Linac-Based Fractionated Stereotactic Radiotherapy with a Micro-Multileaf Collimator for Brainstem Metastasis

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■ BACKGROUND: **To assess the neuroimaging and clinical outcomes in patients with brainstem metastasis (BSM) treated with linac-based fractionated stereotactic radiotherapy (fSRT) with a micro-multileaf collimator.**

■ METHODS: **Between May 2007 and January 2017, 24 patients (15 male and 9 female) with BSM (25 lesions: midbrain, 10; pons, 13; and medulla oblongata, 2) were consecutively treated with linac-based fSRT. BSM originated from the lung (n = 18, 75.0%), colon (n = 3, 12.5%), and breast (n = 3, 12.5%). The median patient age was 67.0 (range: 42–80) years. Recursive partition analysis classified 2 patients as class I, 17 as class II, and 5 as class III. Overall survival was calculated using the Kaplan–Meier method.**

■ RESULTS: **Tumor volume ranged from 0.01 to 7.49 cm^3 (median: 0.233 cm^3), and patients were treated with a dose of 24–40 Gy in 7–13 fractions. The median OS was 9 months after fSRT (95% confidence interval 4.104–13.896). Large tumor volume, presence of brainstem-related symptoms, poor pretreatment Karnofsky performance status, and recursive partition analysis class III were significantly associated with low overall survival. Tumor volume decreased in 18 metastatic lesions, remained stable in 6, and increased in 1. No patient exhibited permanent radiation injury. Grade 2 nausea and vomiting according to the Common Terminology Criteria for Adverse Events 4.0 occurred in 1 patient who received corticosteroids.**

■ CONCLUSIONS: **Linac-based fSRT with a micro-multileaf collimator delivered in the doses of 24–40 Gy in 7–13 fractions is a safe and effective local therapy for patients with BSM.**

INTRODUCTION

Brain metastases are one of the most common brain tumors and are observed in 12%–24% of patients with cancer who undergo autopsy.[1] Most of the brain metastases are located in the cerebrum and cerebellum, and brainstem metastasis (BSM) accounts for only 3%–5% of all brain metastases.[2] The prognosis of BSM is highly unfavorable, with patients having a survival range of 1–6 months.[3] Surgical treatment for BSM is contraindicated due to poor prognosis and risk of development of a new neurologic deficit in patients.

BSM lesions usually exhibit poor response to systemic chemotherapy, but stereotactic radiosurgery (SRS) has become an effective alternative treatment option for BSMs. Several reports have described the use of gamma knife (GK) SRS, CyberKnife (CK) SRS, or linac-based SRS for BSM treatment. Because the brainstem is considered to be a neurologic organ at risk, these treatments should be performed carefully to avoid any adverse

Key words
- Brainstem metastasis
- Fractionated radiotherapy
- Novalis
- Stereotactic radiotherapy

Abbreviations and Acronyms
BSM: Brainstem metastasis
CK: Cyber Knife
EQD2: Equivalent dose of 2Gy
fSRT: Fractionated stereotactic radiotherapy
GK: Gamma Knife
GTV: Gross tumor volume
IMRT: Intensity-modulated radiotherapy
MRI: Magnetic resonance imaging
OS: Overall survival
RPA: Recursive partition analysis
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiation therapy

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Table 1. Characteristics of All Patients with Brainstem Metastasis

Characteristic	Value
Sex, no. of patients	24
Male	15
Female	9
Age, years	
Median	67
Range	42–80
Location of lesion, no. lesions	
Midbrain	10
Pons	13
Medulla oblongata	2
Brain metastases, no. of patients	
Single brainstem	5
Multiple brain metastases	19
KPS score, no. of patients	
Median	80
Range	40–100
RPA class, no. of patients	
I	2
II	17
III	5
Neurologic deficits related to brainstem metastasis	
Yes	6
No	19
Control of primary cancer	
Yes	10
No	14
Extracranial metastasis	
Yes	17
No	7
Primary cancer, no. of patients	
Lung	18
Colon	3
Breast	3
WBRT	
Before	2
After	5
Tumor volume, cm^3	
Median	0.2325
Range	0.01–7.49

