Role of Recursive Partitioning Analysis and Graded Prognostic Assessment on Identifying Non-Small Cell Lung Cancer Patients with Brain Metastases Who May Benefit from Postradiation Systemic Therapy

Shuai Liu[1], Peng Chen[2], Yan-Wei Liu[1], Xue-Nan Gu[2], Xiao-Guang Qiu[1], Bo Li[1]

[1]Department of Radiation Oncology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China
[2]Department of Thoracic Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China

Abstract

Background: The role of postradiation systemic therapy in non-small cell lung cancer (NSCLC) patients with brain metastasis (BM) was controversial. Thus, we explored the role of Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) and graded prognostic assessment (GPA) in identifying population who may benefit from postradiation systemic therapy.

Methods: The clinical data of NSCLC patients with documented BM from August 2007 to April 2015 of two hospitals were studied retrospectively. Cox regression was used for multivariate analysis. Survival of patients with or without postradiation systemic therapy was compared in subgroups stratified according to RTOG-RPA or GPA.

Results: Of 216 included patients, 67.1% received stereotactic radiosurgery (SRS), 24.1% received whole-brain radiation therapy (WBRT), and 8.8% received both. After radiotherapy, systemic therapy was administered in 58.3% of patients. Multivariate analysis found that postradiation systemic therapy (yes vs. no) (hazard ratio [HR] = 0.361, 95% confidence interval [CI] = 0.202–0.648, P = 0.001), radiation technique (SRS vs. WBRT) (HR = 0.462, 95% CI = 0.238–0.849, P = 0.022), extracranial metastasis (yes vs. no) (HR = 3.970, 95% CI = 1.757–8.970, P = 0.001), and Karnofsky performance status (<70 vs. ≥70) (HR = 5.338, 95% CI = 2.829–10.072, P < 0.001) were independent factors for survival. Further analysis found that subsequent tyrosine kinase inhibitor (TKI) therapy could significantly reduce the risk of mortality of patients in RTOG-RPA Class II (HR = 0.411, 95% CI = 0.183–0.923, P = 0.031) or with a GPA score of 1.5–2.5 (HR = 0.420, 95% CI = 0.182–0.968, P = 0.042). However, none of the subgroups stratified according to RTOG-RPA or GPA benefited from the additional conventional chemotherapy.

Conclusion: RTOG-RPA and GPA may be useful to identify beneficial populations in NSCLC patients with BM if TKIs were chosen as postradiation systemic therapy.

Key words: Chemotherapy; Non-Small Cell Lung Cancer; Recursive Partitioning Analysis; Stereotactic Radiosurgery; Tyrosine Kinase Inhibitors; Whole-Brain Radiation Therapy

INTRODUCTION

Brain metastasis (BM) is a common sequela of patients with malignant disease. The results from most studies have indicated that lung cancer is the most common primary cancer, followed by breast cancer and melanoma.[1,2] Up to 40% of patients with non-small cell lung cancer (NSCLC) will develop BM during the course of the disease.[3] In addition, this number grows to nearly 50% in the studies of NSCLC postmortem. Historically, the treatment options for patients with brain metastases include surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or some combination. However, most patients with BM

Address for correspondence: Prof. Bo Li,
Department of Radiation Oncology, Beijing Tiantan Hospital,
Capital Medical University, Beijing 100050, China
E-Mail: linghberg@163.com, linghberg@hotmail.com

die from systemic disease other than intracranial failure, especially in those already with extracranial lesions at the time of BM. Even for those without extracranial metastasis, considering that BM is a type of hematogenous metastasis, patients are at risk of distant dissemination when BM occurs. As a result, many pilot studies, mostly conducted with NSCLC patients, have explored the efficacy of systemic therapy after the completion of radiotherapy. The results from retrospective studies support the application of subsequent systemic therapy because it was found to cause a survival benefit in BM patients.[4-6] Unfortunately, this result failed to be validated by most prospective studies.[7-10]

The reasons for the negative results might be complicated. However, we assumed that the efficacy of systemic therapy is probably confined to certain populations. Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) and graded prognostic assessment (GPA) are both important indexes that have been used for the prognosis evaluation of patients with BM.[11,12] Based on age, Karnofsky performance status (KPS), the number of intracranial lesions, and the presence of extracranial metastasis, BM patients were classified into three or four prognostic groups. It was observed that variables recruited by the indexes were also considered by physicians when systemic therapy was considered. Hence, we assumed that RTOG-RPA and GPA might also be useful to identify populations that could benefit from subsequent systemic therapy after the completion of radiation therapy. To further clarify the hypothesis, we conducted this retrospective study in patients with NSCLC.

METHODS

Ethical approval
The study protocol was reviewed and approved by the Institutional Review Boards and Ethics Committees of the Beijing Tiantan Hospital affiliated with Capital Medical University and the Tianjin Medical University Cancer Institute and Hospital. All patients provided informed consent before their inclusion in the study according to the *Declaration of Helsinki*.

