Therapeutic effect of cranial radiotherapy with or without anlotinib treatment for lung cancer patients with brain metastasis and non-EGFR/ALK-TKIs indication

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Keywords: Radiotherapy, lung cancer, brain metastases, progression-free survival, overall survival

Posted Date: July 24th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-44047/v1

Abstract

Background: Cranial radiotherapy (CRT) is the main treatment for lung malignant tumor with brain metastasis (BM) and lacking EGFR/ALK-TKIs indication. For non-small cell lung cancer with BM, anlotinib can improve progression free survival (PFS). We retrospectively analyzed the clinical effects of anlotinib + CRT versus CRT alone.

Methods: In patients with lung cancer (adenocarcinoma, squamous carcinoma, or small cell carcinoma) with BM and non-EGFR/ALK-TKIs indication, the overall survival (OS) and PFS of anlotinib + CRT treatment versus CRT treatment alone were separately calculated and compared. The Cox proportional hazards model was used to analyze the independent prognostic factors for intracranial PFS (iPFS) and OS. All confounding factors were adjusted, including age, gender, Karnofsky Performance Status (KPS) score, smoking history, physiological characteristics, T/N stage, histology, metastases, and pathological characteristics. Subgroup analysis for iPFS and OS was performed to assess the effects on BM of treatment pattern.

Results: The study included 100 patients with BM at baseline and the follow-up data. Of the 100 patients, 67 patients received CRT treatment alone and 33 patients received CRT + anlotinib treatment. The overall response rates of the CRT + anlotinib group and the CRT alone group were 90.91% and 83.58%, respectively. There was significantly more iPFS in the CRT + anlotinib group compared to CRT alone (median iPFS [miPFS]: 9.0 vs 3.0 months; hazard ratio [HR] 1.59; 95% confidence interval [CI] 1.01-2.52; p = 0.038). The OS, extracranial PFS (ePFS), and systematic PFS (sPFS) of CRT + anlotinib group were longer than those of the CRT alone group, but there was no significant statistical difference (median OS [mOS]: 9.0 vs 7.0 months, HR 1.17, 95% CI 0.74-1.85; median ePFS [mePFS]: 9.0 vs 7.0 months, HR 1.23, 95% CI 0.72-2.11; median sPFS [msPFS]: 7.0 vs 4.0 months, HR 1.37, 95% CI 0.82-2.30). The Cox proportional hazards model analysis revealed that age was an independent prognostic factor of iPFS (HR 1.65, 95% CI 1.05-2.59, p = 0.03). Age (HR 1.74, 95% CI 1.09-2.77, p = 0.02) and KPS score (HR 1.88, 95% CI 1.17-3.01, p = 0.01) were identified as independent prognostic factors of OS. Further subgroup analysis of iPFS showed that when the number of BM in the CRT + anlotinib group was less than or equal to three lesions (≤ 3), the miPFS (12.0 months) was significantly longer than that for CRT alone (> 3) (3.0 months), for CRT alone (≤ 3) (3.0 months), and for CRT + anlotinib (> 3) (7.0 months) (p = 0.014). The OS of the CRT + anlotinib group (≤ 3) (mOS 37.0 months) was much longer than that in CRT alone (> 3) (mOS 6.0 months), CRT alone (≤ 3) (mOS 7.5 months), and CRT + anlotinib (> 3) (mOS 8.5 months) groups, but this difference was not statistically significant (p = 0.051).

Conclusion: Anlotinib can improve the survival of patients with lung cancer BM, with better efficacy of a combined treatment of anlotinib + CRT compared to that of CRT alone, especially for the iPFS of patients with BM ≤ 3.

Background

Lung cancer is the most common of all malignant tumors worldwide (1, 2). The proportion of non-small cell lung cancer (NSCLC) in all lung cancer is about 80%, and 30% – 43% of patients will have brain metastasis (BM) in the process of the disease (3–5). The proportion of small cell lung cancer (SCLC) in all lung cancer is about 15% – 20%, in which about 80% of SCLC patients will have BM in the process of the disease (4–6). The prognosis of lung cancer patients with BM is poor, and the median survival time (mOS) of patients that do not receive treatment is only 1–3 months (1, 3).

In recent years, significantly improved prognosis has been achieved for lung cancer patients by treatment using small molecular targeted tyrosine kinase inhibitors (TKIs) to target anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), and C-ros oncogene 1-receptor tyrosine kinase (ROS1) (1, 3, 7–10). Patients with BM from NSCLC receiving these treatments also showed significantly improved survival. The response rate of brain lesions from NSCLC BM patients with EGFR mutation to first generation TKIs reached 60.0% – 80.0%, with complete remission (CR) rate of 40.0% and mOS of 15–20 months (11). A meta-analysis study also showed that the first generation TKIs had significant effect on BM in patients with EGFR/ALK gene mutations, with median progression free survival (mPFS) of 7.4 months and mOS of 11.9 months (7, 12). Compared with first generation TKIs, second generation TKIs such as afatinib can simultaneously inhibit several ErbB family members (including EGFR, ErbB3, ErbB4, and human epidermal growth factor receptor-2) (13). The use of afatinib for initial treatment of advanced NSCLC patients is better than use for gefitinib with increased time to treatment failure (TTF), median duration of response (mDOR), and progression free survival (PFS) (12–15). However, the ability of afatinib to cross the blood-brain barrier (BBB) to reach the effective concentration in the central nervous system has not been demonstrated (16).

