Efficacy of Apatinib+Radiotherapy vs. Radiotherapy alone in Patients with Advanced Multiline Therapy Failure for NSCLC

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Research

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Abstract

Background: Lung cancer is the leading cause of cancer-associated mortality worldwide, and in China. Central nervous system (CNS) metastasis is a prevalent and serious complication. The most common treatment for BM is still radiation therapy (RT). An increasing number of drugs have been shown to have intracranial activity or to sensitize tumours to radiotherapy.

Methods: Our study aims to demonstrate the clinical efficacy of apatinib combined with radiotherapy vs. radiotherapy alone in the treatment of patients with advanced multiline failure for non-small-cell lung cancer with brain metastasis (BM). Eligible patients were divided into two groups: Apatinib + RT group and RT group. In the apatinib + RT group. Intracranial PFS and OS were analysed using the Kaplan-Meier method. Differences between groups were compared by the log-rank test.

Results: The median intracranial PFS for the RT group and Apatinib+RT group was 5.83 months and 11.81 months (p=0.034). The median OS for the RT group and Apatinib+RT group was 9.02 months and 13.62 months (p=0.311). The Apatinib+RT group had a better intracranial PFS, but there were no significant differences between the two arms in OS. The Apatinib+RT group had significantly reduced symptoms caused by BM, mainly headache and vomiting. Most patients tolerated the side effects well.

Conclusion: RT combined with apatinib could help to control intracranial metastases. The Apatinib+RT group had significantly reduced symptoms caused by BM, the safety of the two treatments was similar.

Introduction

Lung cancer is the leading cause of cancer-associated mortality worldwide, and in China, non-small-cell lung cancer (NSCLC) represents approximately 80%-85% of all lung cancers[1, 2]. Central nervous system (CNS) metastasis is a prevalent and serious complication, with negative effects on quality of life and overall survival (OS)[3]. More than 10% of NSCLC patients present with brain metastasis (BM) at their first visit to hospital[4, 5], and approximately 30%-40% of patients with NSCLC develop BM during the course of their disease, with a poor prognosis and a median survival of 1 to 4 months[6]. There are many therapeutic methods for brain metastases, including surgery, chemotherapy, targeted therapy and radiotherapy.

At present, the most common treatment for BM is still radiation therapy (RT), including stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT). WBRT is the most common method for the treatment of brain metastases because it is suitable for most patients and can rapidly relieve cranial nerve symptoms, with an effective rate of 70%[7]. This may be because brain metastases are often accompanied by brain oedema, and radiotherapy usually aggravates the oedema of the normal brain tissue to some extent[7]. Local approaches, such as surgery and SRS, are indicated in solitary or oligometastatic disease. Several chemotherapy drugs in combination with WBRT fail to improve survival because of the impenetrability of the blood-brain barrier (BBB)[8]. Along with chemotherapy, many targeted agents have been developed to improve the typically dismal outcome associated with NSCLC.

Irrespective of the origin and the site of metastases, the growth and survival of tumour cells depend on the establishment of an adequate blood supply[9], which is mainly supported by neo-angiogenesis. Angiogenesis is regulated by several pro- and anti-angiogenetic factors. Among pro-angiogenetic factors, vascular endothelial growth factor (VEGF) is the most extensively studied and stimulates angiogenesis primarily through activation of vascular endothelial growth factor receptor-2 (VEGFR-2)[10], and both are commonly expressed in NSCLC[11]. The primary goal for using anti-angiogenetic therapies is to block the development of malignant neovasculature, to reduce oxygen availability in the tumour and to decrease its growth. Apatinib is an oral TKI with anti-angiogenic properties, and it is currently approved for the treatment of advanced gastric cancer. In addition, many studies have demonstrated that apatinib is effective in the treatment of advanced NSCLC[12], and some studies suggest that apatinib has some synergistic effects with RT[13]. However, the mechanism of action of apatinib combined with RT for better control of BM is not completely clear.

With the development of targeted therapy and immunotherapy, an increasing number of drugs have been shown to have intracranial activity or to sensitize tumours to radiotherapy. Therefore, finding a highly efficient and relatively nontoxic radiosensitization drug is crucial to improving the therapeutic effects of radiotherapy for brain metastases. Our study aims to demonstrate the clinical efficacy of apatinib combined with radiotherapy vs. radiotherapy alone in the treatment of patients with advanced multiline failure for non-small-cell lung cancer with BM.