Inclusion criteria
Patients who were diagnosed with NSCLC and had documented BMs were selected from the database of two hospitals. Other inclusion criteria were as follows: (1) the primary disease was confirmed by pathology; (2) no sign of secondary malignancy was documented during the follow-up; (3) BM was documented by magnetic resonance imaging and/or computed tomography with contrast; (4) extracranial disease was evaluated at the time of BM; and (5) the medical records of post-BM therapy were complete.

Postbrain metastasis treatment and follow-up
There was a consultation committee that included experts from two hospitals to coordinate the treatment strategies. The SRS dose was prescribed in accordance with the tumor margin. Metastases with a maximum diameter of up to 2 cm were treated with doses of 22–25 Gy in 1–5 fractions, and

those larger than 2 cm were treated with doses of 18–20 Gy in 1–5 fractions. The WBRT dosage schedule was 30 Gy in 10 fractions over 2–2.5 weeks. After the completion of radiotherapy, 4–6 cycles of systemic therapy were recommended routinely by physicians within a month when patients were deemed qualified (KPS was reevaluated before systemic therapy). If tyrosine kinase inhibitors (TKIs) were considered, they would be continued to disease progression or intolerance. The baseline assessments were repeated at the completion of planned therapy and then every 3 months for the first 2 years and every 6 months for the next 3 years.

Statistical analysis
IBM SPSS Statistics 19.0 software (SPSS Inc. and IBM Company, Armonk, New York, USA) was used for data analysis. Cox regression was used for multivariate analysis to identify independent factors for post-BM survival (PBMS). The proportional hazards of factors recruited in the Cox regression model were checked by log-rank test. PBMS was determined from the date of documented BM to the date of death or last follow-up visit. Further analyses were conducted in subgroups stratified according to clinical factors, including RTOG-RPA and GPA, to compare the risk of mortality between radiotherapy followed by systemic therapy and radiotherapy alone. A $P < 0.05$ was used as the criterion of statistical significance, and all statistical tests were two sided.

RESULTS

Patient characteristics
In total, 216 NSCLC patients with documented BM from August 2007 to April 2015 were included in the study. The median age at the time of BM was 57 years (range: 25–84 years). Among these patients, 81.9% (177/216) had adenocarcinoma, 14.4% (31/216) had squamous cell carcinoma, and 3.7% (8/216) had other histology. In terms of radiotherapy, 67.1% of patients (145/216) received SRS, 24.1% of patients (52/216) received WBRT, and 8.8% of patients (19/216) received both. After the completion of radiotherapy, systemic therapy was carried out in 58.3% of patients (126/216). The details of the patient characteristics of the different treatment groups are summarized in Table 1.

Multivariate analysis of variables associated with postbrain metastasis survival
The median time of follow-up after BM was 7 months (range: 1–74 months). Multivariate analysis found that clinical variables such as the presence of extracranial metastasis and KPS were independent factors for PBMS. Those who had extracranial metastasis (hazard ratio [HR] = 3.970, 95% confidence interval [CI] = 1.757–8.970, $P = 0.001$) or lower KPS (<70) ($HR = 5.338$, 95% $CI = 2.829–10.072$, $P < 0.001$) had a significantly higher risk of death. There was a tendency that older patients with BM had a higher risk of mortality, but the difference was not significant ($HR = 1.022$, 95% $CI = 0.997–1.047$, $P = 0.091$). The number of intracranial lesions was not found to be an independent factor when analyzed between those with 1 lesion and 2–3 lesions

Table 1: Comparison of the patient characteristics between radiotherapy plus systemic therapy, radiotherapy plus chemotherapy, radiotherapy plus TKIs, and radiotherapy alone

