

# Bevacizumab in Combination with Pemetrexed and Platinum Significantly Improved the Clinical Outcome of Patients with Advanced Adenocarcinoma NSCLC and Brain Metastases

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Yaru Tian<sup>1</sup>  
Xiaoyang Zhai<sup>2</sup>  
Hairong Tian<sup>1</sup>  
Wang Jing<sup>2</sup>  
Hui Zhu<sup>1,2</sup>  
Jinming Yu<sup>1,2</sup>

<sup>1</sup>Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong University, Jinan, People's Republic of China; <sup>2</sup>Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Science, Jinan, People's Republic of China

Correspondence: Hui Zhu  
Department of Radiation Oncology,  
Shandong Cancer Hospital and Institute,  
Shandong First Medical University and  
Shandong Academy of Medical Science,  
440 Jiyuan Road, Jinan, Shandong Province  
250117, People's Republic of China  
Tel +86 531 6762 6112  
Email drzhuh@126.com

Jinming Yu  
Department of Radiation Oncology,  
Shandong Cancer Hospital and Institute,  
Shandong University, 44 Wen Hua Xi  
Road, Jinan, Shandong Province 250012,  
People's Republic of China  
Tel +86 531 6762 6971  
Email sdyujinming@163.com

**Background:** The study aims to evaluate the clinical efficacy and safety of bevacizumab in combination with the first-line pemetrexed-platinum (PP) in patients with advanced adenocarcinoma non-small-cell lung cancer (NSCLC) and brain metastases.

**Methods:** The clinical data of patients with adenocarcinoma NSCLC and symptomatic or asymptomatic brain metastases were collected in our study. The basic chemotherapy regimen was pemetrexed-platinum (PP). According to whether combined with bevacizumab (B) or not, all enrolled patients were assigned to the B+PP group or the PP alone group.

**Results:** A total of 71 patients were enrolled in the current study. Twenty-six patients were allocated to the B+PP group and 45 were allocated to the PP group. Overall response rates (ORRs), disease control rates (DCRs) of the thoracic tumors and intracranial metastases and overall survival (OS) were not significantly different between the 2 groups. However, progression-free survival (PFS) and intracranial PFS (iPFS) were significantly prolonged in the B+PP group compared with the PP group. The median PFS was 9.2 and 8.2 months, and the 1-year PFS rates were 47.1% and 15.9%, respectively, in the 2 groups ( $P=0.029$ ). And, the median iPFS were 24.3 and 10.9 months, and the 1-year iPFS rates were 80.1% and 40.1%, respectively, in the 2 groups ( $P=0.008$ ). Univariate and multivariate analyses suggested that maintenance therapy and bevacizumab therapy were independent favorable prognostic factors of PFS and iPFS.

**Conclusion:** The addition of bevacizumab to the first-line pemetrexed and platinum significantly improved clinical outcomes of patients with advanced adenocarcinoma NSCLC and brain metastases.

**Keywords:** bevacizumab, non-small cell lung cancer, brain metastases, clinical outcome, toxicity

## Introduction

Worldwide, lung cancer is the leading cause of cancer incidence and mortality, with 2.1 million new cases and 1.8 million deaths predicted in 2018<sup>1</sup>. Approximately 85% of patients with lung cancer have the subtype of non-small-cell lung cancer (NSCLC). The incidence proportions of brain metastases were highest for lung cancer (19.9%), followed by melanoma (6.9%), renal (6.5%), breast (5.1%), and colorectal (1.8%) cancers.<sup>2</sup> Angiogenesis is essential in the development of brain metastases.<sup>3,4</sup> It not only constructs the pathway through which the cancer cells (the “seed”) and their primary stromal components (their own “soil”) spread to the brain

environment (the “soil”), but can also provide sufficient nutrients to support tumor proliferation. Vascular endothelial growth factor (VEGF) mainly mediates tumor angiogenesis and the progressive growth of the majority of metastatic brain tumors.<sup>5–7</sup> These structurally and functionally abnormal blood vessels, exhibiting sluggish blood flow and hyperpermeability, can, therefore, induce tumor interstitial hypertension and impair drug delivery.<sup>5</sup> Besides, the blood-brain barrier (BBB) also creates a sanctuary site protecting tumor cells from systemic treatments.