In patients with the EGFR T790M mutation, the distribution of osimertinib (AZD9291) in brain tissue was significantly higher than that of the first and second generation EGFR/ALK-TKIs (17, 18). AURA3 trial was a phase III clinical study, which tested AZD9291 (80 mg/d) vs standard dual drug chemotherapy (containing platinum), and found that AZD9291 significantly prolonged PFS (mPFS: 11.7 vs 5.6 months; hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.15–0.69; $p = 0.004$), with objective response rate (ORR) of the central nervous system of 70% vs 31% for AZD9291 treatment vs standard dual drug chemotherapy, respectively (19). In FLAURA trial, the intracranial CR rate of AZD9291-treated BM patients with NSCLC was 18%, with 88% of patients experiencing remission times of more than half a year (20). However, for advanced NSCLC and SCLC patients with non-gene mutation or resistance to EGFR/ALK-TKIs, alternative TKIs are not available, so it is urgent to develop specific targeted drugs.

Anlotinib hydrochloride was independently developed in China as a new orally administered, multi-target TKI (21). Anlotinib can inhibit tumor cell proliferation and tumor angiogenesis by inhibiting tumor related kinases, such as VEGFR, FGFR, PDGFR α/β, c-kit, and RET (22, 23). The ALTER1202 trial was a double-blind, randomized, multicenter, phase II clinical trial involving 119 NSCLC patients with measurable lesions and no gene mutation, who were treated with at least two chemotherapy regimens but progressed or relapsed. A total of 81 patients were included in the anlotinib group and the remaining patients received placebo treatment. Of the 119 patients, the mPFS of the anlotinib group was 4.1 months (95% CI

2.8–4.2) and that of the placebo group was 0.7 months (95% CI 0.7–0.8). The HR of tumor recurrence was reduced by 80.8% for the anlotinib treatment group, and this difference was statistically significant (HR 0.192, 95% CI 0.117–0.315, $p < 0.0001$). The mOS was 7.3 months for the anlotinib group (95% CI 6.5–10.5) and 4.9 months for the placebo group (95% CI 2.6–6.7), with a statistically significant 47.2% reduction in the death risk (HR 0.528, 95% CI 0.304–0.918, $p = 0.021$) (24). Moreover, ALTER1202 was also study the the treatment effects of anlotinib for third- and further-line treatment of SCLC (anlotinib group 46 patients, placebo group 22 patients), it indicated the mPFS of anlotinib group vs placebo group (4.1 vs 0.7 months, HR 0.19, 95% CI 2.4–5.8, $p < 0.0001$), and mOS of anlotinib group vs placebo group (7.3 vs 4.9 months, HR 0.53, 95% CI 0.34–0.81, $p < 0.0029$) (25).

The ALTER0302 trial was a double-blind, randomized, multicenter, phase II clinical trial with 117 enrolled patients. The patients had received two or more chemotherapy regimens, and EGFR/ALK gene mutation positive patients had received at least two chemotherapy regimens after EGFR/ALK-TKIs treatment (21, 26). The patients were randomized into two groups at a ratio of 1:1. The PFS of the anlotinib group (mPFS: 4.8 months, 95% CI 3.5–6.4) was significantly better than that of the placebo (mPFS: 1.2 months, 95% CI 0.7–1.6) (21, 26).

The ALTER0303 double-blind, randomized, phase III clinical trial included 31 medical centers in China. A total of 437 advanced NSCLC patients were included in the trial, and were randomly allocated into the placebo group (n = 143) or the anlotinib group (n = 294) at a ratio of 1:2. These results showed that anlotinib prolonged the mOS by 3.3 months (9.6 vs 6.3 months, HR 0.68, 95% CI 0.54–0.87, $p = 0.0018$) and the mPFS by 4.0 months (5.4 vs 1.4 months, HR 0.25, 95% CI 0.19–0.31, $p < 0.0001$) (27–29). In the ALTER0303 trial, the efficacy of anlotinib for the treatment of BM was also evaluated, as 97 (22.2%) patients had BM at baseline. For these patients with BM at baseline, the mPFS for anlotinib treatment was 4.17, considerable higher than the 1.3 months for placebo treatment, and 8.57 for mOS for anlotinib treatment compared to 4.55 months for placebo treatment. The patients in the anlotinib group had a longer time to brain progression (TTBP) than the placebo group, indicating that anlotinib delays the progression of intracranial lesions from advanced NSCLC patients (30). The exploratory subgroup analysis of the ALTER0303 trials showed that patients with either EGFR gene mutation or wild-type exhibited improved PFS and OS with anlotinib treatment (27, 28, 30). Related clinical studies show that both NSCLC and SCLC can significantly prolong PFS and OS (25–28, 30). Therefore, in May 2018 and June 2019, China Food and Drug Administration (CFDA) officially approved anlotinib for single drug treatment for the third-line or higher treatment of advanced NSCLC patients and SCLC patients with non-gene mutation or EGFR/ALK-TKIs resistance.

Clinical studies have confirmed that anlotinib can effectively treat some patients with advanced lung cancer, including patients with BM (27, 28, 30). However, for NSCLC patients with no gene mutation or EGFR/ALK-TKIs resistance, as well as SCLC patients with BM, cranial radiotherapy (CRT) is still considered the standard treatment regime, as this treatment can quickly relieve central nervous system the symptoms and improve the survival time of patients (31). CRT can increase the permeability of the BBB, which may increase the content of anlotinib in brain tissue, so the curative effect of CRT combined

with anlotinib may be better than that of CRT alone for NSCLC patients with no gene mutation or EGFR/ALK-TKIs resistance or for SCLC patients with BM (32, 33). In this study, we retrospectively analyzed the effects of CRT combined with anlotinib treatment compared with CRT alone for patients with lung cancer BM and multi-line chemotherapy failure or patients with EGFR/ALK-TKIs resistance or patients with non-EGFR/ALK mutations or intolerable chemotherapy.