Variables	Radiotherapy (n = 90)	Radiotherapy + systemic therapy (n = 126)	P	Radiotherapy + chemotherapy (n = 61)	P†	Radiotherapy + TKIs (n = 65)	P†
Age, n (%)							
≤60 years	53 (58.9)	80 (63.5)	0.52	42 (68.8)	0.14	38 (58.5)	0.93
>60 years	37 (41.1)	46 (36.5)		19 (31.2)		27 (41.5)	
Gender, n (%)							
Male	54 (60.0)	65 (51.6)	0.25	40 (65.6)	0.38	25 (38.5)	<0.05
Female	36 (40.0)	61 (48.4)		21 (34.4)		40 (61.5)	
Smoking status, n (%)							
Current smoker	34 (37.8)	44 (34.9)	0.65	32 (52.5)	0.04	12 (18.5)	<0.05
Never smoker	56 (62.2)	82 (65.1)		29 (47.5)		53 (81.5)	
KPS, n (%)							
<70	18 (20.0)	18 (14.3)	0.25	9 (14.8)	0.35	9 (13.8)	0.25
≥70	72 (80.0)	108 (85.7)		52 (85.2)		56 (86.2)	
Number of BM, n (%)							
1	49 (54.4)	60 (47.6)	0.60	32 (52.5)	0.94	28 (43.1)	0.14
2–3	15 (16.7)	28 (22.2)		10 (16.4)		18 (27.7)	
>3	26 (28.9)	38 (30.2)		19 (31.1)		19 (29.2)	
Extracranial metastasis, n (%)							
Yes	65 (72.2)	102 (80.9)	0.13	50 (82.0)	0.09	52 (80.0)	0.18
No	25 (27.8)	24 (19.1)		11 (18.0)		13 (20.0)	
RPA, n (%)							
I	16 (17.8)	13 (10.3)	0.09	6 (9.8)	0.07	7 (10.8)	0.13
II	53 (58.9)	92 (73.0)		45 (73.8)		47 (72.3)	
III	21 (23.3)	21 (16.7)		10 (16.4)		11 (16.9)	
GPA, n (%)							
0–1	26 (28.9)	36 (28.6)	0.86	16 (26.2)	0.76	20 (30.8)	0.70
1.5–2.5	48 (53.3)	70 (55.5)		33 (54.1)		37 (56.9)	
3	8 (8.9)	13 (10.3)		8 (13.1)		5 (7.7)	
3.5–4	8 (8.9)	7 (5.6)		4 (6.6)		3 (4.6)	
Local therapy, n (%)							
SRS	66 (73.3)	79 (62.7)	0.26	39 (63.9)	0.31	40 (61.5)	0.21
WBRT	17 (18.9)	35 (27.8)		17 (27.9)		18 (27.7)	
SRS + WBRT	7 (7.8)	12 (9.5)		5 (8.2)		7 (10.8)	
Histology, n (%)							
Adenocarcinoma	72 (80.0)	105 (83.3)	0.28	46 (75.4)	0.46	59 (90.8)	0.01
SCC	16 (17.8)	15 (11.9)		12 (19.7)		3 (4.6)	
Other	2 (2.2)	6 (4.8)		3 (4.9)		3 (4.6)	
EGFR mutation*, n (%)							
Wild-type	10 (45.5)	34 (40.5)	0.47	24 (82.8)	<0.05	10 (30.3)	0.02
Mutation	12 (54.5)	28 (59.5)		5 (17.2)		23 (69.7)	

*EGFR mutation status was available in 84 patients; †Compared with patients receiving radiotherapy only. RPA: Recursive partitioning analysis; GPA: Graded prognostic assessment; BM: Brain metastasis; WBRT: Whole-brain radiation therapy; SRS: Stereotactic radiosurgery; SCC: Squamous cell carcinoma; EGFR: Epidermal growth factor receptor; TKIs: Tyrosine kinase inhibitors; KPS: Karnofsky performance status.

or between those with 1 lesion and more than 3 lesions. Other variables, including gender, histology, and smoking status, were not found to have an association with PBMS. Although age and the number of intracranial lesions were not found to be independent factors of PBMS, RTOG-RPA and GPA were still valuable for prognosis assessment in patients with BM. In our cohort, the median PBMS rates for RTOG-RPA Classes I–III were not reached, 27 months and 5 months, respectively ($P < 0.001$). The median survival times according to the GPA score were as follows: GPA 0–1: 12 months, GPA 1.5–2.5: 24 months, GPA 3: 27 months, and GPA: 3.5–4.0, not reached ($P < 0.001$).

In terms of treatment, cranial surgery was not found to have an association with PBMS, while radiation technique was an independent factor of PBMS. In terms of radiation technique, those who received SRS had a significantly lower risk of death than those who received WBRT ($HR = 0.462$, 95% $CI = 0.238–0.849$, $P = 0.022$). Otherwise, the risk of death was comparable between those who received WBRT and those who received WBRT plus SRS. In terms of

treatment strategy, those who received both radiotherapy and systemic therapy had a significantly lower risk of death than those who received radiotherapy alone (*HR* = 0.361, 95% *CI* = 0.202–0.648, *P* = 0.001), whatever systemic therapy was TKI therapy (*HR* = 0.389, 95% *CI* = 0.190–0.797, *P* = 0.010) or conventional chemotherapy [*HR* = 0.350, 95% *CI* = 0.169–0.728, *P* = 0.005; Table 2].

Role of systemic therapy in the patient subgroups

To further explore the role of additional systemic therapy, additional analyses were conducted in subgroups stratified according to clinical variables. It was found that, if TKIs were chosen as postradiation systemic therapy, the risk of death could be significantly reduced in patients who were female (*HR* = 0.328, 95% *CI* = 0.125–0.864, *P* = 0.024), those younger than 60 years (*HR* = 0.259, 95% *CI* = 0.102–0.655, *P* = 0.004), those who were never smokers (*HR* = 0.313, 95% *CI* = 0.150–0.656, *P* = 0.002), those with adenocarcinoma (*HR* = 0.478, 95% *CI* = 0.248–0.922, *P* = 0.028), those with extracranial lesions (*HR* = 0.340, 95% *CI* = 0.178–0.649, *P* = 0.001), those with better KPS (≥70) (*HR* = 0.440, 95% *CI* = 0.207–0.939, *P* = 0.034), those with more than 3 intracranial lesions (*HR* = 0.205, 95% *CI* = 0.058–0.727, *P* = 0.014), and those with epidermal growth factor receptor (EGFR) mutations [*HR* = 0.084, 95% *CI* = 0.013–0.543, *P* = 0.009; Figure 1]. However, if conventional chemotherapy was applied after radiotherapy,

only those who were younger than 60 years (*HR* = 0.378, 95% *CI* = 0.158–0.909, *P* = 0.030) and those with extracranial lesions (*HR* = 0.464, 95% *CI* = 0.243–0.885, *P* = 0.020) obtained a significant reduction in risk of death [Figure 2].

