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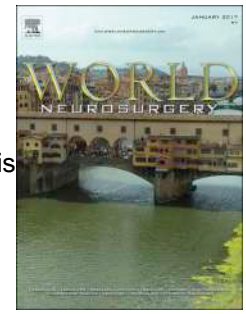

Hypofractionated radiosurgery plus bevacizumab for locally recurrent brain metastasis with previously high-dose irradiation

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PII: S1878-8750(19)32400-3

DOI: https://doi.org/10.1016/j.wneu.2019.08.233

Reference: WNEU 13269

To appear in: *World Neurosurgery*

Received Date: 1 July 2019

Revised Date: 28 August 2019

Accepted Date: 29 August 2019

Please cite this article as: Guan Y, Wang C, Zhu H, Li J, Xu W, Sun L, Pan L, Dai J, Wang Y, Wang E, Wang X, Hypofractionated radiosurgery plus bevacizumab for locally recurrent brain metastasis with previously high-dose irradiation, *World Neurosurgery* (2019), doi: https://doi.org/10.1016/j.wneu.2019.08.233.

Title Page

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The authors declare no conflict of interest. I, Xin Wang, certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium

Key Words: SRS; Bevacizumab; Recurrent Brain Metastasis

Short Title: SRS with bevacizumab for irradiated recurrent BM

Hypofractionated radiosurgery plus bevacizumab for locally recurrent brain metastasis with previously high dose irradiation

Background

Selection of the appropriate treatment for recurrent brain metastasis remains uncertain. Recent studies have demonstrated a significant response rate and acceptable toxicity using fractionated stereotactic radiosurgery (FSRS) in locally recurrent large brain metastasis patients. The purpose of this research was to evaluate the efficacy and toxicity of FSRS with bevacizumab as a new salvage treatment for locally recurrent brain metastases with high dose irradiation previously.

Materials

Patients with recurrent brain metastasis previously irradiated were enrolled. The salvage FSRS ranged from 9.5 to 29 Gy (2-5 fx) with 62–75% isodose line by CyberKnife according to the brain tumor volume, site, and previous dose. Bevacizumab was prescribed for four cycles (5 mg/kg, q3w). The primary objective of this study was to identify the overall survival after salvage treatment. Secondary objectives included the clinical response (KPS), imaging response (MRI) and treatment-related adverse events.

Results

From December 2009 to October 2016, 24 patients were enrolled. The 1-year overall survival (OS) after salvage SRS was 87.5%. Twenty-three (96%) patients had a positive imaging response with a T2 volume reduction range of 6 to 22 cm^3(median 14 cm^3, p= 0.032, paired t-test). Significant clinical improvement was achieved ($p<0.05$, best KPS, paired t-test). Grade 1/2 fatigue was observed in 8 (33%) patients. Grade 3 fatigue and headache occurred in 1 patient.

Conclusions

Salvage FSRS with adjuvant bevacizumab treatment showed favorable clinical and radiologic control as a salvage treatment regimen. The diagnosis of RN and LR after salvage FSRS merit further study.

Key Words: SRS; Bevacizumab; Recurrent Brain Metastasis

Introduction

In patients with malignancies, brain metastases occur in 10-30% in adults. Due to improved systemic therapy and more prolonged survival, the incidence of brain metastases may increase. Patients with recurrent brain metastases have an inferior prognosis and response rate to salvage treatment options due to a lack of clinical efficacy. There are no standard approaches for patients with recurrent brain metastases.

FSRS allows a precise treatment of the tumor while simultaneously limiting the dose to the surrounding previously irradiated normal tissue. Some prospective and retrospective studies have shown that FSRS can be well-tolerated, and the efficacy appears to be promising in central nervous system tumors. [1-2] Recently, researchers have evaluated Fractionated Stereotactic Radiosurgery as a treatment option for recurrent glioblastoma and large brain metastases due to high “therapeutic ratio” (ratio of tumor cell killing to normal tissue toxicity) [3-4].