Methods

Patients

We reviewed the clinical records of patients diagnosed with lung cancer and BM between September 2017 and December 2019 at The First Affiliated Hospital of Bengbu Medical College (China). The clinical records of these patients included their clinical information, imaging data, tumor-related features, treatment process and clinical outcomes. Clinical information included gender, age, smoking and drinking history, previous disease history, and Karnofsky Performance Status (KPS) score. Tumor-related features included pathological type, EGFR/ALK mutation status, extracranial metastasis, number of BM, and treatment process (including CRT and drug therapy) (30). The imaging data were evaluated by two radiologists with single blind evaluation of tumor volume. When the two had different opinions, the third radiologist reviewed them. The TNM staging criteria for patients were based on the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) 8th Edition (34, 35). The inclusion criteria were: 1) 18–75 years old and KPS score ≥ 70; 2) lung cancer diagnosed by histopathology; 3) no EGFR/ALK mutations; 4) if EGFR/ALK mutation, patients must have received EGFR/ALK-TKIs as first-line treatment, and exhibited resistance or intolerance; 5) received at least two chemotherapy regimens or intolerance, 6) BM was diagnosed by computed tomography/magnetic resonance imaging (CT/MRI); 7) patients received CRT and anlotinib concurrent treatment, or CRT treatment alone (Fig. 1). The exclusion criteria were: 1) diagnosis with a previous malignancy or other concomitant malignant disease; 2) CRT or concurrent treatment not completed; 3) previously received CRT treatment; 4) received anlotinib after CRT. According to the treatment process, all collected patients were divided into two groups: CRT combined with anlotinib concurrent therapy group (CRT + anlotinib group) or CRT alone group.

Treatment

Anlotinib treatment was 12 mg daily (recommended dose) for 14 days orally and then 7 days off (21). The CRT treatment was the first time for all patients. CRT treatment included whole brain radiotherapy (WBRT), WBRT plus local CRT, or local CRT, as decided by the multidisciplinary team based on the number of BM, patient KPS score, pathological type, and other factors. For CRT, the dose for WBRT was 30–40 Gy in 10–20 fractions. The dose for local CRT was 25–54 Gy in 5–27 fractions. The dose for WBRT + local CRT was 30–40 Gy for WBRT and 10–24 Gy for local CRT. Clinical follow-up was carried out every 3–6

months, and included imaging, physical, and routine laboratory tests. The therapeutic effect was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Outcomes

Overall response rate (ORR) was defined as the proportion of CR plus partial response (PR) cases of the total number of evaluable cases (36). OS was defined based on the initiation of CRT to the death time or last follow-up time (21). The intracranial PFS (iPFS) and extracranial PFS (ePFS) were defined from the initiation of CRT to intracranial/extracranial progression time or death time, or the last follow-up time for patients who showed no progress or died. Systematic PFS (sPFS) was defined from the initiation of CRT to dead time, or tumor progression, or the last follow-up time for patients who showed no progress or died (21, 37, 38). The last follow-up time was June 2020. The primary endpoints included iPFS and OS, and the secondary endpoints included ePFS and sPFS.

Statistical Analysis

Patient characteristics were expressed as categorical variables and analyzed by Pearson's chi-square test or Fisher's exact test. The age as a patient characteristic was calculated as mean ± standard deviation (S.D). Differences in PFS and OS between CRT + anlotinib group and CRT alone group were compared using Cox proportional hazards models. Subgroup analyses in PFS and OS were accomplished by randomized stratification factors and stratified Cox proportional hazards models. Statistical analyses were carried out using SPSS 25.0 (International Business Machines Corporation, Armonk, New York, USA). The figures were prepared using GraphPad Prism v8.3 (GraphPad Software Inc., San Diego, USA). A value of $p < 0.05$ with 2 sides was defined as statistical significance.

Results

Patient Characteristics

According to the included and excluded criteria, 116 NSCLC or SCLC brain metastasis patients with CRT and non-EGFR/ALK-TKIs indication were included in this retrospective study. Sixteen cases lacking sufficient follow-up data were excluded (Fig. 1). Finally, 100 patients were included in the study, including 12 cases of squamous carcinoma (12%), 57 cases of adenocarcinoma (57%), and 31 cases of SCLC (31%). The median and average ages of all patients were 58 and 58.93 years (range 30–75 years), respectively. Sixty-one patients (61%) were male and 75 patients (75%) were never smokers. The KPS score of 67 patients (67%) were in the range of 90–100, and 33 patients (33%) were in the range of 70–80. The left lung was the primary cancer site for 54 patients (54%), and the right lung was the primary cancer site for the other 46 patients (46%). There were 7 (7%), 26 (26%), 15 (15%), and 22 (22%) of patients classified as stage T1, T2, T3, and T4, respectively; the classifications for the remaining 26 patients (26%) were not available. The patients classified as stage N0, N1, N2, and N3 were 8 (8%), 7 (7%),

48 (48%) and 19 (19%); the remaining 18 patients (18%) lacked classification data. A total of 28 patients (28%) lacked extracranial distant metastasis, and for 10 patients (10%), it was not clear if there was extracranial distant metastasis. One patient had ALK mutation and 27 patients had the EGFR gene mutation; these 28 patients exhibited resistance to treatment with EGFR/ALK-TKIs and then started CRT after BM diagnosis. The patient baseline characteristics of the CRT alone group and the anlotinib + CRT group are listed in Table 1. Of the 100 patients, 33 cases received anlotinib plus CRT (16 cases with WBRT, 7 cases with WBRT + local CRT, and 10 cases with local CRT), and the other 67 cases received CRT alone (55 cases with WBRT, 11 cases with WBRT + local CRT, and 1 case with local CRT).

Table 1
Clinical baseline characteristics of included patients.