Methods And Patients

Patients

Consecutive advanced multiline therapy failure in patients with non-small-cell lung cancer with BM at the authors' hospital from January 2016 to August 2020 were retrospectively reviewed. The eligibility criteria for this study were as follows: BM occurred in patients with non-small-cell lung cancer after failure of >2 lines of treatment; patients were historically diagnosed with NSCLC and had confirmed multiple BM by magnetic resonance imaging (MRI); they had >3 measurable BM according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; patients were diagnosed without a mutation in endothelial growth factor (EGFR), anaplastic lymphoma kinase (ALK), repressor of silencing 1 (ROS1), the RET and MET proto-oncogenes etc.; they had no serious dysfunction of major organs (e.g., heart failure or uraemia); and they had adequate haematologic function (absolute neutrophil $\geq 1.5*10^9$/L or platelet count $\geq 100*10^9$/L).

Study design

Eligible patients were divided into two groups: Apatinib + RT group and RT group. In the apatinib + RT group, patients with NSCLC received radiation to BM at the same time that apatinib was used to treat lung cancer or other metastatic lesions. In the RT group, patients only received RT to BM.

All patients were evaluated weekly during RT. Evaluation included a complete history, neurologic examination, blood counts, and biochemistry profile. Evaluation during follow-up was done monthly, including physical examination, neurologic examination, a complete blood count measurement, liver function test, and chest computed tomography (CT) scan. Brain CT with and without contrast, abdominal CT, or bone scan, as well as MRI if necessary, was performed when there were relevant symptoms.

Statistical analyses

Pearson's chi-square or Fisher's exact test was used to compare the baseline characteristics between the apatinib + RT group and RT group. Tumour response was assessed according to RECIST 1.1. OS was defined as the interval from the date of initial BM diagnosis to the date of death. Intracranial progression-free survival (PFS) was defined as the interval between the WBRT initiation and the date of confirming CNS progression or death from CNS progression if death had occurred within 60 days of the last CNS assessment date. If the complete survival time of a patient was impossible to obtain or the disease did not progress, the patient's status was assumed to be the last known survival and/or contact date. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

Intracranial PFS and OS were analysed using the Kaplan-Meier method. Differences between groups were compared by the log-rank test. The Cox proportional hazards model was used for univariate and multivariate analyses to identify the independent prognostic factors for PFS and OS. Statistical analyses were carried out with SPSS 22.0 software. Tests were two-sided. A P-value < 0.05 was considered statistically significant, and robust estimates of the standard error were used in all regression analyses.

Result

Patient characteristics

Among the total of 63 NSCLC patients with advanced BM after undergoing multiline therapy in hospital from January 2016 to August 2020, 31 (49.2%) were in the RT group and 32 (50.8%) were in the Apatinib + RT group. In the RT group, all patients received RT for brain metastases. According to the number of brain metastases, patients with three or fewer brain metastases received SRS, and patients with more than four lesions were treated with WBRT. In the Apatinib + RT group, patients received radiotherapy in the same way as in the RT group, but they also received apatinib (500 mg/d) targeted therapy at the same time, until the disease progressed. When patients developed intolerable side effects, the dose was reduced to 250 mg/d. Patients in the RT group and Apatinib + RT group were well balanced with regard to sex, age, smoking, Karnofsky performance status (KPS), and histologic type (Table 1).

Table 1
Clinical characteristics of patients

Characteristics	All patients N(%)	RT group N(%)	Apatinib + RT group N(%)	p
All patients	63(100)	31(100)	32(100)	
Gender				
Female	21(33.3)	15(48.4)	9(28.1)	
Male	42(66.7)	16(51.6)	23(71.9)	0.098
Age				
< 65	49(77.8)	24(77.4)	25(78.1)	
≥ 65	14(22.2)	7(22.6)	7(21.9)	0.946
Smoking				
Never	30(47.6)	19(61.3)	12(37.5)	
Current/former	33(52.4)	12(38.7)	20(62.5)	0.059
KPS				
< 70	18(28.6)	8(25.8)	10(31.2)	
70–100	45(71.4)	23(74.2)	22(68.8)	0.633
Histology				
Adenocarcinoma	39(61.9)	22(71.0)	17(53.1)	
Non-adenocarcinoma	24(38.1)	9(29.0)	15(46.9)	0.145
Abbreviations: Radiation therapy: RT; Karnofsky Performance Status: KPS;				