RPA, recursive partition analysis; KPS, Karnofsky Performance Scale; WBRT, whole-brain radiotherapy.

effects resulting from surgery-related brainstem injury. Considering that the brainstem has a low tolerance for radiation, single-fraction dosing for this part of the brain may increase the probability of toxicities, such as hemorrhage and radiation necrosis, compared with such dosing in non-eloquent areas.[4] Thus, fractionated stereotactic radiotherapy (fSRT) may be an effective method to maintain high local control rates without increasing toxicities.[5,6] Recent advances in targeting precision and the development of a less-invasive fixation technique have increased irradiation safety using a fractionated schedule. The purpose of this study was to evaluate the efficacy and safety of linac-based fSRT for BSM.

METHODS

Patients and Tumor Characteristics

Clinical data were retrospectively collected to evaluate the efficacy and limitations of fSRT. The Nara Medical University Ethics Committee approved this retrospective study in March 2019 (No. 2158). Between May 2007 and January 2017, 25 consecutive BSM lesions in 24 patients were treated at the Nara Medical University Hospital. Before stereotactic radiotherapy, each patient was evaluated by a multidisciplinary team, including neurosurgeons, neuro-oncologists, neuroradiologists, and radiation oncologists, to define the appropriate therapy. fSRT was offered either as an initial treatment or in the salvage setting after failed whole-brain radiotherapy (WBRT). **Table 1** summarizes the clinical characteristics of the 25 lesions in the 24 study patients. According to the Radiation Therapy Oncology Group guidelines based on recursive partitioning analysis (RPA),[7] 2 patients were classified as class I, 17 as class II, and 5 as class III.

Stereotactic Radiotherapy

fSRT planning was based on computed tomography with 1- to 2-mm slice thickness. All patients were immobilized in a thermoplastic mask (BRAINLAB AG, Munich, Germany). The gross tumor volume (GTV) for each lesion was delineated on magnetic resonance imaging (MRI) with 1- to 2-mm slice thickness. The planning target volume was defined as GTV plus 1 mm for all dimensions. The treatment was performed within 1 week of computed tomography planning. Treatment planning was performed using BrainSCAN or iPlan RT (BRAINLAB AG). Irradiation dose was prescribed to ensure coverage for 90% of the planning target volume, and dose calculations were performed using a pencil beam algorithm. fSRT was performed using 6-MV X-rays delivered by a linear accelerator (Novalis; BRAINLAB AG) with a micro-multileaf collimator (minimum leaf width of 3 mm). Patient positioning and positioning verification were performed using the BRAINLAB ExacTrac system (BRAINLAB AG), which contains 2 infrared cameras and 2 dual diagnostic kV X-ray tubes to automatically move the patient into treatment position and minimize setup errors.[8,9]

All patients were treated with a dose of 24–40 Gy in 7–13 fractions with multiple non-coplanar beams, multiple non-coplanar arcs, or a combination of both. In the former part of our series, patients were mainly treated using 30 Gy in 10 fractions, and in the latter part of our series, they were mainly treated using 39 Gy in 13 fractions or 40 Gy in 10 fractions. In the others,

Table 2. Fractionation Radiation Dose in EQD2 for Brainstem Metastasis

Total Dose/Fraction	Cases	EQD2 (α/β: 2), Gy	EQD2 (α/β: 10), Gy
24 Gy/8fx	1	30	26
30 Gy/10fx	5	37.5	32.5
31.5 Gy/10fx	1	40.56	34.52
35 Gy/7fx	1	61.25	43.75
36 Gy/10fx	2	50.4	40.8
36 Gy/12fx	1	45	39
39 Gy/13fx	11	48.75	42.25
40 Gy/10fx	3	60	46.67

EQD2, radiobiological equivalent dose of 2 Gy.

dose fractionation scheme was modified on each case. The patient who had received WBRT was further treated with 24 Gy in 8 fractions and 30 Gy in 10 fractions to avoid the adverse effect.