Bevacizumab (Avastin, Genentech, San Francisco, CA, USA) is a humanized murine monoclonal antibody that is used directly against VEGF. The use of bevacizumab has resulted in a significant improvement of outcomes in several diseases such as lung, kidney, colorectal and breast cancer and high-grade malignant gliomas [5]. Previously, VEGF was referred to as a “vascular permeability factor” with the potential to cause capillary endothelial leakage in cerebral tissues.

Prospective clinical trials have reported the safety and efficacy of concurrent stereotactic radiosurgery with bevacizumab for the treatment of recurrent high-grade gliomas. Recurrent brain metastatic lesions with high dose irradiation previously are quite often accompanied by perilesional edema, which causes neurological symptoms. Corticosteroids are used to alleviate brain edema and reduce the mass effect, but they are associated with several debilitating long-term side effects.

Thus, the goal of intervention in recurrent brain metastasis, especially those with high dose irradiation previously is to improve quality of life by controlling the local disease while minimizing the risk of significant toxicity. For this reason, we hypothesized that FSRS combined with prophylactic treatment of low-dose bevacizumab would provide the most effective approach in the management of recurrent brain metastases while minimizing acute toxicity [6]. The purpose of this research was to evaluate the efficacy and toxicity of FSRS combined with the early use of low dose bevacizumab as a new salvage treatment scheme for locally recurrent brain metastases which were treated previously with high-dose irradiation.

Materials and Methods

Eligibility Criteria

This prospective study was performed according to the Declaration of Helsinki. The protocol was reviewed and approved by the local ethical institutional review board. All patients provided written informed consent.

The eligibility criteria were as follows: (1) locally recurrent intracranial metastasis previously treated with SRS or WBRT plus SRS; (2) lesions diagnosed based on the clinical course, serial magnetic resonance (MR) imaging features, and PET when available; (3) lesions causing progressive neurological deterioration and refractory to conservative management; (4) 6 months after previous irradiation; (5) >18 years of age; (6) patient refused surgery due to physical conditions and the risk of surgery; (7) no contraindications for bevacizumab; (8) KPS > 40.

Exclusion criteria were as follows: (1) hypertension; (2) cerebrovascular or cardiovascular disease; (3) nonhealing ulcers or wounds; (4) proteinuria, renal dysfunction.

Baseline Evaluation and Treatment

The following data were recorded: age, sex, primary cancer, number of brain metastases, interval from initial radiotherapy to salvage SRS, volume of recurrent lesion, previous radiation dose, and imaging, and baseline Karnofsky performance score. Blood routine, hepatorenal function, and medical records were also analyzed. BED was calculated using the LQ model with an alpha/beta ratio of 10.

FSRS was performed using the CyberKnife Radiosurgical System (Accuray, Sunnyvale, CA, USA). Thin-slice (1.25 mm) computed tomography (CT, GE Light speed Ultra 16 Slice, USA) with iohexol contrast (Omnipaque, Amersham, Norway) and fat-suppressed thin-slice (2 mm) MRI were used to scan the region of interest. CT and MRI scans were then fused using the CyberKnife planning system to identify the target. Radiation oncologists, neurosurgeons, and radiation physicists participated in tumor delineation, planning, and dose selection. The gross tumor volume was defined by an enhanced tumor on fused images. The radiation dose was determined according to the brain tumor volume, site and previous irradiation dose, ranging from 9.5 to 29 Gy in two to five sessions, prescribed to the 62–75% isodose line. The dose was prescribed to cover the gross tumor volume [1]. Bevacizumab (5 mg/kg, every three weeks) was prescribed to all patients after completion of the CyberKnife treatment. Patients continued to receive 4 courses of bevacizumab [6-7]. Systemic therapy was chosen by the physician because no standard second-line treatment approach has been accepted for patients with recurrent brain metastases. Also, the regimens need to be individualized according to the tumor mutation status and histology.

Assessment and Toxicity

After treatment, all patients underwent clinical and radiological follow-up every three months. The radiological examination included MRI and other necessary examinations. KPS after treatment, adverse event occurrence, and associated clinical outcomes were recorded. Toxicity was assessed using the CTCAE 4.0 (Common Terminology Criteria for Adverse Events).