With the burgeoning biologic knowledge of brain metastases, normalizing tumor vasculature with anti-angiogenic treatment is a new paradigm for combination therapy in clinical applications.<sup>8</sup> Bevacizumab, a monoclonal antibody targeting VEGF, has demonstrated significant clinical benefit in the first- and second-line treatment across many cancer types including colorectal cancer, renal cell carcinoma, breast cancer and non-squamous NSCLC.<sup>9–16</sup> Multiple studies have confirmed that bevacizumab prolonged PFS in patients with newly diagnosed and progressive glioblastoma, the most common intracranial carcinoma.<sup>17–19</sup> Compared with chemotherapy alone, first-line bevacizumab in combination with standard chemotherapy followed by single-agent bevacizumab maintenance significantly improved clinical outcomes with manageable adverse events among patients with advanced non-squamous NSCLC.<sup>13–15</sup> However, the efficacy of bevacizumab in patients with brain metastases has not been systematically studied because these patients were generally excluded in the literature to avoid the potential risk of intracranial hemorrhage. However, a retrospective exploratory analysis found that patients with brain metastases from advanced breast, NSCLC, renal and colorectal cancers were at similar risk of developing cerebral hemorrhage, irrespective of bevacizumab therapy.<sup>20</sup> What’s more, some prospective trials (PASSPORT, ATLAS, BeTa, ERACLE and PRONOUNCE) included patients with brain metastases and reported a low rate of central nervous system (CNS) hemorrhage.<sup>21–25</sup> Pemetrexed plus cisplatin was better than gemcitabine plus cisplatin in patients with lung adenocarcinoma in the phase III study and was one of the standard chemotherapy regimens in the clinic.<sup>26</sup> There is a lack of studies involving bevacizumab for the brain metastases of NSCLC. Therefore, we conducted this retrospective study to explore the clinical efficacy and safety of first-line regimen of bevacizumab plus pemetrexed and platinum in NSCLC patients with brain metastases and further support clinical application of bevacizumab.

## Materials and Methods

### Patients

Patients with advanced adenocarcinoma NSCLC and brain metastases at diagnosis in Shandong Cancer Hospital and Institute (Jinan, Shandong, China) were enrolled in this retrospective study. The eligible criteria were as follows: histologically or cytologically diagnosed with adenocarcinoma NSCLC; no previous treatment; stage IV with brain metastases confirmed by a brain-computed tomography (CT) or magnetic resonance imaging (MRI) scan; Karnofsky performance status (KPS) score  $\geq 70$ ; symptomatic (headache, dizziness, nausea, vomit, visual disturbance et al) or asymptomatic. Exclusion criteria were predominantly squamous histology; severe hemoptysis (more than one-half teaspoon of bright red blood in recent 3 months); tumors invading major blood vessels; medically uncontrolled hypertension; current or recent (within 10 days of first-line therapy) therapeutic use of anticoagulants; and regular use of aspirin. This study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute. All procedures involving patients were conformed to Declaration of Helsinki. All patients provided written informed consent before their participation in this study.

### Treatments

Patients received either PP (pemetrexed 500mg/m<sup>2</sup> on day 1 and cisplatin 30 mg/m<sup>2</sup> on days 1–3 or carboplatin 400 or 500 mg on day 1) or B+PP (bevacizumab 7.5mg/kg on the day before PP). PP and bevacizumab were administered intravenously and repeated every 21 days for a total of 4 to 6 cycles. After the first-line therapy, patients who had a responsive or stable disease could receive maintenance therapy including pemetrexed monotherapy, tyrosine kinase inhibitors (TKIs), BP (bevacizumab plus pemetrexed) and BT (bevacizumab plus TKIs). During the first-line therapy or after disease progression, thoracic radiation and brain radiation were also available. The total dose of thoracic radiation was 45–60 Gy delivered at 1.8–2.0 Gy per fraction for 5 days weekly. Whole brain radiation therapy (WBRT) (30–60 Gy at 1.8–3.0 Gy per fraction) with/without additional localized boost (10–20 Gy).

### Assessments of Response and Toxicity

Responses of primary tumors and brain metastases were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. From the initial treatment, tumors evaluation was conducted every 2 cycles for 4–6

cycles, then every 2 months for the remainder of the treatment course and every 3 to 6 months after the completion of treatment. AEs were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0.

## Endpoints

The primary endpoint was OS and the secondary endpoints were PFS, iPFS and AEs. OS was measured from the initial diagnosis to the date of death from any cause or the date of the last known follow-up. PFS was defined as the duration from the initial diagnosis to the date of disease failure, the date of death or the last known follow-up. Intracranial PFS (iPFS) was from the diagnosis of brain metastases to the date of the intracranial progression, the date of death or the last known follow-up. AEs were evaluated in all patients of the 2 groups.