The treatment methods for fSRT were conformal beams, dynamic conformal arcs, intensity-modulated radiotherapy (IMRT), and hybrid arcs, which is a novel treatment technique blending aperture-enhanced optimized arcs with discrete IMRT elements, allowing selection of arcs with a set of static IMRT beams.[10]

Follow-Up Examination

Follow-up MRI and clinical examinations were performed every 3 months after fSRT. The maximum diameter of the irradiated lesion in the axial image was measured. Overall survival (OS) was calculated from the date of starting fSRT using the Kaplan–Meier method. Analyses were performed to determine the association between OS and prognostic factors including patient age (>75 years vs. <75 years), sex, GTV (>1 cm^3 vs. <1 cm^3), other brain metastases besides BSM, brainstem-related symptom(s), pretreatment Karnofsky Performance Scale (>80 vs. <70), RPA class (class I or II vs. class III), and control of primary cancer. For the analysis of local control, a complete response was defined as disappearance of the treated lesion, a partial response as shrinkage of >50% of the GTV, and progressive disease as a >25% increase in GTV. All the other changes in size were considered as a stable disease. Local control was defined as stabilization or improvement (complete response, partial response, or stable disease) in the treated lesion.

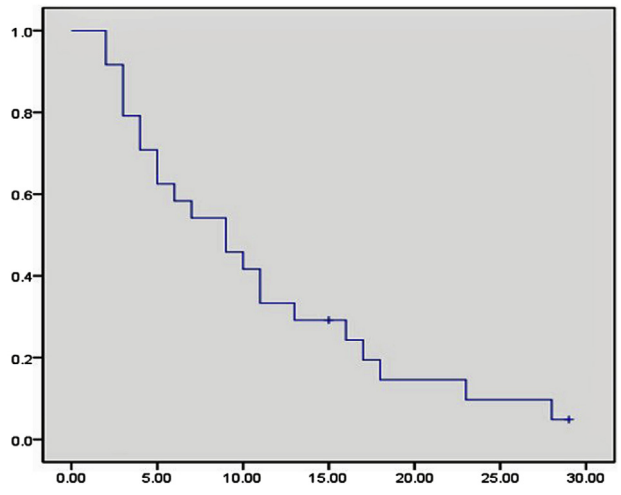

Figure 1. Overall survival of patients treated with fractionated stereotactic radiotherapy for brainstem metastasis estimated using the Kaplan–Meier method.

Statistical Analysis

Median survival time was calculated using the Kaplan–Meier method. The log-rank test was used for the univariate analyses. A $P < 0.05$ denoted statistical significance. Statistical analysis was performed using SPSS II (SPSS Inc., Chicago, Illinois, USA).

RESULTS

In total, 24 patients underwent fSRT for 25 lesions at our institution during the study period. Tumor volume ranged from 0.01 to 7.49 cm^3 (median: 0.233 cm^3). All patients were treated with a dose of 24–40 Gy in 7–13 fractions, with 39 Gy in 13 fractions for 11 lesions, 30 Gy in 10 fractions for 5 lesions, 40 Gy in 10 fractions for 3 lesions, 36 Gy in 10 fractions for 2 lesions, 36 Gy in 12 fractions for 1 lesion, 35 Gy in 7 fractions for 1 lesion, 31.5 Gy in 10 fractions for 1 lesion, and 24 Gy in 8 fractions for 1 lesion. The main prescription dose was 39 Gy in 13 fractions. The radiation dose was calculated to radiobiologic equivalent dose of 2 Gy (EQD2) using α/β ratio of 2 and 10 (Table 2). EQD2 (α/β: 2) ranges from 30 to 61.25 Gy and EQD2 (α/β: 10) ranges from 26 to 46.67 Gy.

At the time of analysis, 22 of the 24 patients who had undergone fSRT had died; however, their deaths were unrelated to BSM. The median OS was 9 months after fSRT (95% confidence interval 4.216–13.784) (Figure 1). Large GTV, presence of brainstem-related symptom, poor pretreatment Karnofsky Performance Scale, and RPA class III were significantly associated with a low OS (Table 3).

After fSRT, follow-up MRI showed a complete response in 1 lesion, a partial response in 17 lesions, and stable disease in 6 lesions. In 1 lesion, tumor progression was observed at 3 months after fSRT; the patient died 5 months after fSRT due to primary colon cancer without neurological aggravation. Tumor control in this series was observed in 96.0% (24 of 25) lesions.