Endpoints and Statistics

The primary objective of this study was to identify the overall survival after salvage treatment. Secondary objectives included the clinical response (KPS), imaging response and treatment-related adverse events.

All characteristics were described by the frequency of categorical variables, by means and standard deviations for normal distributional continuous data, and by the median for nonmoral distributional continuous data.

Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test.

Univariate and multivariate analysis was performed using a Cox proportional hazards regression model.

RESULTS

Patient Characteristics

Between December 2009 and October 2016, 24 patients were enrolled in this prospective study (Figure 1). The patient characteristics are listed in Table 1; 12 of the patients were male and 12 females, the median age was 58 years (range from 36 to 73 years). All patients enrolled in this study were diagnosed based on the clinical course, serial magnetic resonance imaging features, and PET when available.

Twelve (50%) of the patients were diagnosed with non-small cell lung cancer (NSCLC), four (17%) with digestive system cancer, four (17%) with breast cancer, three (13%) with small-cell carcinoma (SCLC) and one

(3%) with adenoid cystic carcinoma. The median tumor volume was 17.3 cm^3 (range from 3.7 cm^3 to 76.2 cm^3). Eight (33%) patients had tumor volume smaller than 10 cm^3 and 16 (67%) larger than 10 cm^3. The median KPS was 60 (range from 50 to 90).

Nine (37.5%) patients received WBRT followed by SRS, and 15 (62.5%) underwent SRS previously. The previous median BED was 60 (Figure 2, range from 41.6 to 81.6).

Treatment Outcomes and Long-term Prognosis

With a median follow-up of 13.5 months (range from 8 to 29 months), the median overall survival after salvage treatment was 18 months (Figure 3).

Fourteen patients died, 5 died of the primary tumor, 3 of intracranial metastasis, 2 of pneumonia, 1 of heart disease and 3 of other reasons. The positive imaging response was defined as both the MRI T1 and T2 high-intensity volume reduction at the first follow-up after treatment. Twenty-three (96%) patients had a positive imaging response within a T2 volume range of 6 to 22 cm^3 (median 14 cm^3, $p = 0.032$, paired *t*-test). One patient showed no significant lesion volume reduction.

No patient experienced a decrease of KPS after treatment. Six patients (25%) had the best KPS after treatment range from 50 to 70, and 18 (75%) of the best KPS were greater than 80 (Table 2). Significant neurological improvement was achieved (Best KPS, paired *t*-test $p<0.05$, Figure 4).

Compliance and Toxicities

FSRS with bevacizumab was completed at the full dose among all patients as planned. Fatigue and headache were the main toxicities. Grade 3 fatigue and headache occurred in 1 patient. No grade 4 toxicity was observed.

Grade 1/2 fatigue was observed in 8 (33%) patients. Grade 1 or 2 toxicities included headache, hypertension, and nausea (Table 3).

Univariate and Multivariate Analysis of OS after salvage treatment

All potential prognostic factors, including demographic and clinical features, were evaluated using the Kaplan-Meier and Cox model in univariate and multivariate analysis. No prognostic factors were found to be associated with OS after salvage treatment.

Discussion

In patients with malignancies, brain metastases occur in 10-30% in adults, and up to 50% of surviving patients with brain metastases will develop progression of previously treated or new lesions [7]. For recurrent disease, treatment with salvage SRS, WBRT, surgery or systemic therapy can be administered, depending on the extent and location of the disease and the overall condition of the patient. Determination of the best option for locally recurrent brain metastases remains unknown. However, due to the poor performance status and tumor location, most patients with local recurrent brain metastases are not eligible for surgery. In recurrent lesions previously treated with radiotherapy, radiation necrosis (RN) is a severe complication associated with salvage re-irradiation [8]. CyberKnife is a radiosurgery system that allows highly conformal image-guided radiotherapy and shows a promising local control rate for central nervous system tumors [9]. Bevacizumab was found to be effective in controlling extensive edema caused by BM and RN according to our experience. In this study, the results demonstrated that FSRS combined with low-dose bevacizumab achieved promising radiological and clinical outcomes for locally recurrent BM patients irradiated with high dose previously.