Characteristic	CRT alone (n = 67)	CRT + anlotinib (n = 33)	*p* value
Age (years)			
Average (mean ± S.D)	59.09 ± 8.94	58.61 ± 10.31	0.82
Median	58	59	
Range	30–75	41–73	
Gender			
Female	24 (35.82%)	15 (45.45%)	0.35
Male	43 (64.18%)	18 (54.55%)	
KPS score			
90–100	43 (64.18%)	24 (72.73%)	0.39
70–80	24 (35.82%)	9 (27.27%)	
Smoking history			
Yes	18 (26.87%)	7 (21.21%)	0.54
No	49 (73.13)	26 (78.79%)	
Primary site			
left	34 (50.75%)	20 (60.61%)	0.35
right	33 (49.25%)	13 (39.39%)	
Pathological type			
Adenocarcinoma	38 (56.72%)	19 (57.58%)	0.65
Squamous carcinoma	6 (8.96%)	6 (18.18%)	
SCLC	23 (34.33%)	8 (24.24%)	
T stage			
T1	2 (2.99%)	5 (15.15%)	0.06
T2	17 (25.37%)	9 (27.27%)	
T3	9 (13.43%)	6 (18.18%)	
T4	19 (28.36%)	3 (9.10%)	

Note: cranial radiotherapy, CRT; Karnofsky Performance Status, KPS.

Characteristic	CRT alone (n = 67)	CRT + anlotinib (n = 33)	*p* value
Not available	16 (23.88%)	10 (30.30%)	
N stage			
N0	4 (5.97%)	4 (12.12%)	0.83
N1	4 (5.97%)	3 (9.10%)	
N2	37 (55.22%)	11 (33.33%)	
N3	10 (14.93%)	9 (27.27%)	
Not available	12 (17.91%)	6 (18.18%)	
Extracranial distant metastasis			
Yes	42 (62.69%)	20 (60.61%)	0.53
No	17 (25.37%)	11 (33.33%)	
Not available	8 (11.94%)	2 (6.06%)	
Note: cranial radiotherapy, CRT; Karnofsky Performance Status, KPS.			

Efficacy

The median follow-up time of all patients was 21.0 months. The ORR values of the CRT + anlotinib group and the CRT alone group were 90.91% and 83.58%, respectively. Of the 67 patients in the CRT alone group, 6 patients (8.96%) were alive without evidence of disease progression, and 52 patients (77.61%) died with intracranial progression, 43 patients (64.18%) died with extracranial progression, and 5 patients (7.46%) were alive with detected intracranial progression. Of the 33 patients in the CRT + anlotinib group, 6 patients (18.18%) were alive without evidence of disease progression, 20 patients (60.61%) were dead with intracranial progression, 19 patients (57.58%) were dead with extracranial progression, and 3 patients (9.09%) were alive with intracranial progression. For the whole group, the median iPFS (miPFS) and mOS were 5.0 and 8.5 months, respectively. The miPFS values were 9.0 months for the anlotinib + CRT group and 3.0 months for the CRT alone group (HR 1.59, 95% CI 1.01–2.52, $p = 0.038$) (Fig. 2). This indicated that anlotinib treatment was closely associated with a significantly longer iPFS when combined with CRT. The mOS of the anlotinib + CRT group was longer than that of the CRT alone group (9.0 vs 7.0 months), although this difference was not statistically significant (HR 1.17, 95% CI 0.74–1.85, $p = 0.5$). A total of 40.3% of patients in the CRT + anlotinib group were alive 12 months later from the initial of the therapy. It was slightly more than that of CRT alone group (36.36%). The CRT + anlotinib group vs CRT alone group was 9.0 vs 7.0 months for median ePFS (mePFS, HR 1.23, 95% CI 0.72–2.11, $p = 0.43$) and 7.0 vs 4.0 months for median sPFS (msPFS, HR 1.37, 95% CI 0.82–2.30, $p = 0.21$). There was not

significant different for ePFS and sPFS in these two groups, although the mePFS and msPFS in the concurrent treatment group were higher than that of CRT alone group.

The value of $p = 0.2$ was considered a significant difference for univariate analysis. The analysis revealed that iPFS was significantly related to age, gender, KPS score, smoking history, pathological type, number of brain metastases, and primary site (Table 2). OS was related to age, gender, KPS score, primary site, and pathological type.

Table 2
The univariate analysis between different characteristics and iPFS or OS.

Variable	iPFS		OS	
	HR (95% CI)	p value	HR (95% CI)	p value
Age				
< 58 years vs ≥ 58 years	1.71 (1.11–2.64)	0.02	1.85 (1.17–2.91)	0.01
Gender				
Male vs Female	0.69 (0.45–1.08)	0.1	0.54 (0.34–0.88)	0.01
KPS score				
90–100 vs 70–80	1.58 (1.01–2.47)	0.05	1.86 (1.16–2.98)	0.01
Smoking history				
No vs Yes	1.51 (0.95–2.51)	0.08	1.36 (0.82–2.26)	0.23
T stage				
T1-2 vs T3-4	1.08 (0.81–1.44)	0.59	1.07 (0.80–1.43)	0.66
N stage				
N0-1 vs N2-3	1.24 (0.87–1.77)	0.24	1.13 (0.77–1.65)	0.54
Pathological type				
Adenocarcinoma	1.26 (1.002–1.59)	0.048	1.45 (1.14–1.85)	0.003
Squamous carcinoma				
SCLC				
Brain metastases				
≤3 vs > 3	1.54 (0.95–2.51)	0.08	1.36 (0.82–2.26)	0.23
Extracranial distant metastasis				
No vs Yes	1.31 (0.77–2.21)	0.32	1.14 (0.66–1.95)	0.64
Primary site				
left vs right	1.54 (0.97–2.44)	0.07	0.69 (0.44–1.10)	0.12

Note: overall survival, OS; intracranial progression free survival, iPFS; Karnofsky Performance Status, KPS.