If patients were stratified according to RTOG-RPA and GPA, it was shown that TKIs could significantly reduce the risk of death in patients classified as RTOG-RPA Class II (*HR* = 0.411, 95% *CI* = 0.183–0.923, *P* = 0.031) or with a GPA score of 1.5–2.5 (*HR* = 0.420, 95% *CI* = 0.182–0.968, *P* = 0.042). However, none of the subgroups stratified according to RTOG-RPA or GPA was found to benefit from additional conventional chemotherapy.

DISCUSSION

In this study, we explored the role of RTOG-RPA and GPA in identifying patients with BM who may benefit from systemic therapy after the completion of radiotherapy. As a result, we found that patients classified as RTOG-RPA Class II or with a GPA score of 1.5–2.5 achieved a significant reduction in the risk of death when TKIs were applied as postradiation systemic therapy. However, none of the subgroups of RTOG-RPA or GPA was found to benefit from conventional chemotherapy after the completion of radiotherapy.

Studies from RTOG found that variables such as age, extracranial metastasis, KPS, and the number of intracranial lesions were independent factors of survival in patients with BM.[1,11-13] In addition, the prognostic significance of these variables was validated in the NSCLC setting.[1] KPS is an important variable that is considered by physicians when anticancer therapy is indicated. Numerous Phase III trials have confirmed the superiority of first-line systemic therapy over best supportive care for patients with metastatic NSCLC who have a good performance status (PS 0–1). In addition, a Cochrane review demonstrated a survival benefit. Considering that almost half of the patients in our cohort developed BM heterogeneously, second-line or beyond systemic therapy was applied. At least in the second-line setting, there is also evidence that survival benefit was confined in those with good PS. Hence, in patients with PS 0–1, systemic therapy has been the strong recommendation of American Society of Clinical Oncology clinical practice of metastatic NSCLC.[14] In patients with PS 2, combination or single-agent chemotherapy was also recommended. However, the strength was weak. Data from our study showed that, although both TKIs and chemotherapy could significantly reduce the risk of mortality of BM patients, there was a difference between groups stratified according to KPS status. In patients who received TKIs as postradiation therapy, only those BM patients with better PS (KPS ≥70) achieved a significant reduction in the risk of death from subsequent systemic therapy. Even in patients receiving conventional chemotherapy, the survival benefit was marginal in those with a better PS. However, in patients with a poorer PS (KPS <70), additional systemic therapy provides no survival benefit.

Table 2: Multivariate analysis of post-BM survival in NSCLC patients

Variables	HR	95% CI	P
Gender			
Female versus male	1.263	0.657–2.429	0.484
Histology			
SCC versus adenocarcinoma	1.560	0.756–3.220	0.229
Others versus adenocarcinoma	1.700	0.489–5.909	0.404
Age at the time of BM	1.022	0.997–1.047	0.091
KPS			
<70 versus ≥70	5.338	2.829–10.072	<0.001
Number of BMs			
2–3 versus 1	0.940	0.460–1.924	0.866
>3 versus 1	1.278	0.651–2.510	0.476
Extracranial metastasis			
Yes versus no	3.970	1.757–8.970	0.001
Smoking status			
Current smokers versus never smokers	1.265	0.659–2.429	0.480
Cranial surgery			
Yes versus no	0.507	0.101–2.546	0.409
Radiotherapy			
SRS versus WBRT	0.462	0.238–0.894	0.022
WBRT + SRS versus WBRT	1.173	0.520–2.647	0.701
Following systemic therapy			
Yes versus no	0.361	0.202–0.648	0.001