## Statistical Analysis

Comparisons of patient characteristics, response rates and AEs between the 2 groups were performed using Chi-square test and Fisher's exact test. The Kaplan-Meier method was used to calculate OS, PFS and iPFS. The survival difference between the 2 groups was compared using log-rank test. Using the Kaplan-Meier method, univariate survival analysis was performed to determine associations between survival (OS, PFS and iPFS) and clinical characteristics. All clinical variables were brought into a multivariate model in which a Cox proportional hazards model was used to determine significant factors. Two-sided *P* values <0.05 were considered statistically significant in all reported results and confidence intervals (CIs) are at the 95% level.

## Results

### Patient Characteristics

Between February 2013 and December 2017, approximately 5680 patients were diagnosed with stage IV adenocarcinoma NSCLC in our cancer center, and approximately 1620 patients had confirmed brain metastases. Since pemetrexed was expensive, and bevacizumab was not covered by medical insurance, only a number of patients received the first-line pemetrexed or in combination with bevacizumab. As a result, 76 NSCLC patients with confirmed brain metastases in our cancer center were evaluated. The follow-up rate was 93.4% with 5 patients lost during follow-up. Seventy-one patients had fully eligible information and were enrolled in the study

finally. The median follow-up time was 14.5 months (range, 1.2–47.4 months) for the total patients and 14.8 months (range, 1.5–47.4 months) for the living patients. For the 2 cohorts of patients, the median age was 55 and their age ranged from 27 to 76. Nine patients were 65 years and older. Thirty-four (47.9%) were male while 37 (52.1%) were female. According to the treatment modality, 26 (36.6%) patients were allocated to the B+PP group and 45 (63.4%) patients were allocated to the PP group.

Table 1 summarizes patient characteristics of the 2 groups. The distribution of all characteristics was balanced. Thirty-nine patients were assessable for epidermal growth

**Table 1** Patient Characteristics

Characteristic	No. of Patients (%)			P
	Total	B+PP (n=26)	PP (n=45)	
<b>Age, years</b>				
Median	55	58	54	0.880
Range	27–76	27–76	34–74	
≥65	9 (12.7)	4 (15.4)	5 (11.1)	
<65	62 (87.3)	22 (84.6)	40 (88.9)	
<b>Sex</b>				
Male	34 (47.9)	16 (61.5)	18 (40.0)	0.080
Female	37 (52.1)	10 (38.5)	27 (60.0)	
<b>KPS score</b>				
≥80	63 (88.7)	22 (84.6)	41 (88.5)	0.657
<80	8 (11.3)	4 (15.4)	4 (11.5)	
<b>Smoking status</b>				
Never	53 (74.6)	19 (73.1)	34 (75.6)	0.817
Ever	18 (25.4)	7 (26.9)	11 (24.4)	
<b>Histology</b>				
Adenocarcinoma	70 (98.6)	25 (96.2)	45 (100)	0.366
Others	1 (1.4)	1 (3.8)	0 (0)	
<b>Hypertension</b>				
Yes	14 (19.7)	4 (7.7)	10 (7.7)	0.485
No	57 (80.3)	22 (92.3)	35 (92.3)	
<b>EGFR mutation status assessment*</b>	39	19	20	
Positive	21 (53.8)	9 (47.4)	12 (60)	0.527
Wild type	18 (46.2)	10 (52.6)	8 (40)	
<b>Brain metastasis</b>				
Symptomatic	28 (39.4)	9 (34.6)	19 (42.2)	0.527
Asymptomatic	43 (60.6)	17 (65.4)	26 (57.8)	

**Note:** \*Indicates that the patients' EGFR mutation status was assessable.

**Abbreviations:** B+PP, bevacizumab plus pemetrexed-platinum; PP, pemetrexed-platinum; KPS, Karnofsky performance status; EGFR, epidermal growth factor receptor.

factor receptor (EGFR) mutation status and 21(53.8%) patients were EGFR mutation positive. More patients in the PP group have symptomatic brain metastases than the B+PP group (42.2% v 34.6%,  $P=0.527$ ). Table 2 is the summarization of treatment details. Most treatment characteristics were not significantly differ except for brain radiation between the 2 groups. The rate of patients receiving brain radiation was significantly higher in the PP group compared with B+PP group (68.9% v 38.5%,  $P=0.012$ ). One reason was that more patients in the PP group had symptomatic brain metastases than the other group.