Outcomes stratified by group

The median intracranial PFS for the RT group and Apatinib + RT group was 5.83 months (95% CI, 2.99–8.67 months) and 11.81 months (95% CI, 8.31–16.50 months, p = 0.034), respectively, as shown in Fig. 1. The median OS for the RT group and Apatinib + RT group was 9.02 months (95% CI, 6.30–11.70 months) and 13.62 months (95% CI, 8.13–16.80 months, p = 0.311), respectively, as shown in Fig. 2. The Apatinib + RT group had a better intracranial PFS (11.81 vs. 5.83 months, p = 0.034), but there were no significant differences between the two arms in OS (13.62 vs. 9.02 months, p = 0.311). The above results suggest that RT combined with apatinib could help to control intracranial metastases and delay the progression of intracranial metastases, but there was no significant effect on overall survival.

Multivariate analysis and toxicities

Multivariate analysis of intracranial PFS and OS for all NSCLC patients and for the RT group and Apatinib + RT group is shown in Table 2. Among all patients, sex (0.008), KPS (0.006), and smoking (0.008) were associated with OS. Within the Apatinib + RT group, sex (0.012) was associated with intracranial PFS, and sex (0.006) and smoking (0.027) were associated with OS. In the RT group, no significant factors affected the intracranial PFS and OS.

Table 2
Multivariate analysis of factors affecting intracranial PFS and OS in the patients

Factors	Intracranial PFS			OS		
	HR	95%CI	p	HR	95%CI	p
All patients						
Gender	0.393	0.141–1.101	0.076	0.242	0.085–0.692	0.008
Age	1.190	0.545–2.601	0.663	1.260	0.593–2.678	0.548
KPS	1.065	0.979–3.357	0.057	1.950	0.370–5.349	0.006
Smoking	0.430	0.180–1.026	0.057	0.297	0.121–0.728	0.008
Histology	0.875	0.457–1.674	0.686	0.637	0.337–1.205	0.166
RT group						
Gender	0.824	0.221–3.071	0.773	0.464	0.100-2.161	0.328
Age	1.751	0.576–5.317	0.323	1.748	0.529–5.774	0.360
KPS	1.232	0.707–6.050	0.171	1.178	0.901–7.202	0.072
Smoking	0.261	0.063–1.085	0.065	0.242	0.054–1.088	0.064
Histology	0.502	0.183–1.375	0.180	0.675	0.229–1.992	0.476
Apatinib + RT group						
Gender	0.050	0.005–0.519	0.012	0.083	0.014–0.494	0.006
Age	0.895	0.310–2.586	0.838	1.185	0.442–3.176	0.736
KPS	1.587	0.708–3.555	0.262	1.300	0.941–4.622	0.068
Smoking	0.463	0.139–1.536	0.208	0.277	0.089–0.862	0.027
Histology	0.874	0.335–2.281	0.784	0.774	0.321–1.867	0.569

Abbreviations: progression-free survival: PFS; overall survival: OS; hazard ratio: HR; confidence interval: CI; Karnofsky Performance Status: KPS.

In the Apatinib + RT group, the disease control rate (DCR) and object response rate (ORR) were 38.7% (N = 12) and 56.3% (N = 18), respectively. In the RT group, the DCR and ORR were 19.4% (N = 6) and 37.5% (N = 12), respectively. The DCR and ORR were both higher in the Apatinib + RT group than in the RT group, but there were no statistically significant differences between the two groups (p = 0.163 and 0.111).

The Apatinib + RT group had significantly reduced symptoms caused by BM, mainly headache (21.9% and 19.4%) and vomiting (28.1% and 16.1%). Toxicities were reported in all patients in the RT group and Apatinib + RT group, such as headache (54.8% and 28.1%, respectively), nausea (67.7% and 37.5%) and vomiting (61.3% and 34.4%) (Table 3). Myelosuppression was also one of the more common adverse reactions in both groups, manifesting as anaemia (51.6% and 50.0%, respectively), neutropenia (45.2% and 53.1%) and thrombocytopenia (45.2% and 46.9%) in the RT group and Apatinib + RT group. Most patients tolerated the side effects well. Overall, all toxicities were generally brief, reversible, and manageable. They were well tolerated after symptomatic treatments.