HR: Hazard ratio; *CI*: Confidence interval; SCC: Squamous cell carcinoma; BM: Brain metastasis; WBRT: Whole-brain radiation therapy; SRS: Stereotactic radiosurgery; NSCLC: Non-small cell lung cancer; KPS: Karnofsky performance status.
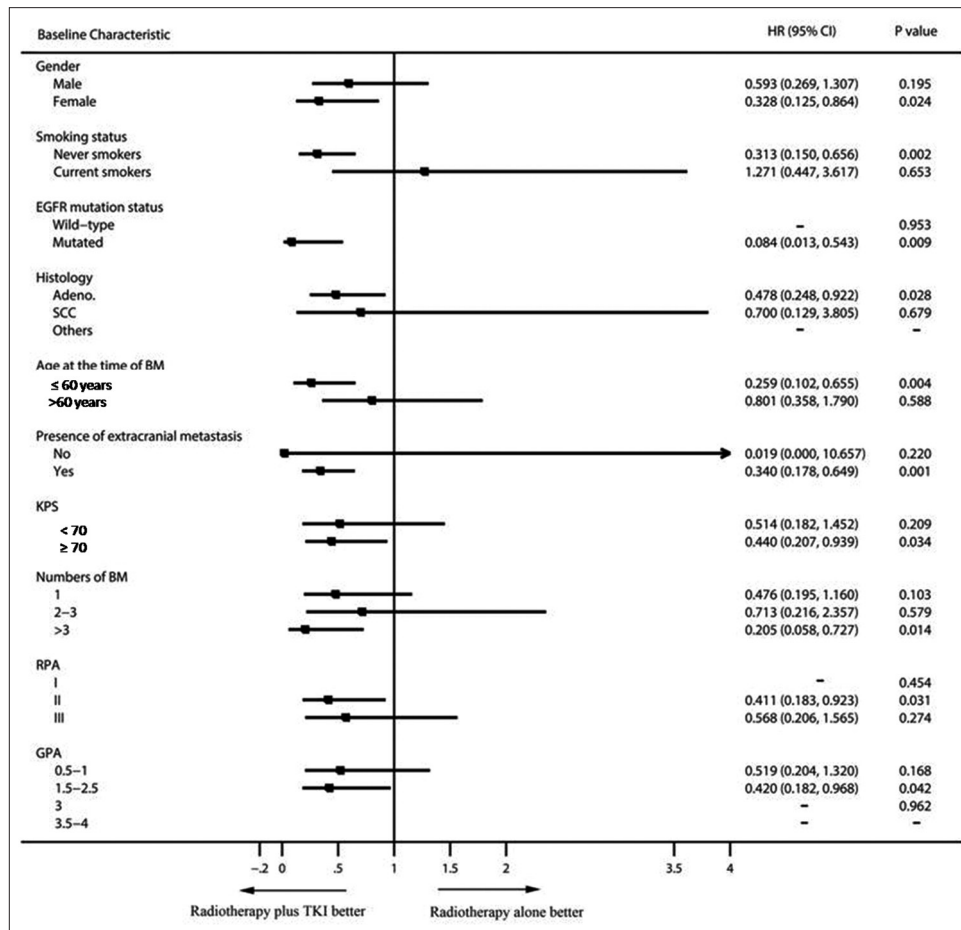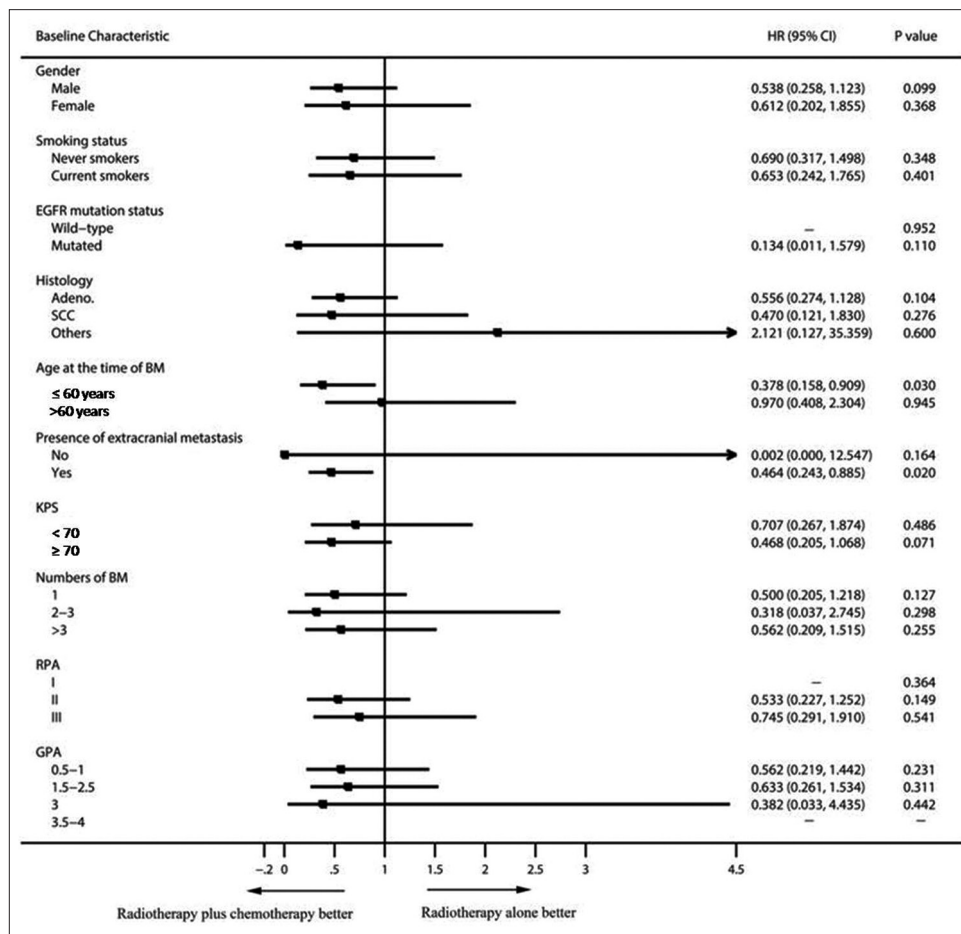
Figure 1: Subgroup comparison of postbrain metastasis survival between radiotherapy plus tyrosine kinase inhibitor and radiotherapy alone. EGFR: Epidermal growth factor; Adeno: Adenocarcinoma; SCC: Squamous cell carcinoma; BM: Brain metastasis; RTOG-RPA: Radiation Therapy Oncology Group recursive partitioning analysis; GPA: Graded prognostic assessment; TKI: Tyrosine kinase inhibitor.