**Table 2** Treatment Details

Treatment	No. of Patients (%)			P
	Total	B+PP (n=26)	PP (n=45)	
<b>First-line chemotherapy cycles</b>				
Median	6	4	6	0.209
Range	1–9	1–8	1–9	
≥6	37	11 (42.3)	26 (57.8)	
<6	34	15 (57.7)	19 (42.2)	
<b>Maintenance</b>				
Yes	41 (57.7)	17 (65.4)	24 (53.3)	0.322
No	30 (42.3)	9 (34.6)	21 (46.7)	
<b>Maintenance regimens</b>	41	17	24	
BP	10	10	0	
BT	1	1	0	
Pemetrexed	23	3	20	
TKIs	7	3	4	
<b>Thoracic radiation</b>				
Yes	19 (26.8)	6 (23.1)	13 (28.9)	0.322
No	52 (73.2)	20 (76.9)	32 (71.1)	
<b>Brain radiation</b>				
Yes	41 (57.7)	10 (38.5)	31 (68.9)	0.012
No	30 (42.3)	16 (61.5)	14 (31.1)	
<b>Second-line therapy</b>	60			
Yes	41	9 (56.3)	32 (72.7)	0.225
No	19	7 (43.8)	12 (27.3)	
<b>Second-line regimens</b>	41			
Single	22	2 (22.2)	20 (62.5)	
Double or more	19	7 (77.8)	12 (37.5)	

**Abbreviations:** B+PP, bevacizumab plus pemetrexed-platinum; PP, pemetrexed-platinum; TKI, tyrosine kinase inhibitor; BP, bevacizumab plus pemetrexed; BT, bevacizumab plus TKIs.

## Response

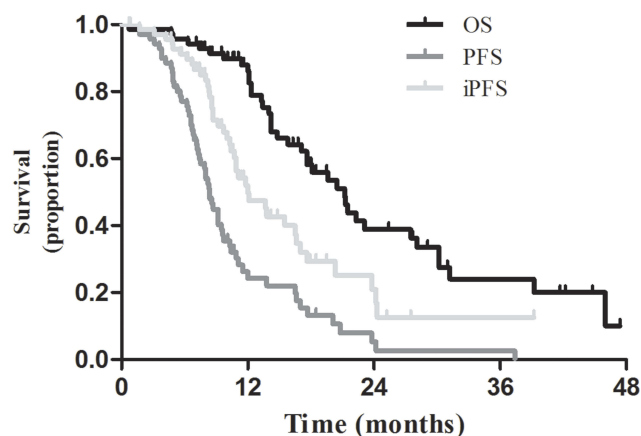
Among all patients in the 2 groups, ORR was 47.9% and DCR was 81.7%. ORRs and DCRs were not significantly different between the 2 groups (ORRs, 53.8% v 44.4%,  $P=0.445$ ; DCRs, 88.5% v 88.5%,  $P=0.422$ , for the B+PP and PP groups, respectively, Table S1). For intracranial metastases, ORR was 50.7% and DCR was 91.5% for the total patients. Intracranial response rates were 53.8% and 48.9% in the B+PP and PP groups, respectively ( $P=0.565$ , Table S2). Among patients who received B+PP, 3 (11.5%) achieved a complete response of the intracranial metastases. DCRs of the intracranial tumors were 96.2% and 88.9% in the 2 groups, respectively ( $P=0.537$ ).

## Survival

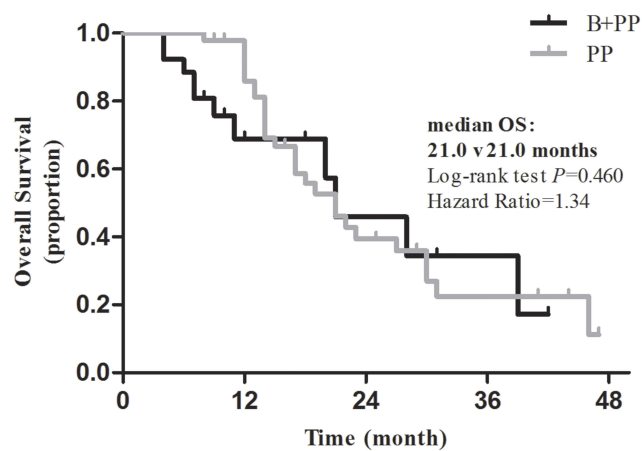
For the entire cohort of patients, the median survival was 21.2 months, and the 1-year and 2-year OS rates were 86.2% and 38.9%, respectively (Figure 1). Overall survival was not significantly different between the 2 groups ( $P=0.460$ , Figure 2). The median survival was 21 months, and the 1-year and 2-year OS rates were 68.8% and 45.9%, respectively, in the B+PP group. In the PP group, the median survival was 33.4 months, and the 1-year and 2-year OS rates were 85.9% and 39.5%, respectively.

The median PFS was 8.4 months and the 1-year and 2-year PFS rates were 24.3% and 5.3%, respectively for the entire cohort of patients (Figure 1). Patients receiving B+PP had significantly longer PFS than those receiving PP ( $P=0.029$ , Figure 3). The median PFS was 9.2 and 8.2 months, the 1-year PFS rates were 47.1% and 15.9%, and 2-year PFS rates were 17.6% and 0%, respectively, in the 2 groups.

