. The GPA system incorporates the number of BM but does not take into account primary tumor control, and thus has some subjectivity in clinic practice.[6] Sperduto *et al.* generated their prognostic index based on a total of 1960 cases in five Radiation Therapy Oncology Group clinical trials by eliminating this factor and adding the BM numbers into the GPA system.[6] The values ranged from 0 to 4 and are now widely adopted in clinical practice.[7] However, the ideal prognostic index for BM has not been defined, especially for patients with different primary tumors. To identify significant diagnosis-specific prognostic factors and indices, the DS-GPA was developed. The prognostic factors in the NSCLC DS-GPA are the same as in the GPA.[8] As our results showed that EGFR mutation in lung adenocarcinoma indicated prognostic value for BM, we incorporated EGFR mutation status into our prognostic model. This may be more suitable than the previous prognostic models for these specific BM patients. We also categorized our patient sample into the GPA, BSBM, and RPA systems separately. Log-rank testing showed prognostic differences between the three models. While all were proven to have predictive ability, our proposed model was superior when comparing the area under the receiver operating characteristic curve to test prediction of three, six, and 12-month survival. As our prognostic model had the highest predictive value in this cohort of patients, it may be used to assess patient progression, make treatment decisions, and compare clinical trials specific for patients with BM from lung adenocarcinoma. Its applicability warrants further validation.

As a preliminary study, there are several limitations. Firstly, because of the retrospective nature, bias may have been introduced in the patient sample. Female nonsmokers have the highest rates of EGFR mutation.[25,26] As EGFR mutation status is easier to detect in these patients, this may have reduced the reproductivity of our model to some extent. Secondly, we could not validate our proposed model because of the relatively small sample size. All of the patients in this study were from Chinese populations, and the rate of EGFR mutation in lung adenocarcinoma is different between ethnic groups. It has been reported that EGFR mutation rates in Asian patients are higher than in Westerners, at rates of 50% and 20%, respectively.[27,28] As such, our prognostic model may be more suitable to Asian patients. Finally, we used two kinds of test methods that might have different positive detectable rates of EGFR mutations. This would underestimate the scores in a small group of patients with false negative testing results, which should be addressed in future prospective research.

In summary, this retrospective study of a cohort of patients with BM from lung adenocarcinoma identified with EGFR mutations has confirmed that performance status and EGFR mutations were significant prognostic factors. Although the existing three prognostic systems are valid for BM from lung adenocarcinoma, our proposed prognostic model is more powerful in terms of predictive ability. It is specific for BM from lung adenocarcinoma and is the first to incorporate EGFR mutation status. Verification of our model via prospective testing with large sample sizes is warranted.

Disclosure

No authors report any conflict of interest.

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