The Effectiveness of Bevacizumab

The effectiveness of bevacizumab for the treatment of RN has been demonstrated in several retrospective case series and two randomized trials [10]. In an American double-blind trial, 14 cerebral RN patients were randomly signed to bevacizumab (7.5 mg/kg every three weeks for four courses) or the placebo group. Patients enrolled in the bevacizumab group showed improvements in MRI findings and neurologic symptoms. No responses were observed in the placebo group, but the patients had a response after crossover treatment [6]. The other randomized open-label Chinese trial enrolled 112 temporal lobe radiation necrosis patients after

nasopharyngeal cancer treatment, comparing bevacizumab (5 mg/kg every two weeks for four courses) to glucocorticoids. The bevacizumab group had a radiographic response rate of 66% compared with 32% in the control group. The clinical improvement at 60 days was higher in the bevacizumab group (62% versus 43%) with a similar recurrence rate (29% versus 27%). Additionally, in a retrospective study reported by our center, bevacizumab was found to be useful in preventing RN after SRS [7]. Furthermore, considering the anti-tumor effect of bevacizumab, this agent was administered in the regimen applied in this study.

Reirradiation for Recurrent Brain Metastasis

There is limited data published on recurrent BM reirradiation. Surgical resection can be performed to achieve symptom relief and confirm the histological diagnosis. However, surgery is limited to treat lesions in deep locations or functional areas. Age, life expectancy and systemic disease should also be taken into consideration [11]. In several studies, the benefit of salvage SRS for recurrent BM patients has been discussed [3, 12-13]. In these studies, the dose and fractions were performed according to prior therapies, tumor site, and lesion size. Salvage WBRT may provide benefit for patients who are not eligible for surgery or SRS. Reirradiation may result in delayed toxicity by exceeding the tolerance of the brain. Although the risk of RN is higher in previously irradiated patients, short-term symptom palliation in patients with a limited life expectancy and radiation-related delayed toxicity should be weighed.

The safety and effectiveness of salvage reirradiation had been confirmed in several retrospective studies [14-17]. Minniti et al. reported a 1-year OS of 37% after salvage FSRS with 3 fractions of 7-8 Gy [14]. Another salvage SRS study reported by Rana et al. showed a 1-year OS of 90.6% [15]. For FSRS, the anticipated biologic

benefit of fractionation is to minimize damage to normal neural structures while suppressing the growth of the neoplasm. It resulted in the highest "therapeutic ratio". Besides, bevacizumab can contribute to symptom improvement by controlling RN and brain enema. A Japanese study using adjuvant bevacizumab [9], Yomo et al. reported that the application of salvage SRS with adjuvant bevacizumab in 5 patients, which achieved good tumor control and symptom relief. Thus, FSRS with bevacizumab seems to be a promising salvage regimen.

This is the first study to combine adjuvant low-dose bevacizumab and salvage FSRS for recurrent BM treated with high dose irradiation previously. The tumor volume in our study (median GTV of 17.3 cm^3) was much larger than in previous studies (smaller than 5 cm^3, only one study had a median GTV volume of 12.3 cm^3 [14]). Consistent with previous studies, patients who underwent this new therapeutic regimen achieved both clinical and radiological improvement (Figure 5), and the 1-year OS after salvage treatment was 87.5%. This OS is longer than previously reported. The addition of adjuvant bevacizumab to FSRS may have contributed to the better survival due to its role in tumor control and reducing edema. Thus, the findings of this study provide a safe and effective regimen for locally recurrent large brain metastases.

Limitations

Our study demonstrates that lose-dose bevacizumab can be safely administered with FSRS and provides a feasible method for locally recurrent brain metastases. Fatigue was the most frequent (33%) grade 1-2 toxicity, followed by headache (25%) and hypertension (13%). Only one patient had a grade 3 headache and fatigue, the patient had undergone WBRT plus SRS and more than one line of systematic therapy. No grade 4 toxicity was recorded.