Table 3
Toxicity profile for all patients

Side effects	RT gruop (%) (N = 31)		Apatinib + RT group (N = 32)	
	All grades, N. (%)	Grade III/IV, N. (%)	All grades, N. (%)	Grade III/IV, N. (%)
Fatigue	17(54.8)	3(9.7)	18(56.3)	4(12.5)
Anorexia	13(41.9)	2(6.5)	13(40.6)	2(6.3)
Diarrhea	3(9.7)	0(0)	3(9.4)	1(3.1)
Nausea	21(67.7)	5(16.1)	12(37.5)	2(6.3)
Vomiting	19(61.3)	4(12.9)	11(34.4)	1(3.1)
Headache	17(54.8)	3(9.7)	9(28.1)	2(6.3)
Anemia	16(51.6)	1(3.2)	16(50.0)	1(3.1)
Neutropenia	14(45.2)	3(9.7)	17(53.1)	2(6.3)
Thrombocytopenia	14(45.2)	1(3.2)	15(46.9)	2(6.3)
Abbreviations: Radiation therapy: RT.				

Discussion

CNS metastasis is a prevalent and serious complication of NSCLC, with negative effects on quality of life and OS[3]. BM from NSCLC remains a difficult problem in clinical practice. The purpose of this study was to investigate the clinical efficacy of apatinib added to RT in patients with BM after failure of multiline therapy.

Systemic therapies have been deemed ineffective in BM under the hypothesis that the BBB limits their delivery to the brain[8]. The BBB serves as a functional and structural barrier, limiting the passive diffusion of hydrophilic and charged compounds into the brain. Its tight junctions limit the passage of large molecules from the blood to the brain. Lockman et al. suggested that the BBB and the blood-tumour barrier present a significant obstacle in the treatment of brain metastases by limiting drug uptake to subtherapeutic levels[14]. RT is one of the most effective treatments for brain metastases[15–17]. Here, the patients with three or fewer brain metastases received SRS[15], and patients with more than four lesions were treated with WBRT[17]. However, there are few studies on whether VEGFR inhibitor combined with radiotherapy has better clinical efficacy. Our study showed that the Apatinib + RT group had a better intracranial PFS (11.81 vs. 5.83 months, p = 0.034). RT combined with apatinib could help to control intracranial metastases and delay the progression of intracranial metastases, but it did not significantly extend OS. In addition, the safety of the two treatments was similar, and apatinib combined with RT did not increase the toxic effects or side effects compared with RT alone.

Apatinib is an oral TKI with anti-angiogenic properties, and many studies have demonstrated that apatinib was effective in the treatment of advanced non-small-cell lung cancer[12]. Tang J et al. demonstrated that apatinib combined with systemic cytotoxic chemotherapy had clinical efficacy in patients with disease-refractory metastatic NSCLC and provides evidence for further studies investigating apatinib-based combination regimens. Xu J et al. pointed out that apatinib was effective and well tolerated in patients with advanced NSCLC and had a good clinical effect in the treatment of brain metastases[18]. In our study, when using apatinib for advanced NSCLC, we found that apatinib combined with RT for BM prolonged the intracranial PFS and significantly reduced the symptoms caused by BM, such as intracranial oedema, severe headache, nausea and vomiting. Apatinib, a first-generation oral antiangiogenic drug, selectively inhibits VEGFR-2, leading to decreased vascular endothelial cell proliferation and migration and tumour microvascular density[19]. Apatinib targets VEGFR-2, RET, platelet-derived growth factor-β (PDGFR-β), v-Src sarcoma viral oncogene homologue (c-Src), and stem cell factor receptor (c-Kit) [20, 21]. Apatinib can effectively inhibit the proliferation, migration, and tube formation of human umbilical vein endothelial cells, can block the budding of rat aortic rings and can inhibit the growth of several established human tumour xenograft models with little toxicity[19]. Previous studies reported that apatinib could reverse ATP-binding cassette transporter (ABC) subfamily B member 1 (ABCB1/MDR1/P-glycoprotein)- and ABC subfamily G member 2 (ABCG2/BCRP)-mediated multidrug resistance, which suggested the potential usefulness of combining apatinib with other chemotherapy drugs[20, 22].