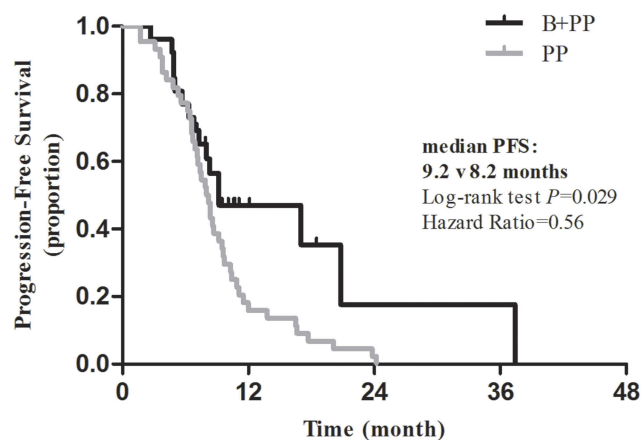
The median iPFS for the intracranial metastases was 12 months and the 1-year and 2-year PFS rates were 49.8%



**Figure 1** OS, PFS and iPFS for the entire cohort of patients.

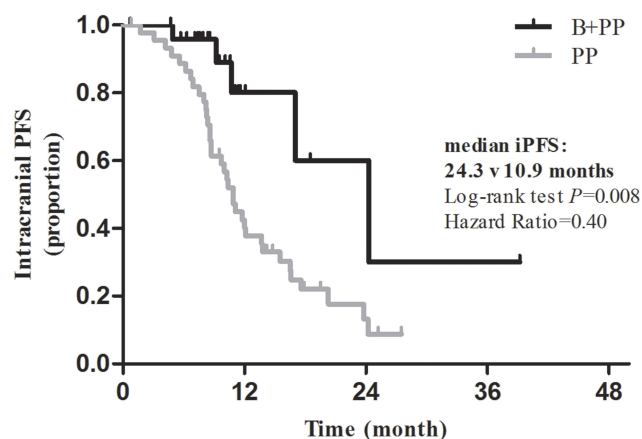


**Figure 2** OS between the B+PP group and the PP group. Median OS, 21.0 v 21.0 months; log-rank test,  $P=0.460$ ; Hazard Ratio=1.34.



**Figure 3** PFS between the B+PP group and the PP group. Median PFS, 9.2 v 8.2 months; log-rank test,  $P=0.029$ ; Hazard Ratio=0.56.

and 21.0%, respectively (Figure 1). As shown in Figure 4, iPFS was significantly longer in the B+PP group than the PP group ( $P=0.008$ ). In the 2 groups, the median iPFS



**Figure 4** iPFS between the B+PP group and the PP group. Median iPFS, 24.3 v 10.9 months; log-rank test,  $P=0.008$ ; Hazard Ratio=0.40.

were 24.3 and 10.9 months, the 1-year iPFS rates were 80.1% and 40.1%, and 2-year iPFS rates were 60.1% and 13.2%, respectively.

## Prognostic Factors

Univariate and multivariate analyses indicated that all clinical factors, including age at diagnosis, sex, KPS score, smoking status, brain metastases, EGFR mutation status, first-line chemotherapy cycles, maintenance therapy, thoracic radiation, brain radiation and bevacizumab therapy, were not associated with overall survival (Table 3). However, for PFS, univariate analysis suggested that maintenance therapy and bevacizumab therapy were significant favorable prognostic factors. Multivariate analysis revealed that maintenance therapy ( $P=0.003$ ), brain radiation ( $P=0.030$ ) and bevacizumab therapy ( $P=0.004$ ) were favorable prognostic factors of PFS (Table 4). Similarly, as shown in Table 4, univariate analysis indicated that maintenance therapy and bevacizumab therapy were significantly associated with favorable iPFS. Multivariate analyses also indicated that maintenance therapy ( $P=0.001$ ) and bevacizumab therapy ( $P=0.012$ ) were favorable prognostic factors of iPFS (Table 4).

## Toxicities

As shown in Table 5, the incidence of any grade AE was significantly higher in the B+PP group than the PP group (73.1% v 46.7%,  $P=0.031$ ). For the total patients, the incidence of any grade AE was 56.3%. None of the patients suffered from thrombosis, hemorrhage or proteinuria after bevacizumab treatment. However, there was no significant difference in the prevalence of grade  $\geq 3$  AEs between the 2 groups (7.7% v 4.4%,  $P=0.970$ ). One patient in the B+PP group experienced drug withdrawal due to intolerable toxicity. None of the total patients died of AEs.