Patient Outcomes and Adverse Effects

Of all, 3 (12.5%) patients experienced a resolution of symptoms after fSRT (truncal ataxia in 1 patient; sensory disturbance in 1 patient; and hemiparesis, diplopia, and sensory disturbance in 1 patient). Three patients, 1 with diplopia, 1 with hemiparesis, and 1 with gazed palsy before fSRT, experienced no symptom resolution after fSRT.

Toxicity was recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). One patient with grade 2 nausea was treated with corticosteroids. Toxicity grade 3 or greater observed was not observed in this study after fSRT.

Table 3. Log-Rank Tests for Prognostic Factors Affecting Overall Survival

Factor	*P* Value
Sex	0.965
Age (≥75 years vs. <75 years)	0.165
Tumor volume (≥1 cc vs. <1 cc)	0.039
Other brain metastasis	0.487
Symptom of brainstem	0.021
Pretreatment KPS	0.000
RPA (class I/II vs. class III)	0.000
Control of primary cancer	0.800

KPS, Karnofsky Performance Scale; RPA, recursive partition analysis.

Illustrative Case

A 55-year-old woman patient with adenocarcinoma in the lung presented with diplopia and right hemiparesis. This patient had received WBRT. MRI revealed a brainstem metastasis in her midbrain with a tumor volume of 2.86 cm^3. She was treated with linac-based stereotactic radiotherapy (fSRT) using 30 Gy in 10 fractions. Three months after treatment, MRI revealed the tumor size decreased significantly (Figure 2).

DISCUSSION

SRS with a Single Fraction for BSM

To enhance the management of metastatic brain tumors in the modern era, SRS and radiotherapy using radiosurgical modalities such as GK, CK, and Novalis have been developed to provide excellent local control with less toxicity in lieu of WBRT. Previous studies examining SRS or fSRT for BSM are summarized in Table 4.[11-34] Huang et al.[11] first assessed SRS for BSMs using GK in 1999. With a median prescription dose of 16 Gy and a mean tumor volume of 1.1 cm^3, they observed a local control rate of 95% and a median OS of 9 months. In previous studies involving patient series, tumor control rates for BSM with GK radiosurgery ranged from 76% to 100%. The most commonly prescribed median dose for BSM is 16 Gy,[22] and marginal doses for BSM can range