Thus, we believed that KPS was an important indicator in the clinical decision-making of systemic therapy in patients with BM.

The presence of extracranial lesions was another independent prognostic factor of survival in patients with BM. Furthermore, we found that, in BM patients with extracranial lesions, both subsequent conventional chemotherapy and TKI therapy could significantly reduce the risk of mortality. However, in patients without extracranial lesions, the risk of mortality was unchanged with subsequent systemic therapy. In clinical practice, the presence of extracranial lesions seems to be the strongest indicator for systemic therapy in patients with BM after the completion of radiotherapy. However, there is still a lack of evidence from randomized studies. Several Phase II studies have explored the efficacy of systemic therapy when combined with radiotherapy in patients with BM. The patients included in these studies had heterogeneous histology, with lung cancer being the most common. Temozolomide and TKIs were frequently used in combination with radiotherapy. Although the response rate and local control rate were improved, OS was not prolonged significantly.[7,9,10] The reasons for the negative results might be complicated. However, we found that the proportion of

patients with extracranial lesions ranged from 39% to 56% in these studies. Combined with our findings, it was deduced that those without extracranial lesions might compromise the survival benefit of combination therapy because they did not obtain a survival benefit from additional systemic therapy. A Phase II study with positive findings that compared the efficacy of WBRT alone or WBRT plus erlotinib in BM patients with lung adenocarcinoma was conducted by Zhuang et al.[15] In that study, 87% of the included patients had extracranial metastasis. As a result, patients treated with combination therapy had a significantly longer overall survival than those treated with radiotherapy alone. In addition, multivariate analysis found that erlotinib was an independent factor of OS. Based on these results, there is a rationale that systemic therapy should be administered in BM patients with extracranial metastasis after the completion of radiotherapy. However, the optimal systemic therapy regimen still needs further exploration. Furthermore, in patients without extracranial metastasis, it seems that postradiation systemic therapy is unnecessary.

Age and the number of intracranial lesions were two other independent factors that were identified by RTOG studies. Unfortunately, probably due to the smaller sample number,

Figure 2: Subgroup comparison of postbrain metastasis survival between radiotherapy plus conventional chemotherapy and radiotherapy alone. EGFR: Epidermal growth factor; Adeno: Adenocarcinoma; SCC: Squamous cell carcinoma; BM: Brain metastasis; RTOG-RPA: Radiation Therapy Oncology Group recursive partitioning analysis; GPA: Graded prognostic assessment.

they were not verified in our cohort. In NSCLC patients with Stage IV disease (without BM), multiple trials did not identify age as an independent predictor of survival and pretreatment risk factor for either the tolerance or response to treatment with cytotoxic therapy.[16,17] The guideline for chemotherapy for Stage IV NSCLC strongly supports treatment based on the functional status and comorbidity. In our cohort, bivariate analysis found that age has a negative correlation with KPS ($P = 0.019$, correlation coefficient = 0.160). In addition, the number of intracranial lesions was positively correlated with the presence of extracranial lesions ($P < 0.001$, correlation coefficient = 0.268). Hence, although we found that only select patients (those younger than 60 years or with >3 intracranial lesions) could benefit from subsequent systemic therapy, the results should be considered carefully.

In addition to the variables mentioned above, we found that TKIs could significantly reduce the risk of mortality in those who were female, were nonsmokers, or had adenocarcinoma histology or EGFR mutations. Former studies have been proven that treatment with TKIs is most effective in female patients, those who have never smoked, those with adenocarcinoma histology, and those of Asian origin. In these populations, TKIs were associated with favorable

efficacy.[18,19] The results from the IPASS study also found that TKI therapy is superior to conventional chemotherapy as an initial treatment for pulmonary adenocarcinoma among nonsmokers or former light smokers in eastern populations.[20] Currently, it is well known that the dramatic efficacy of TKIs shown in these populations is due to the higher prevalence of EGFR mutations, even in patients with BM.[21-23] Furthermore, EGFR was proved to be another independent factor instead of original four factors used in the GPA index. Adenocarcinoma patients with EGFR mutation had better prognosis than those with wild-type EGFR.[24] Besides, in patients with EGFR mutation, survival was improved only for TKIs-naïve patients compared with those who previously received and failed TKIs.[25] Combined with our findings, in BM patients with known EGFR mutations, TKI therapy was one of the main options. However, if the EGFR mutation status was not available, variables such as gender, smoking history, and histology were also useful indicators for the decision-making of TKI treatment.