## Discussion

In the current study, the addition of bevacizumab to the first-line PP chemotherapy significantly improved PFS and intracranial PFS compared with chemotherapy alone. Univariate and multivariate analyses indicated that maintenance therapy and bevacizumab therapy are independent favorable factors of PFS and iPFS. Our study supported that bevacizumab was beneficial and safe for patients with advanced adenocarcinoma and brain metastases.

Brain metastasis is a serious obstacle in the treatment of solid tumors and indicates poor prognosis, always determining a fatal outcome of these cancers. With improved systemic therapy and prolonged survival, and the early

**Table 3** Univariate and Multivariate Analyses of the Prognostic Factors for OS in NSCLC Patients with Brain Metastases

Factors	Univariate Analysis				Multivariate Analysis			
	mOS, mo	2-Year OS, %	$\chi^2$	P	HR	95% CI	$\chi^2$	P
<b>Age, years</b>								
≥65	20.5	0.0	0.60	0.438	1.319	0.431–4.039	0.235	0.628
<65	21.3	42.2						
<b>Sex</b>								
Male	21.2	32.5	1.51	0.220	1.643	0.624–4.321	1.011	0.315
Female	22.3	44.2						
<b>KPS score</b>								
≥80	21.2	39.4	0.02	0.897	0.771	0.254–2.337	0.211	0.646
<80	22.3	35.0						
<b>Smoking status</b>								
Never	20.5	39.0	0.19	0.666	1.192	0.427–3.327	0.112	0.738
Ever	21.2	37.0						
<b>Brain metastasis</b>								
Symptomatic	27.5	54.9	3.65	0.056	0.479	0.218–1.053	3.358	0.067
Asymptomatic	17.6	26.5						
<b>EGFR mutation status assessment*</b>								
Positive	23.1	44.0	0.59	0.443				
Wild type	20.5	45.3						
<b>No. of first-line chemotherapy cycles</b>								
≥6	21.5	40.4	0.68	0.409	0.615	0.228–1.315	1.571	0.210
<6	20.5	37.2						
<b>Maintenance</b>								
Yes	22.3	41.4	0.39	0.531	0.939	0.449–1.963	0.028	0.867
No	17.6	34.5						
<b>Thoracic radiation</b>								
Yes	20.5	49.0	0.30	0.585	0.869	0.351–2.151	0.092	0.762
No	21.2	33.4						
<b>Brain radiation</b>								
Yes	21.3	40.4	0.94	0.332	0.856	0.347–2.115	0.113	0.737
No	21.2	36.8						
<b>Bevacizumab</b>								
Yes	21.0	45.9	0.55	0.460	1.173	0.528–2.608	0.154	0.695
No	21.0	39.5						

**Note:** \*Indicates that the patients' EGFR mutation status was assessable.

**Abbreviations:** OS, overall survival; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; EGFR, epidermal growth factor receptor.

detection of asymptomatic metastases, the frequency of brain metastases is increasing. Although large-randomized phase III trials showed that bevacizumab produced significant clinical benefits and was well tolerated in patients with advanced non-squamous NSCLC. Nevertheless, most studies concerning bevacizumab excluded brain metastases to avoid the fetal CNS hemorrhage.<sup>13–15</sup> The lack of the current trials of bevacizumab in treating metastatic brain

tumors of NSCLC gave us a fresh impetus to conduct this retrospective study.

In our study, compared with the PP group, bevacizumab plus PP improved tumor responses and significantly prolonged PFS and iPFS in patients with adenocarcinoma and brain metastases. In the B+PP group, ORRs were 53.8% and 50.7% for thoracic tumors and intracranial metastases, respectively. The median PFS, 1-year and

**Table 4** Univariate and Multivariate Analyses of the Prognostic Factors for PFS and iPFS in NSCLC Patients with Brain Metastases