The significant characteristics of univariate analysis were selected to analyze the correlation between these characteristics and iPFS or OS using adjusted Cox multivariate analyses. In multivariate analyses,

only age significantly influenced iPFS (HR 1.65, 95% CI 1.05–2.59, $p = 0.03$) (Fig. 3A). Only age (HR 1.74, 95% CI 1.09–2.77, $p = 0.02$) and KPS score (HR 1.88, 95% CI 1.17–3.01, $p = 0.01$) showed significant influence on OS (Fig. 3B). No statistic differences were observed between T stage, N stage, pathological type, extracranial distant metastasis, and number of brain metastases and iPFS or OS in this study ($p > 0.05$).

Subgroup analyses indicated that iPFS of CRT + anlotinib group in patients with ≤ 3 BM (miPFS 12.0 months) exhibited the strongest benefits of the groups (Fig. 4A). Although there was no statistical significance of the effect of CRT + anlotinib on OS of patients with ≤ 3 BM, the p value was 0.051, very close to 0.05 (Fig. 4B). The mOS of CRT + anlotinib in patients with ≤ 3 BM was 37 months, also higher than the other groups. The second highest iPFS and OS values were for the CRT + anlotinib group with > 3 BM (miPFS 7.0 months; mOS 8.5 months). These results suggest that concurrent use of anlotinib and CRT can improve the survival of lung cancer patients with BM, especially for intracranial local control.

Discussion

The mechanism of BM from lung cancer is complex, but is closely related to angiogenesis (39). Angiogenesis in metastasis lesions can develop through multiple signal pathways, and a primary important one is the VEGF pathway (40). There were some studies confirmed that the expression level of VEGF in tumor is negatively related to poor prognosis (41). As a new type of small molecule and multi-targeting TKI, anlotinib mainly acts through the VEGF pathway to exert an anti-tumor role (39, 42). In 2020, oncologists from the European Cancer Research Institute suggested that anlotinib has intracranial activity and could control intracranial tumors. The ALTER0303 study also showed that anlotinib can prolong PFS in lung cancer patients with BM (30). However, no preclinical study has shown that anlotinib can cross the BBB (18). The detailed mechanism of anlotinib action in lung cancer patients with BM should be further studied. The clinical guidelines from the National Comprehensive Cancer Network (NCCN) for patients with BM from lung cancer without EGFR/ALK-TKIs indications are still based on CRT (20, 43). CRT can increase the permeability of the BBB, and increase drug concentration in the central nervous system (33). Anlotinib normalizes the blood vessels in a metastatic tumor, improves the internal microenvironment of the tumor, restores the normal permeability of the blood vessels, and plays a synergistic role with CRT to enhance radiosensitivity and reduce brain edema (8, 41–44). However, further work is required to determine whether the combination of anlotinib and CRT is better than CRT alone for patients with BM from lung cancer who failed to respond to multi-line chemotherapy or were resistant to treatment with EGFR/ALK-TKIs.

In our study, CRT + anlotinib treatment was significantly superior to treatment with CRT alone (miPFS: 9.0 vs 3.0 months, $p = 0.038$). It was not obviously superior for mOS and mePFS ($p > 0.05$), although mOS and mePFS of CRT + anlotinib group were longer than those of the CRT alone group. These results were consistent with those reported for the ALTER0303 study, where anlotinib mainly affected PFS but did not significantly prolong OS in patients with BM. In our study, the mOS of the CRT + anlotinib group (9.0 months) was slightly longer than that of the anlotinib group (8.57 months) in the ALTER0303 trial, and

the msPFS of CRT + anlotinib group (7.0 months) was obviously longer than that of the anlotinib group (4.17 months) in the ALTER0303 trial. The combined results of our study and the results of the ALTER0303 trial suggest that CRT + anlotinib treatment may be superior to CRT alone or anlotinib alone for the control of BM from lung cancer (26, 29). In our study, intracranial control was more effective than systemic control, this was related to CRT main control intracranial lesions. Univariate analysis and multivariate analysis of clinic baseline characteristics and patient survival data showed that age was an independent prognostic factor of iPFS ($p < 0.05$), and age and KPS score were independent prognostic factors of OS ($p < 0.05$). This may be because good physical condition of a patient is related to more effective treatment later. The subgroup analysis of survival data showed that CRT + anlotinib treatment of lung cancer patients with ≤ 3 BM is significantly superior and longer than those of the other treatment groups for iPFS ($p = 0.014$). The treatment pattern and the number of BM for OS showed no significant effects ($p = 0.051$), but the p value was close to 0.05. This suggests that the addition of anlotinib is most beneficial for CRT patients with ≤ 3 BM lesions.

Our study is limited in that it is retrospective, which does not allow randomization of patients and affects homogeneity, thus reducing the level of evidence. Another defect is that the number of cases does not reach the ideal number. Therefore, future studies should utilize an expanded sample size, conduct prospective research, eliminate heterogeneity, and improve the demonstration ability. However, our study can still serve as strategic reference for current clinical treatment of lung cancer patients with BM and non-EGFR/ALK-TKIs indications.

Conclusion

In this study, we analyzed the efficacy of anlotinib (multi-target inhibitors) combined with CRT for patients with BM from advanced SCLC/NSCLC and with non-EGFR/ALK-TKIs indications. The results confirmed that the concurrent use of anlotinib has obvious clinical value to prolong the iPFS of patients with CRT, especially in patients with ≤ 3 BM lesions. Our study has important reference significance for the clinical treatment of BM from lung cancer with non-EGFR/ALK-TKIs indications.