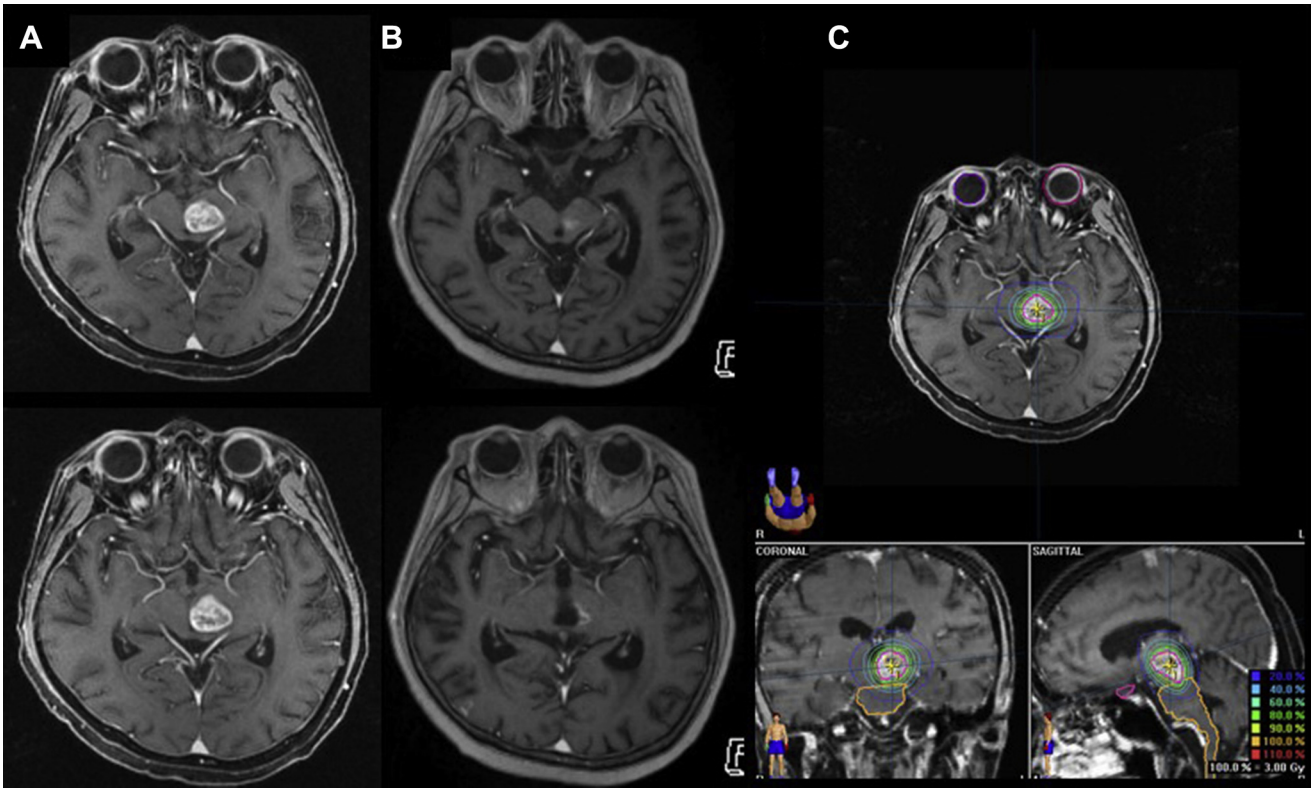

Figure 2. An illustrative case of a 55-year-old woman with lung adenocarcinoma presenting with diplopia and right hemiparesis. (**A**) Magnetic resonance imaging (MRI) revealed a brainstem metastasis in her midbrain with a tumor volume of 2.86 cm^3. She was treated with linac-based stereotactic radiotherapy (fSRT) using 30 Gy in 10 fractions. (**B**) Three months later, MRI revealed a considerable decrease in tumor size. (**C**) fSRT for this patient was performed using this treatment plan.

Table 4. Stereotactic Radiosurgery and Radiotherapy for Brainstem Metastasis

Series	STI Type	Patient/ Lesions	Median Tumor Volume, cm^3	Median Dose, Gy	Median Survival, Months	Tumor Control, %	WBRT Before SRS or SRT	Crude Toxicity Rate, %
Huang et al., 1999[11]	GK	26/27	1.1	16	9	95	24 (92%)	12% (3/26)
Shuto et al., 2003[12]	GK	25/31	2.1	13	4.9	77.4	9 (36%)	3% (2/25)
Fuentes et al., 2006[13]	GK	28/28	2.1 (mean)	19.6 (mean)	12	92	6 (21%)	11% (3/28)
Yen et al., 2006[14]	GK	53/53	2.8 (mean)	17.6 (mean)	11	86	21 (39%)	NA
Hussain et al., 2007[15]	GK	22/25	0.9	16	8.5	100	3 (14%)	5% (1/22)
Kased et al., 2008[16]	GK	42/44	0.26	16	9	85	19 (45%)	10% (4/42)
Lorenzoni et al., 2009[17]	GK	25/27	0.6	20	11.1	95	11 (44%)	NA
Koyfman et al., 2010[18]	GK	43/43	0.37	15	5.8	100	22 (51%)	0%
Yoo et al., 2011[19]	GK	32/32	1.52 (mean)	15.9 (mean)	7.7	87.5	NA	3% (1/32)
Kawabe et al., 2018[20]	GK	200/222	0.2	18	6	82	13 (7%)	1% (1/200)
Jung et al., 2013[21]	GK	32/32	0.71	13	5.2	88	17 (53%)	0%
Li et al., 2012[22]	GK	28/32	0.78	16	9	90.6	0 (0%)	4% (1/28)
Şengöz et al., 2013[23]	GK	44/46	0.6	16	8	96	23 (52%)	0%
Kilburn et al., 2014[24]	GK	44/52	0.13	18	6	82	25 (57%)	9% (4/44)
Voong et al., 2015[25]	GK	74/77	0.13	16	8.5	94	22 (30%)	10% (7/74)
Valery et al., 2011[26]	Linac	30/43	2.8	13.4	10	90	8 (27%)	0%
Kelly et al., 2011[27]	Linac	24/24	0.2	13	5.3	82	23 (96%)	8% (2/24)
Leeman et al., 2012[28]	CK	36/38	0.94	12–24/1–5fr	NA	93	15/36 (44%)	8% (3/36)
Lin et al., 2011[29]	Linac	45/48	0.4	14	11.6	91	17 (38%)	4% (2/45)
Hatiboglu et al., 2011[30]	Linac	60/60	1	15	4.2	76	9 (15%)	20% (12/60)
Joshi et al., 2016[31]	GK	48/51	0.12	15	7.6	89	19/48 (40%)	4% (2/48)
Liu et al., 2016[32]	CK	54/66	0.14	18	5	80	33/66 (50%)	NA
Trifiletti et al., 2016[33]	GK	547/596	0.8	16	5.6	81.8	266/547 (49%)	7.4% (44/596)
Nakamura et al., 2017[34]	CK	20/26	0.33	18–30/3 or 5fr	NA	96	5/26 (19%)	25% (5/20)
Present study (2019)	Linac	24/25	0.925	24–40/7–13fr	9	96	3 (20%)	4.2% (1/24)