Factors	PFS						iPFS					
	Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
	Median, mo	$\chi^2$	P	HR	$\chi^2$	P	Median, mo	$\chi^2$	P	HR	$\chi^2$	P
<b>Age, years</b>												
≥65	9.2	0.02	0.894	0.556	1.12	0.291	10.4	0.03	0.866	0.463	1.09	0.297
<65	8.2						12.1					
<b>Sex</b>												
Male	8.0	0.25	0.619	1.532	1.16	0.282	11.8	0.15	0.702	1.764	1.16	0.291
Female	9.2						12.1					
<b>KPS score</b>												
≥80	8.4	1.34	0.247	1.319	0.27	0.606	11.1	1.01	0.315	1.237	0.11	0.738
<80	7.1						15.5					
<b>Smoking status</b>												
Never	8.3	0.08	0.774	1.182	0.15	0.699	12.0	0.28	0.598	2.269	1.85	0.174
Ever	8.4						13.7					
<b>Brain metastasis</b>												
Symptomatic	8.4	0.24	0.624	0.978	0.00	0.952	16.5	2.35	0.126	0.441	3.04	0.081
Asymptomatic	8.3						11.1					
<b>EGFR mutation status assessment*</b>												
Positive	10.3	0.34	0.559				11.8	2.78	0.096			
Wild type	7.9						NR					
<b>No. of first-line chemotherapy cycles</b>												
≥6	8.7	0.43	0.511	0.533	3.63	0.057	12.0	0.02	0.876	0.680	0.84	0.360
<6	8.0						12.1					
<b>Maintenance</b>												
Yes	10.3	7.50	0.006	0.391	8.88	0.003	16.5	15.24	<0.001	0.279	10.77	0.001
No	8.0						8.8					
<b>Thoracic radiation</b>												
Yes	9.2	1.83	0.177	0.551	2.28	0.131	11.1	0.07	0.799	0.660	0.79	0.373
No	7.5						12.1					
<b>Brain radiation</b>												
Yes	9.2	3.09	0.079	0.435	4.71	0.030	11.8	0.00	0.957	0.982	0.00	0.971
No	7.1						15.5					
<b>Bevacizumab</b>												
Yes	9.2	4.79	0.029	0.368	8.40	0.004	24.3	7.15	0.008	0.274	6.33	0.012
No	8.2						10.9					

**Note:** \*Indicates that the patients' EGFR mutation status was assessable.

**Abbreviations:** PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; EGFR, epidermal growth factor receptor.

2-year PFS rates were 9.2 months, 47.1% and 17.6%, respectively, and the median intracranial PFS, 1-year and 2-year PFS rates were 23.4 months, 80.1% and 60.1%,

respectively. These results were consistent with BRAIN, a phase II prospective study, which demonstrated encouraging efficacy and tolerable safety profile of bevacizumab

**Table 5** Adverse Events

Adverse Events	No. of Patients (%)			P
	Total	B+PP (n=26)	PP (n=45)	
<b>Any grade</b>	40 (56.3)	19 (73.1)	21 (46.7)	0.031
Hematologic	19 (26.8)	8 (30.7)	11 (24.4)	
Gastrointestinal	27 (38.0)	13 (50.0)	14 (31.1)	
Hypertension	2 (2.8)	2 (7.7)	0 (0)	
Thrombosis	0 (0)	0 (0)	0 (0)	
Hemorrhage	0 (0)	0 (0)	0 (0)	
Proteinuria	0 (0)	0 (0)	0 (0)	
<b>Grade <math>\geq 3</math></b>	4 (5.6)	2 (7.7)	2 (4.4)	0.970
Hematologic	3 (4.2)	2 (7.7)	1 (2.2)	
Gastrointestinal	1 (1.4)	0 (0)	1 (2.2)	
Hypertension	0 (0)	0 (0)	0 (0)	
<b>AE leading to drug death</b>	0 (0)	0 (0)	0 (0)	
<b>AE leading to drug withdrawal</b>	1 (1.4)	1 (3.8)	0 (0)	

**Abbreviations:** B+PP, bevacizumab plus pemetrexed-platinum; PP, pemetrexed-platinum.

with the first-line paclitaxel and carboplatin (PC) in NSCLC patients with asymptomatic untreated brain metastases.<sup>27</sup> Of the total 67 patients, 6-month PFS rate was 56.5%, the median PFS was 6.7 months and the median OS was 16.0 months. Investigator-assessed ORR was 62.7%, with 61.2% in intracranial lesions and 64.2% in extracranial lesions. What's more, the PRONOUCÉ study, which enrolled 54 (15%) NSCLC patients with brain metastasis, also indicated that PFS without grade 4 toxicity was also favorable in the first-line B+PC group compared with the PC group.<sup>25</sup> The ARIES observational cohort study included 150 (7.6%) NSCLC patients with brain metastases showed a median PFS of 6.6 months in the first-line bevacizumab-containing group.<sup>28</sup> Thus, bevacizumab could achieve a good response and disease control both in the thoracic tumors and the intracranial metastases.