Although our results are gratifying, we cannot overemphasize the preliminary nature of these findings. In addition to the small population size of our data, there are other limitations to this report. First, the optimal number of courses of bevacizumab has not been defined, though the median number is 4, according to most studies [18-19]. Thus, in this study, we administered 4 courses of bevacizumab. This problem should also be addressed considering the balance between medical costs and clinical efficacy. Next, for previously irradiated BM patients, the differentiation diagnosis of local recurrence (LR) and RN is important for the decision regarding salvage treatment. Both the previous studies and our experience encountered the same dilemma that for recurrent brain metastases after salvage reirradiation, the diagnosis of LR and RN was extremely difficult [9]. Despite many diagnostic methods, including MR-based spectroscopy, perfusion [20-21] and methionine positron emission tomography [22], diagnosis remains difficult due to the overlapping radiographic appearance. Such is why we excluded progression-free survival and local control as endpoints.

Conclusions

Salvage FSRS with early use of low dose adjuvant bevacizumab treatment showed favorable clinical and radiologic control with manageable toxicity for locally recurrent brain metastasis patients who underwent high dose irradiation previously. The diagnosis of RN and LR after salvage FSRS merit further study.

Acknowledgements

Yun Guan, Chaozhuang Wang, Huaguang Zhu, and Xin Wang contributed equally to this study and are responsible for the conception design, analysis, and interpretation of data.

Huaguangzhu, Chaozhuang Wang, Jing Li and Wenqian Xu, and Lei Sun are responsible for the acquisition of data.

Li Pan, Jiazhong Dai, and Yang Wang are responsible for article revising.

Enmin wang and Xin wang approved the final version to be published.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Figure legends

Figure 1. CONSORT diagram of this trial.

Figure 2. Radar chart of initial and salvage BED in Gy (Cases are numbered circumferentially and BEDs are plotted from the center).

Figure 3. Overall Survival After Treatment.

Figure 4. Paired t-test of best KPS before and after treatment.

Figure 5. Magnetic resonance imaging (MRI) of the patients. (A) Gadolinium-enhanced MRI study before the initial irradiation. (B) Follow-up at 3 months after the initial treatment. (C) Gadolinium-enhanced MRI study before the salvage FSRS treatment with adjuvant use of bevacizumab. (D) Follow-up at 3 months after the salvage treatment.

Table 1. Baseline Characteristics of Patients (n=24)

	N	%
Gender		
Male	12	50
Female	12	50
Age, years		
<60	14	58

>=55	10	42
Primary tumor		
NSCLC	12	50
SCLC	3	13
Digesting system	4	17
Breast	4	17
Adenoid cystic carcinoma	1	3
Intervention before salvage SRS		
SRS	15	63
WBRT+SRS	9	37
Tumor volume (cm^3)		
<=10	8	33
> 10	16	67
Time to recurrence after initial therapy (months)		
<= 12	8	33
12 - 24	9	38
> 24	7	29
Initial BED*		
<=60	15	63
> 60	9	37
KPS†		
50 - 70	16	67
>= 80	8	33
Total	24	100

* Biological effective dose;
† Karnofsky performance scale.