STI, stereotactic irradiation; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; GK, gamma knife; NA, not available; CK, Cyber Knife.

from 13 to 20 Gy in a single session. Despite the fact that SRS is commonly used to manage patients with BSMs, certain complications, such as peritumoral edema, intratumoral hemorrhage, and radiation necrosis, need to be considered. Hatiboglu et al.[30] have reported that 12 of 60 (20%) patients developed a total of 15 complications related to linac-based SRS. Of these complications, 9 developed within 1 month of radiosurgery and 6 developed after 1 month. Trifiletti et al.[33] have reported that 7.4% of their study patients developed a grade 3–4 toxicity such as hemorrhage, hemiparesis, or cranial nerve paresis as a result of single-session GK radiosurgery for BSM at any time point in follow-up.

fSRT for BSM

Research from the 1990s suggests that fractionation is more beneficial than single-session radiosurgery because it expands the therapeutic window between tumor control and late effects, particularly for malignant brain tumors.[5,35] The frameless head-fixation system is advantageous for fractionation compared with more invasive frame-based fixation systems such as GK radiosurgery system. The frameless fixation system combines the precise radiation delivery and tumor localization capabilities of SRS with the tissue-sparing advantage of fractionation. By capitalizing on the differential repair capabilities of neoplastic and non-neoplastic cells, fSRT is better equipped to achieve neoplastic cell death with relative sparing of the normal, slowly dividing cells in the vicinity.[36,37] Thus, fSRT excels in the treatment of neoplastic tissue lying in close proximity to critical and radiosensitive structures. The brainstem is a critical structure that has a low tolerance for radiation. Therefore, fSRT may be beneficial for achieving tumor control and avoiding complications in the treatment of BSM.

Two studies have reported the use of fSRT for the treatment of BSM. Leeman et al.[28] have reported that SRS/fSRT with CK or Trilogy (12–24 Gy in 1–5 fractions) resulted in a local control rate of 93% in 36 patients. Nakamura et al.[34] have reported that fSRT with CK (18–30 Gy in 3–5 fractions) resulted in 100% and 90% local control rates at 6 and 12 months after radiotherapy, respectively. In this study, EQD2 (α/β: 10) ranges from 30 to 61.25 Gy and EQD2 (α/β: 2) ranges from 26 to 46.67 Gy. In 16-Gy single-fraction, EQD2 (α/β: 10) is 34.67 Gy and EQD2 (α/β: 2) is 72 Gy. EQD2 (α/β: 10) in 16-Gy single-fraction is similar to this study, but EQD2 (α/β: 2) is greater than this study. Compared with 16-Gy single-fraction, it may be estimated that fractionated radiotherapy has similar efficacy and decrease of treatment-related complications. In the present study, using fSRT with Novalis, the total prescription dose was 24–40 Gy in 7–13 fractions and the tumor control rate (96.0%) was consistent with that observed in previous studies on the use of SRS/fSRT for the treatment of BSM.