Some studies suggest that apatinib has some synergistic effects with RT[13]. The mechanism through which apatinib combined with RT achieved better control of BM was not completely clear. It may be related to the following points. First, some studies suggest that VEGFR drugs can interfere with tumour metastasis pathways. Angiogenesis, which is mainly mediated by the VEGF pathway, is crucial for tumour survival, growth and invasion both in primary and metastatic brain lesions. As a primary driver of angiogenesis, VEGF is secreted by tumour cells in response to decreased vessel density and hypoxia. VEGF is highly expressed in breast, colorectal, and non-small-cell lung carcinomas[23–25]. Therefore,

VEGFR inhibitors (such as apatinib) downregulate this pathway and reduce the number of tumour cells entering the brain, which may enhance the sensitivity to RT. Furthermore, several studies have shown that VEGFR promotes the normalization of blood vessels, which can improve the delivery of drugs to the brain and play a role in RT sensitization[26–27]. Tong R.T. et al.[26] indicated that inhibition of VEGF signalling by a monoclonal antibody that binds to the VEGF ligand, preventing receptor phosphorylation, has been shown to improve drug delivery through vascular normalization. Jain R.K. et al. [27] also found that VEGFR inhibition reduces tumour angiogenesis. In addition, a rationale for the use of VEGFR inhibition in BM was the concept of vascular normalization[28, 29].

Other studies have suggested that apatinib can penetrate the blood-brain barrier and play a synergistic role in radiotherapy[30–35]. BM can induce neovascularization, with leaky vessels, but can also co-opt existing brain vasculature, with a near-normal BBB, particularly in a tumour-infiltrated brain around tumour (BAT) [35]. Clinically, brain metastases can show highly variable permeability, and this has been recapitulated in haematogenous metastases in animal models[30]. Blocking VEGF signalling in systemic tumours produces a morphologically and functionally normalized vasculature by pruning immature vessels and improving perivascular cell and basement membrane coverage and function[31]. It was hypothesized that normalization of existing tumour vasculature will improve chemotherapy delivery and chemotherapy/radiotherapy efficacy. All of these mechanisms imply that an antiangiogenic agent would always augment the response to radiation or chemotherapy.

There are some limitations to this study. First, this study was done retrospectively at a single institution, which may have led to inherent bias. Second, the number of patients enrolled in this study may be insufficient. Factors that may impact the outcomes could not be fully evaluated. The follow-up period may not be long enough. External validation should be done using another large database to further evaluate the value RT combined with apatinib for patients with BM after failure of multiline therapy.

Conclusions

RT combined with apatinib could help to control intracranial metastases and delay the progression of intracranial metastases, but there was no significant effect on overall survival. The Apatinib + RT group had significantly reduced symptoms caused by BM, mainly headache (21.9% and 19.4%) and vomiting (28.1% and 16.1%). In addition, the safety of the two treatments was similar, and apatinib combined with RT did not increase the toxic effects or side effects compared with RT alone.

Abbreviations

Central nervous system :CNS; brain metastasis: BM; radiation therapy: RT; non-small-cell lung cancer: NSCLC; progression-free survival: PFS; overall survival: OS; stereotactic radiosurgery: SRS; whole-brain radiotherapy: WBRT; brain blood barrier: BBB; vascular endothelial growth factor: VEGF; vascular endothelial growth factor receptor-2: VEGFR-2; magnetic resonance imaging: MRI; Response Evaluation Criteria in Solid Tumors: RECIST; endothelial growth factor: EGFR; anaplasticlymphoma kinase: ALK,

repressor of silencing 1: ROS1; chest computed tomography: CT; National Cancer Institute Common Terminology Criteria for Adverse Events: NCI-CTCAE; Karnofsky Performance Status: KPS; disease control rate: DCR; object response rate: ORR; growth factor-β: PDGFR-β; v-Src sarcoma viral oncogene homolog: c-Src; stem cell factor receptor: c-Kit; ATP-binding cassette transporter: ABC; subfamily B member 1: ABCB1/MDR1/P-glycoprotein; ABC subfamily G member 2: ABCG2/BCRP; brain around tumor: BAT.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

HP, CX and XC acquired and analyzed the data, XC and SC drafted the manuscript. YL and XW made contributions to follow up the patients. All authors read and approved the final manuscript.