However, there was no significant difference in overall survival between the 2 groups (21 v 21 months,  $P=0.460$ ). We speculate that the higher percentage of patients receiving the first-line chemotherapy cycles, brain radiation and the second-line therapy in the PP group may be involved in this issue. Brain radiation therapy, including WBRT and SRS (stereotactic radiosurgery), has been used as the primary nonsurgical therapeutic modality for brain metastases.<sup>8</sup> And

the combination of brain radiation therapy with systemic chemotherapy and targeted therapy also improved the control of brain metastases and clinical outcomes in NSCLC patients with brain metastases. Maintenance therapy, with either chemotherapy or TKIs, is an important part of the whole course treatment, and has significantly improved overall survival in patients with advanced NSCLC according to multiple large studies.<sup>29–33</sup> In the current study, the differences in the maintenance and the second-line therapy between the 2 groups may also influence the overall survival. However, the second-line bevacizumab therapy was unlikely to affect the overall survival, since only 3 and 4 patients in the 2 groups received bevacizumab-containing regimens as the second-line therapy.

Asian population had a more favorable survival outcome compared with a mainly white population with advanced NSCLC.<sup>34</sup> The median OS, median PFS and ORR in our study were 21 months, 9.2 months and 53.8% in the B+PP group, which is comparable with BEYOND.<sup>14</sup> In BEYOND, the median OS, median PFS and ORR were 24.3 months, 9.2 months and 54%, respectively, in the B+PC group. It is suspected that the higher EGFR positive mutation rate in Chinese patients (27% in BEYOND and 53.8% in our study) may partly account for the better clinical outcome compared with the West.

Toxicity, especially hemorrhage, was the major concern of bevacizumab therapy. Our study suggested that bevacizumab was safe in treating NSCLC patients with brain metastases. The incidence of grade  $\geq 3$  AEs was similar between the 2 groups. Intracranial, pulmonary and gastrointestinal hemorrhage did not occur in the entire cohort of patients. A retrospective study demonstrated that the risk of developing intracranial hemorrhage was independent of bevacizumab therapy among patients with brain metastases from advanced breast cancer, NSCLC, renal and colorectal cancer.<sup>20</sup> What's more, bevacizumab was safe and produced clinical benefit in the form of relieved symptoms and reduced corticosteroid requirements among 6 patients with active brain metastases from NSCLC.<sup>35</sup> An evidence-based review also showed that there was no significant increased risk of intracranial hemorrhage in NSCLC patients with brain metastases treated with anti-VEGF therapy.<sup>36</sup> The incidence of intracranial hemorrhage was relatively low for NSCLC patients with brain metastases in prospective trials.<sup>16,21,22,27,28</sup> Our study, in consistent with previous studies, demonstrates that bevacizumab has tolerable toxicity profile in the treatment of NSCLC patients with brain metastases.



There are also some limitations in our study. First, as a retrospective study, some important clinical information, such as the baseline lung and heart function, which could influence the clinical outcome of the treatment, was not fully introduced. Second, the patient population was too small to be representative of the patients of the whole country. Third, possible selection biases could also exist, as patients with a history or high risk of hypertension, bleeding or thrombosis tended to be included in the PP group, which could influence the final survival results. All possible confounding factors could not be controlled despite the adjustment of a Cox regression model.

## Conclusion

In conclusion, our study indicates that the addition of bevacizumab to pemetrexed-platinum was associated with the better local control of both primary tumors and intracranial metastatic lesions, and prolonged PFS and intracranial PFS in NSCLC patients with symptomatic or asymptomatic brain metastases. Adverse events were manageable with no pulmonary or intracranial hemorrhage observed after bevacizumab therapy. Consistent with previous analyses and early phase studies, our study demonstrated that bevacizumab in combination with the first-line chemotherapy could produce clinical benefit and was tolerable for NSCLC patients with brain metastases. In this respect, bevacizumab can be considered for NSCLC patients with brain metastases, and prospective trials concerning bevacizumab in the treatment of advanced NSCLC should also include patients with brain metastases.

## Abbreviations

NSCLC, non-small-cell lung cancer; VEGF, vascular endothelial growth factor; AE, adverse event; CNS, central nervous system; OS, overall survival; PFS, progression-free survival; CT, computed tomography; MRI, magnetic resonance imaging; KPS, Karnofsky performance status; PP, pemetrexed-platinum; B+PP, bevacizumab plus PP; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; BP, bevacizumab plus pemetrexed; BT, bevacizumab plus TKI; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; ORR, overall response rate; DCR, diseases control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BBB, blood-brain barrier; RECIST, Response Evaluation Criteria in Solid Tumors; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; HR, hazard ratio; CI, confidence interval.

## Author Contributions

Yaru Tian, Hairong Tian, Xiaoyang Zhai and Wang Jing contributed to the acquisition, analysis and interpretation of the clinical data. They also drafted the manuscript. Hui Zhu and Jinming Yu contributed to the conception and design of the study, and made revisions for the manuscript critically for important intellectual content. All authors approved the final manuscript to be published and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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