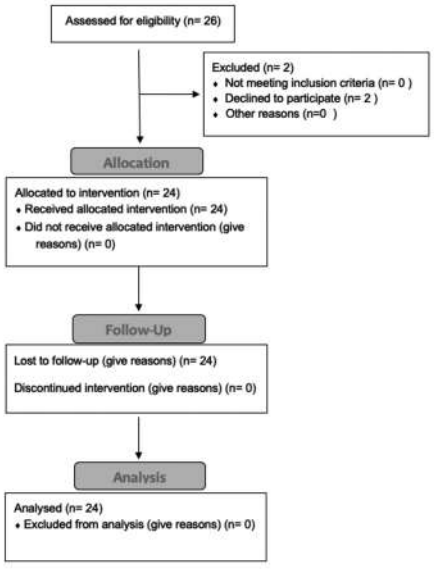
Table 2. Treatment Outcomes

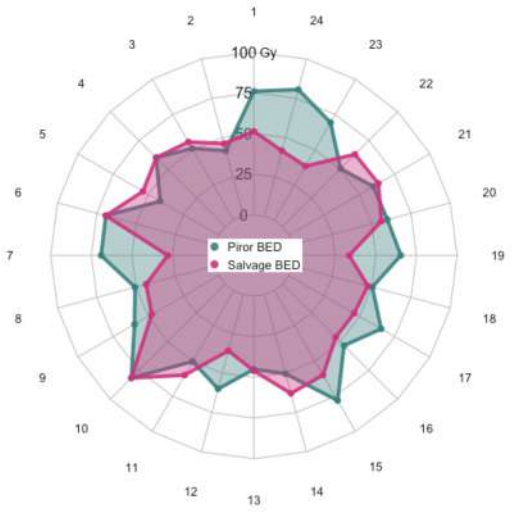
	N	%
Imaging Response		
Positive‡	23	96
Negative	1	4
Clinical Response (Best KPS)		
50 – 70	6	25
>= 80	18	75
Total	24	100%

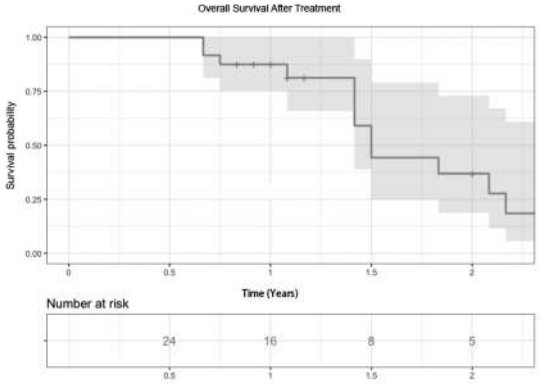
‡Positive: Both T1 and T2 high intensify volume reduce after treatment.

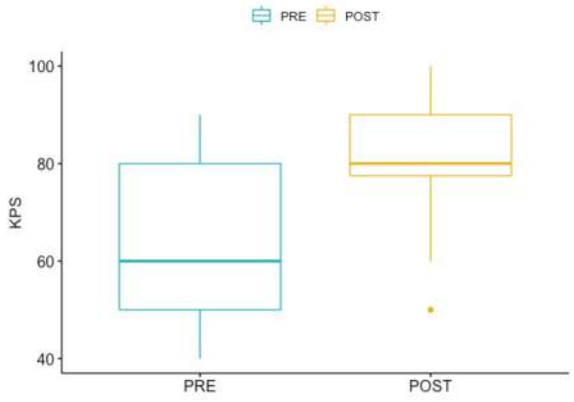
Table 3. Treatment-related adverse events

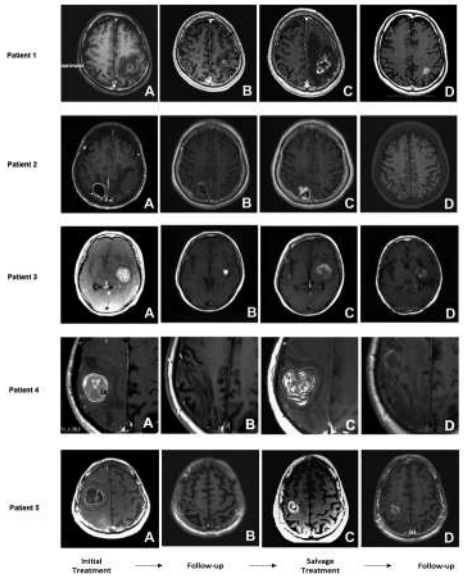
Adverse Events	Grade 1-2		Grade 3	
	N	%	N	%
Fatigue	8	33	1	4
Headache	6	25	1	4
Hypertension	3	13	0	0
Nausea and vomiting	2	8	0	0











Abbreviations list

Abbreviations	Meanings
BED	Biologically Effective Dose
CTCAE	Common Terminology Criteria for Adverse Events
FSRS	Fractionated Stereotactic Radiosurgery
KPS	Karnofsky Performance
LR	Local Recurrence
RN	Radiation Necrosis
MRI	Magnetic Resonance Imgaing
NSCLC	Non-small Cell Lung Cancer
OS	Overall Survival