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Figures

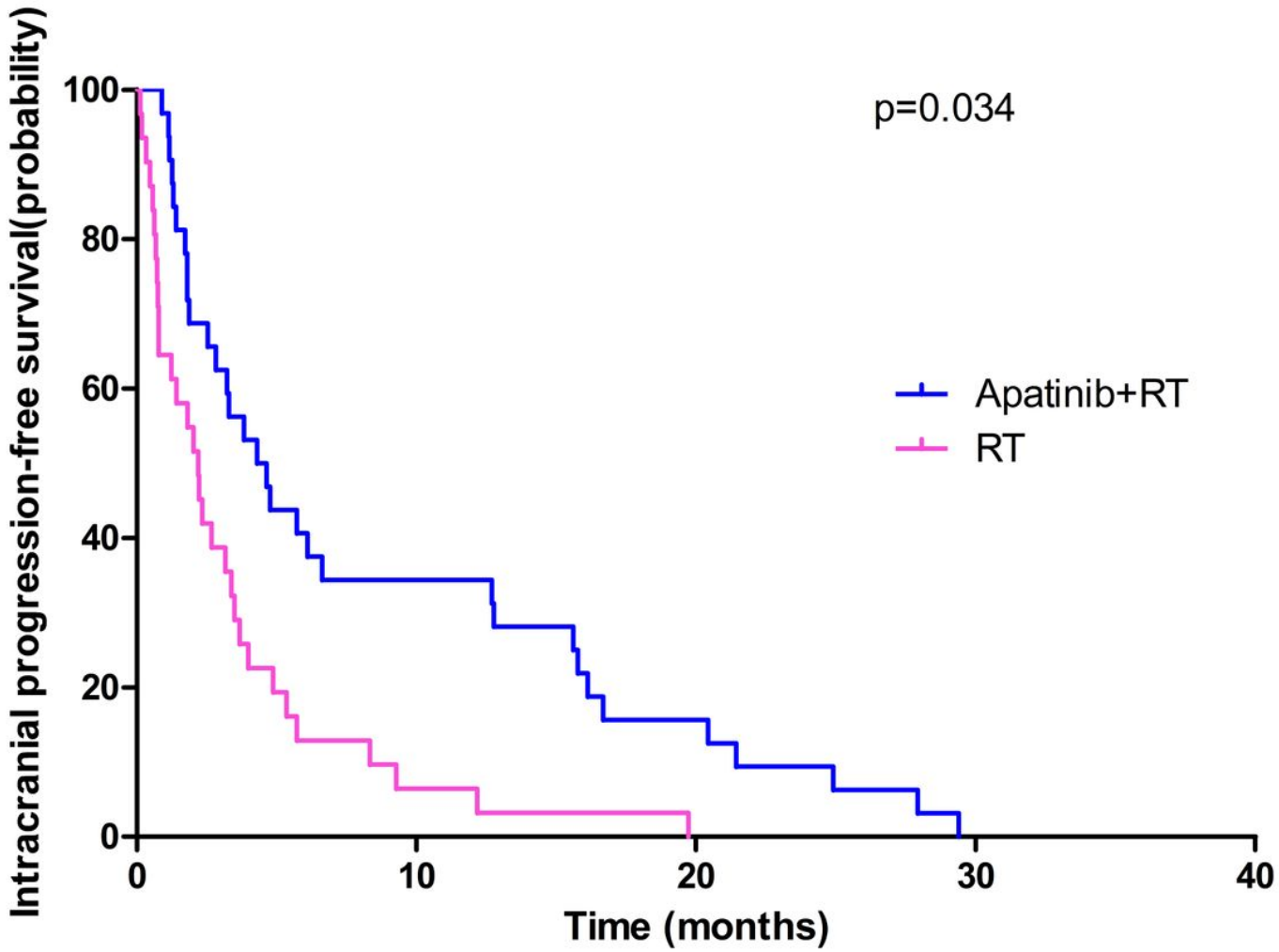

Figure 1

Intracranial Progression-free Survival of Patients between RT group and Apatinib+RT group.