RTOG-RPA and GPA are both valuable prognostic indexes for patients with BM. In addition, factors recruited by the index are considered when systemic therapy is indicated. Consequently, it might be more appropriate to weigh the

application of systemic therapy based on all these factors at the same time. We found that, if BM patients were grouped by RTOG-RPA, only those with RTOG-RPA Class II could benefit from subsequent systemic therapy. However, none of the subgroups of GPA achieved a significant reduction of mortality from subsequent systemic therapy. However, if stratification was conducted according to systemic agent, TKIs were found to significantly reduce the mortality of patients in RTOG-RPA Class II or with a GPA score of 1.5–2.5. However, conventional chemotherapy could not improve the prognosis of any subgroup of RTOG-RPA or GPA. Another retrospective study conducted in 101 breast cancer patients performed a similar analysis.[5] They found that systemic therapy could bring a survival benefit in RTOG-RPA Class II/ III patients. In terms of GPA, patients were grouped into breast-GPA 0–2.0 and breast-GPA 2.5–4.0. In addition, the survival benefit brought by combination therapy reached the marginal significance in breast-GPA 0–2.0 ($P = 0.051$). In contrast to that of NSCLC patients with BM, only KPS was an independent factor of survival in BM patients with breast cancer. Thus, the role of RTOG-RPA and GPA in identifying patients who would benefit from systemic therapy may be different among malignancies. At least in BM patients with NSCLC, those with a medium risk according to RTOG-RPA or GPA could obtain a survival benefit from TKI therapy. However, in NSCLC patients receiving conventional chemotherapy, RTOG-RPA or GPA seems to be important to identify beneficial populations.

It should be noticed that the sample of patients other than RTOG-RPA Class II or GPA 1.5–2.5 was relatively small, which may contribute to the negative findings. In addition, the RTOG-RPA and GPA assessment systems were developed from BM patients receiving radiation therapy. They might not be the most proper algorithms for predicting the prognosis of patients receiving systemic therapy, especially when conventional chemotherapy is applied. Furthermore, a recent randomized study indicated that WBRT provided little clinical benefit compared with optimal supportive care in NSCLC patients with BM, indicating that WBRT might be omitted from future clinical practice.[26] Thus, better prognostic factors of systemic therapy should be explored in those receiving systemic therapy alone or, perhaps, systemic therapy plus SRS.

In this study, we explored the role of variables presented at the time of BM in identifying NSCLC patients with BM who may benefit from subsequent systemic therapy after the completion of radiotherapy. As a result, we found that the benefit of subsequent systemic therapy was confined to patients with a better PS or with extracranial metastasis. If patients were stratified according to RTOG-RPA or GPA, only those in RTOG-RPA Class II or with a GPA score of 1.5–2.5 obtained a benefit from TKI systemic therapy. These findings are useful for tailoring future studies concerning systemic therapy in NSCLC patients with BM.

Financial support and sponsorship

Conflicts of interest
There are no conflicts of interest.

References

1. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, *et al.* Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: A multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010;77:655-61. doi: 10.1016/j.ijrobp.2009.08.025.
2. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep 2012;14:48-54. doi: 10.1007/s11912-011-0203-y.
3. Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E, *et al.* Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii56-64. doi: 10.1093/annonc/mds226.
4. Lin CH, Hsu KH, Chang SN, Tsou HK, Sheehan J, Sheu ML, *et al.* Increased survival with the combination of stereotactic radiosurgery and gefitinib for non-small cell lung cancer brain metastasis patients: A nationwide study in Taiwan. Radiat Oncol 2015;10:127. doi: 10.1186/s13014-015-0431-7.
5. Zhang Q, Chen J, Yu X, Ma J, Cai G, Yang Z, *et al.* Systemic treatment after whole-brain radiotherapy may improve survival in RPA class II/III breast cancer patients with brain metastasis. J Neurooncol 2013;114:181-9. doi: 10.1007/s11060-013-1169-4.
6. Li B, Dai ZX, Chen YD, Liu YW, Liu S, Gu XN, *et al.* Systemic therapy after radiotherapy significantly reduces the risk of mortality of patients with 1-3 brain metastases: A Retrospective study of 250 patients. Chin Med J 2017;130:2916-21. doi: 10.4103/0366-6999.220296.
7. Chua D, Krzakowski M, Chouaid C, Pallotta MG, Martinez JI, Gottfried M, *et al.* Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small-cell lung cancer: A randomized, open-label phase II study. Clin Lung Cancer 2010;11:176-81. doi: 10.3816/CLC.2010.n.022.
8. Lee SM, Lewanski CR, Counsell N, Ottensmeier C, Bates A, Patel N, *et al.* Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. J Natl Cancer Inst 2014;106. pii: dju151. doi: 10.1093/jnci/dju151.
9. Ge XH, Lin Q, Ren XC, Liu YE, Chen XJ, Wang DY, *et al.* Phase II clinical trial of whole-brain irradiation plus three-dimensional conformal boost with concurrent topotecan for brain metastases from lung cancer. Radiat Oncol 2013;8:238. doi: 10.1186/1748-717X-8-238.
10. Gamboa-Vignolle C, Ferrari-Carballo T, Arrieta Ó, Mohar A. Whole-brain irradiation with concomitant daily fixed-dose temozolomide for brain metastases treatment: A randomised phase II trial. Radiother Oncol 2012;102:187-91. doi: 10.1016/j.radonc.2011.12.004.
11. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, *et al.* Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745-51. doi: 10.1016/S0360-3016(96)00619-0.
12. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: An analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 2008;70:510-4. doi: 10.1016/j.ijrobp.2007.06.074.
13. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 2000;47:1001-6. doi: 10.1016/S0360-3016(00)00547-2.
14. Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr., Brahmer JR, *et al.* Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol 2015;33:3488-515. doi: 10.1200/jco.2015.62.1342.
15. Zhuang H, Yuan Z, Wang J, Zhao L, Pang Q, Wang P, *et al.* Phase II study of whole brain radiotherapy with or without erlotinib in patients with multiple brain metastases from lung adenocarcinoma. Drug Des Devel Ther 2013;7:1179-86. doi: 10.2147/DDDT.S53011.
16. Langer CJ, Manola J, Bernardo P, Kugler JW, Bonomi P, Cella D,