List Of Abbreviations

non-small cell lung cancer: NSCLC

brain metastasis: BM

small cell lung cancer: SCLC

median survival time: mOS

survival time: OS

tyrosine kinase inhibitors: TKIs

anaplastic lymphoma kinase: ALK

epidermal growth factor receptor: EGFR

C-ros oncogene 1-receptor tyrosine kinase: ROS1

complete remission: CR

median progression free survival: mPFS

time to treatment failure: TTF

median duration of response: mDOR

progression free survival: PFS

blood-brain barrier: BBB

hazard ratio: HR

confidence interval: CI

objective response rate: ORR

time to brain progression: TTBP

China Food and Drug Administration: CFDA

cranial radiotherapy: CRT

Karnofsky Performance Status: KPS

Union for International Cancer Control: UICC

American Joint Committee on Cancer: AJCC

computed tomography/magnetic resonance imaging: CT/MRI

whole brain radiotherapy: WBRT

Response Evaluation Criteria in Solid Tumors: RECIST

Overall response rate: ORR

partial response: PR

intracranial progression free survival: iPFS

extracranial progression free survival: ePFS

Systematic progression free survival: sPFS

standard deviation: S.D

median intracranial progression free survival: miPFS

median extracranial progression free survival: mePFS

median systematic progression free survival: msPFS

National Comprehensive Cancer Network: NCCN

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the First Affiliated Hospital of Bengbu Medical College. All processes conformed to the Declaration of Helsinki. For the retrospective manner, written informed consent was not obtained.

Consent for publication

Not applicable.

Availability of data and materials

The data used and/or analyzed in this study is available from the correspondence author based on reasonable request.

Competing interests

No competing interests was declared by the authors.

Funding

The study were supported by National Natural Science Foundation of China (Nos. 81602727 and 81602545), the First Affiliated Hospital of Bengbu Medical College Science Fund for Distinguished Young Scholars (No. 2019byyfyjq04), Bengbu Medical College Science Fund for “excellent young teachers in 512 talent development programme”, Program of Natural Science Foundation of the Anhui Higher Education Institutions (No. KJ2019A0313), Bengbu - Bengbu Medical College Joint Research Project (No. BYLK201810).

Authors' contributions

HJ, ZH and JH designed the study, statistics data and revised MS. HZ, lJ, LH and QJ conducted the study. HZ drawing and writed the draft. CZ, WY, CX and WG assisted with collect the cases and the follow-up data. All authors reviewed and approved the final article.

Acknowledgments

We are grateful to all individuals participated in this study.

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Figures

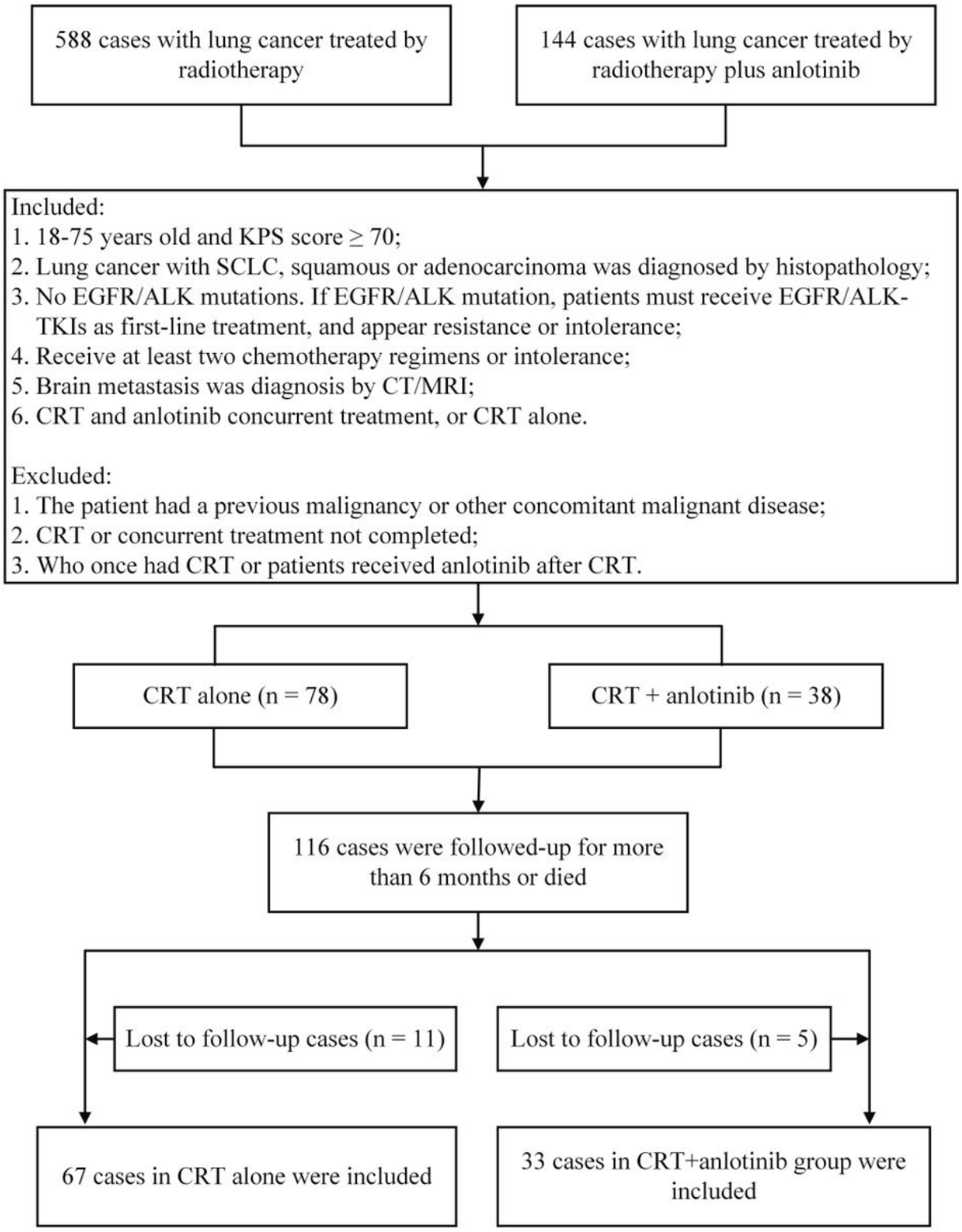

Figure 1

The flow diagram of included patients.