Adverse Events After Radiosurgery and fSRT

Complications arising from SRS for BSM include the following: intratumoral hemorrhage, radiation necrosis, ataxia, vomiting, motor weakness, dysequilibrium, paresthesia, and seizures.[11,16,18] Previous studies have reported complication rates ranging from 0% to 25% following SRS for BSM. After using fSRT for metastatic brainstem lesions, Leeman et al. reported no grade 3 or 4 toxicities among 16 patients and Nakamura et al. reported grade 3 intracranial hemorrhage in only 1 of 20 patients. In the present series, we observed only 1 patient with acute nausea after fSRT, which was controlled with corticosteroids. Although the dose was hypofractionated, like the 2–5 fractions administered in the past 2 reports on fSRT for the management of BSM, we suggest that the treatment can be made safer and less toxic by lowering the dose and increasing the fractions to maintain a good local control of BSM. fSRT as per our treatment plan for BSM treatment yields high local control probabilities without increasing severe adverse events.

Limitations

The small sample size and retrospective design of this study do not allow comparisons between each treatment for BSM. Although similar clinical studies recently have been published, each study has evaluated different treatment modalities as well as radiosurgical doses and fractions. A randomized trial should be performed in future studies to fully determine the ideal treatment conditions for BSM.

CONCLUSIONS

Linac-based fSRT with a micro-multileaf collimator delivered in the doses of 24–40 Gy in 7–13 fractions is a safe and effective local therapy for patients with BSM.

REFERENCES

1. Chason JL, Walker FB, Landers JW. Metastatic carcinoma in the central nervous system and dorsal root ganglia: a prospective autopsy study. *Cancer*. 1963;16:781-787.
2. Johnson JD, Young B. Demographics of brain metastasis. *Neurosurg Clin N Am*. 1996;7:337-344.
3. Matsumoto K, Tada E, Tamesa N, Tomita S, Ohmoto T. Stereotactic brachytherapy for a cystic metastatic brain tumor in the midbrain. Case report. *J Neurosurg*. 1998;88:141-144.
4. Williams BJ, Suki D, Fox BD, et al. Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications. *J Neurosurg*. 2009;111:439-448.
5. Hall EJ, Brenner DJ. The radiobiology of radiosurgery: rationale for different treatment regimes for AVMs and malignancies. *Int J Radiat Oncol Biol Phys*. 1993;25:381-385.
6. Ogura K, Mizowaki T, Ogura M. Outcomes of hypofractionated stereotactic radiotherapy for metastatic brain tumors with high risk factors. *J Neurooncol*. 2012:425-432.
7. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37:745-751.
8. Bilger A, Frenzel F, Oehlke O, et al. Clinical and translational radiation oncology local control and overall survival after frameless radiosurgery: a single center experience. *Clin Transl Radiat Oncol*. 2017;7:55-61.
9. Mori Y, Hashizume C, Kobayashi T, Shibamoto Y, Kosaki K, Nagai A. Stereotactic radiotherapy using Novalis for skull base metastases developing with cranial nerve symptoms. *J Neurooncol*. 2010; 98:213-219.
10. Gevaert T, Engels B, Garibaldi C, et al. Implementation of HybridArc treatment technique in preoperative radiotherapy of rectal cancer: dose patterns in target lesions and organs at risk as compared to helical Tomotherapy and RapidArc. *Radiat Oncol*. 2012;7:120.
11. Huang CF, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brainstem metastases. *J Neurosurg*. 1999;91:563-568.
12. Shuto T, Fujino H, Asada H, Inomori S, Nagano H. Gamma knife radiosurgery for metastatic tumours in the brain stem. *Acta Neurochir (Wien)*. 2003;145:755-760.
13. Fuentes S, Delsanti C, Metellus P, Peragut JC, Grisoli F, Regis J. Brainstem metastases: management using Gamma Knife radiosurgery. *Neurosurgery*. 2006;58:37-40.
14. Yen CP, Sheehan J, Patterson G, Steiner L. Gamma Knife surgery for metastatic brainstem tumors. *J Neurosurg*. 2006;105:213-219.
15. Hussain A, Brown PD, Stafford SL, Pollock BE. Stereotactic radiosurgery for brainstem metastases: survival, tumor control, and patient outcomes. *Int J Radiat Oncol Biol Phys*. 2007;67:521-524.
16. Kased N, Huang K, Nakamura JL, et al. Gamma Knife radiosurgery for brainstem metastases: the UCSF experience. *J Neurooncol*. 2008;86:195-205.
17. Lorenzoni JG, Devriendt D, Massager N, et al. Brain stem metastases treated with radiosurgery: prognostic factors of survival and life expectancy estimation. *Surg Neurol*. 2009;71:188-195.
18. Koyfman S, Tendulkar R, Chao S, et al. Stereotactic radiosurgery for single brainstem metastases: the Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys*. 2010;78:409-414.
19. Yoo TW, Park ES, Kwon DH, Kim CJ. Gamma knife radiosurgery for brainstem metastasis. *J Korean Neurosurg Soc*. 2011;50:299-303.
20. Kawabe T, Mineura K, Barfod BE, et al. Gamma Knife surgery for patients with brainstem metastases. *J Neurosurg*. 2018;117:23-30.
21. Jung EW, Rakowski JT, Delly F, et al. Gamma Knife radiosurgery in the management of brainstem metastases. *Clin Neurol Neurosurg*. 2013;115: 2023-2028.
22. Li Y, Xu D, Zhang Z, et al. Gamma Knife surgery for brainstem metastases. *J Neurosurg*. 2012; 117(suppl):13-16.
23. Şengöz M, Kabalay IA, Tezcanli E, Peker S, Pamir N. Treatment of brainstem metastases with gamma-knife radiosurgery. *J Neurooncol*. 2013;113: 33-38.
24. Kilburn JM, Ellis TL, Lovato JF, et al. Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: is there a