et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: Implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 2002;94:173-81. doi: 10.1093/jnci/94.3.173.

17. Bunn PA Jr., Lilenbaum R. Chemotherapy for elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2003;95:341-3. doi: 10.1093/jnci/95.5.341.

18. Mok TS, Kim SW, Wu YL, Nakagawa K, Yang JJ, Ahn MJ, *et al.* Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): Overall survival and biomarker analyses. J Clin Oncol 2017;35:4027-34. doi: 10.1200/jco.2017.73.9250.

19. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, *et al.* Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:1454-66. doi: 10.1016/s1470-2045(17)30608-3.

20. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57. doi: 10.1056/NEJMoa0810699.

21. Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, *et al.* Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer 2012;77:556-60. doi: 10.1016/j.lungcan.2012.05.092.

22. Li B, Sun SZ, Yang M, Shi JL, Xu W, Wang XF, *et al.* The correlation between EGFR mutation status and the risk of brain metastasis in patients with lung adenocarcinoma. J Neurooncol 2015;124:79-85. doi: 10.1007/s11060-015-1776-3.

23. Shin DY, Na II, Kim CH, Park S, Baek H, Yang SH, *et al.* EGFR mutation and brain metastasis in pulmonary adenocarcinomas. J Thorac Oncol 2014;9:195-9. doi: 10.1097/JTO.0000000000000069.

24. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, *et al.* Estimating survival in patients with lung cancer and brain metastases: An update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncol 2017;3:827-31. doi: 10.1001/jamaoncol.2016.3834.

25. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, *et al.* The effect of gene alterations and tyrosine kinase inhibition on survival and cause of death in patients with adenocarcinoma of the lung and brain metastases. Int J Radiat Oncol Biol Phys 2016;96:406-13. doi: 10.1016/j.ijrobp.2016.06.006.

26. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, *et al.* Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): Results from a phase 3, non-inferiority, randomised trial. Lancet 2016;388:2004-14. doi: 10.1016/s0140-6736(16)30825-x.

递归分割分析和分级预后评估在筛选非小细胞肺癌脑转移患者放疗后全身治疗获益人群中的作用

摘要

背景： 对于接受了头部放疗的非小细胞肺癌（non-small cell lung cancer，NSCLC）脑转移患者，后续全身治疗的作用存在争议。因此，我们对美国肿瘤放射治疗协作组递归分割分析（Radiation Therapy Oncology Group recursive partitioning analysis, RTOG-RPA）和分级预后评估（graded prognostic assessment, GPA），用于筛选全身治疗获益人群的可行性进行了研究。

方法： 对过去10年内，来自两家医院的NSCLC脑转移患者的临床资料进行回顾性分析。应用Cox回归进行多因素分析。并比较RTOG-RPA或GPA亚组内，接受或未接受放疗后全身治疗患者的生存差异。

结果： 总共216例患者进入分析，61.7%的患者接受了立体定向外科放疗（stereotactic radiosurgery，SRS），24.1%接受了全脑放疗（received whole-brain radiation therapy，WBRT），8.8%接受上述两种放疗。总共有58.3%的患者，在放疗后接受了全身治疗。多因素分析发现，全身治疗（有 vs.无）（hazard ratio [HR] = 0.361, 95% confidence interval [CI] = 0.202 - 0.648, P = 0.001），放疗方式（SRS vs. WBRT）（HR = 0.462, 95% CI = 0.238 - 0.849, P = 0.022），颅外转移（有vs无）（HR = 3.970, 95% CI = 1.757 - 8.970, P = 0.001）和卡氏评分（Karnofsky performance status，KPS）（<70 vs ≥70）（HR = 5.338, 95% CI = 2.829 - 10.072, P < 0.001）是脑转移后生存的独立预后因素。进一步分析发现，对于RTOG-RPA II级（HR = 0.411, 95% CI = 0.183 - 0.923, P = 0.031）或GPA 1.5-2.5分（HR = 0.420, 95% CI = 0.182 - 0.968, P = 0.042）的患者，放疗后接受酪氨酸激酶抑制剂（Tyrosine kinase inhibitors，TKIs）治疗，可显著降低患者的死亡风险。但常规化疗未发现可以降低RTOG-RPA或GPA任何亚组患者的死亡风险。

结论： 在NSCLC脑转移患者中，以TKIs作为放疗后全身治疗者，RTOG-RPA或GPA有助于筛选获益人群。