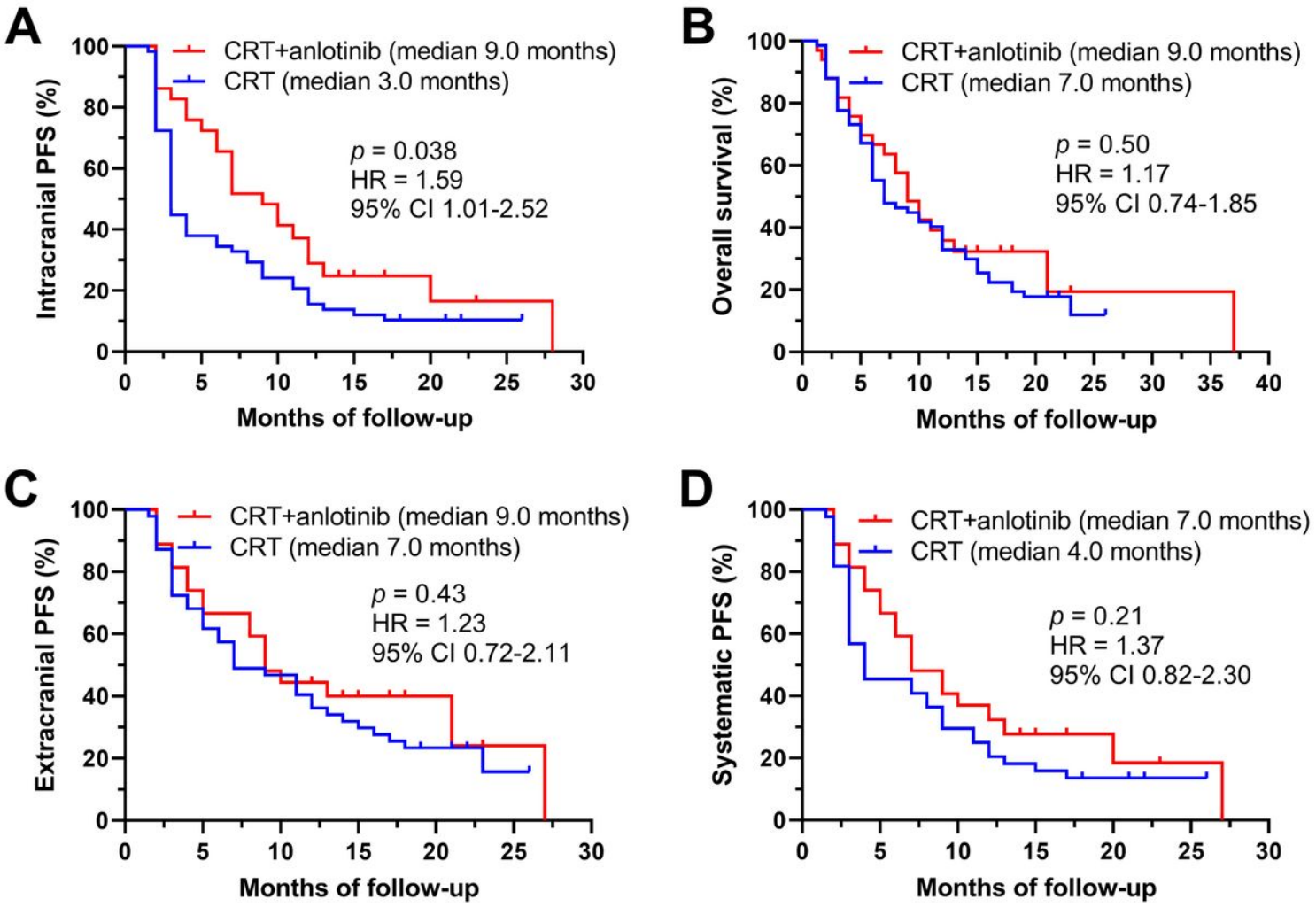

Figure 2

The survival analysis of different treatment groups. (A) iPFS, (B) OS, (C) ePFS and (D) sPFS for patients with BM at baseline.