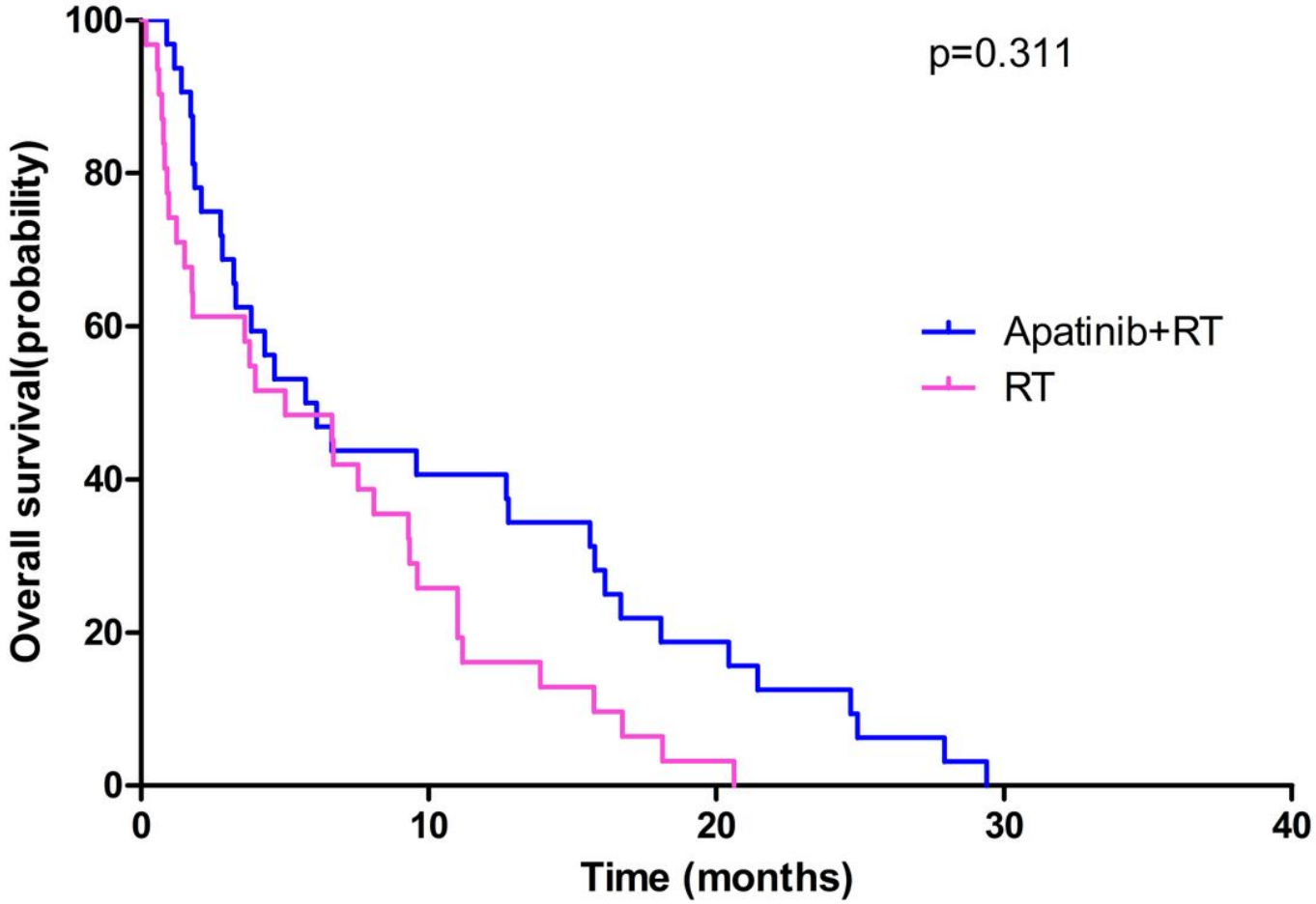

Figure 2

Overall Survival of Patients between RT group and Apatinib+RT group.