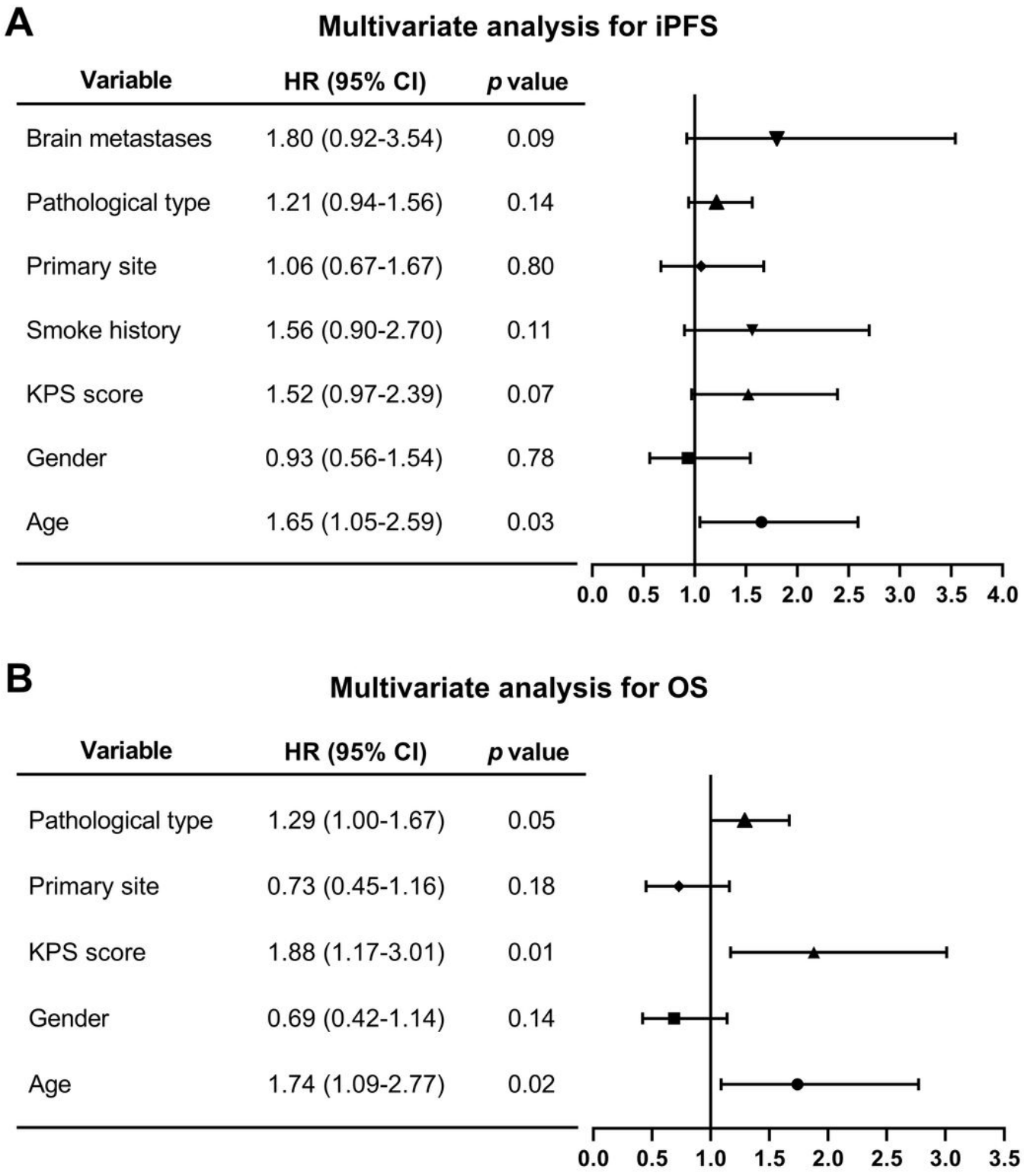

Figure 3

After univariate analysis, the significant variables were chosen for multivariate analysis for iPFS and OS. In multivariate analysis, only age was correlated with iPFS ($p < 0.05$); only age and KPS score were correlated with OS ($p < 0.05$).

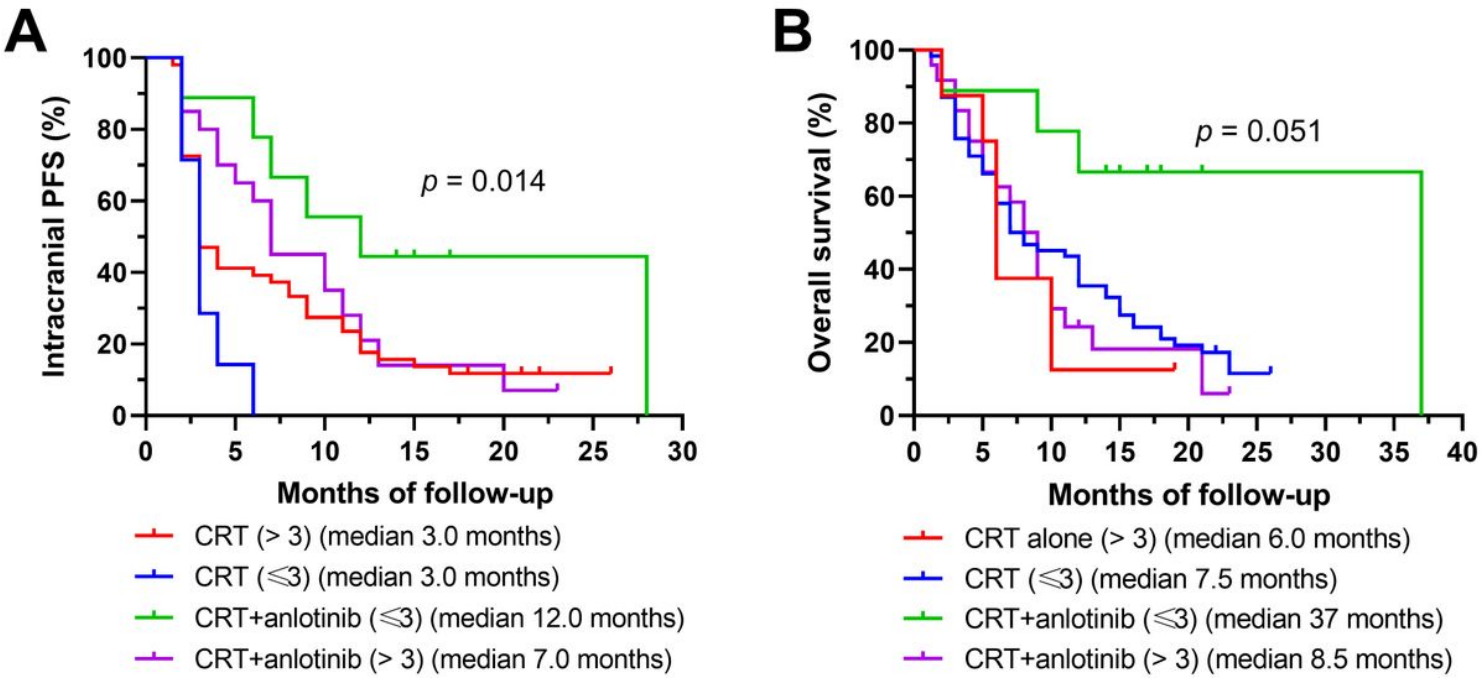

Figure 4

The subgroup analysis of different treatments for patients with different number of BM at baseline. (A) iPFS and (B) OS of CRT alone group and CRT + anlotinib group for patients with different number of BM.