volume threshold for toxicity? *J Neurooncol*. 2014; 117:167-174.

25. Voong KR, Farnia B, Wang Q, et al. Gamma knife stereotactic radiosurgery in the treatment of brainstem metastases: the MD Anderson experience. *Neuro-Oncology Pract*. 2015;2:40-47.

26. Valery CA, Boskos C, Boisserie G, et al. Minimized doses for linear accelerator radiosurgery of brainstem metastasis. *Int J Radiat Oncol Biol Phys*. 2011;80:362-368.

27. Kelly PJ, Lin YB, Yu AYC, et al. Linear accelerator-based stereotactic radiosurgery for brainstem metastases: the Dana-Farber/Brigham and Women's Cancer Center experience. *J Neurooncol*. 2011;104:553-557.

28. Leeman JE, Clump DA, Wegner RE, Heron DE, Burton SA, Mintz AH. Prescription dose and fractionation predict improved survival after stereotactic radiotherapy for brainstem metastases. *Radiat Oncol*. 2012;7:107.

29. Lin C-S, Selch TM, Hong DS, et al. Accelerator-based stereotactic radiosurgery for brainstem metastases. *Neurosurgery*. 2011;70:953-958.

30. Hatiboglu MA, Chang EL, Suki D, Sawaya R, Wildrick DM, Weinberg JS. Outcomes and prognostic factors for patients with brainstem metastases undergoing stereotactic radiosurgery. *Neurosurgery*. 2011;69:796-806 [discussion: 806].

31. Joshi R, Johnson MD, Maitz A, Marvin KS, Olson RE, Grills IS. Utility of graded prognostic assessment in evaluation of patients with brainstem metastases treated with radiosurgery. *Clin Neurol Neurosurg*. 2016;147:30-33.

32. Liu SH, Murovic J, Wallach J, et al. CyberKnife radiosurgery for brainstem metastases: management and outcomes and a review of the literature. *J Clin Neurosci*. 2016;25:105-110.

33. Trifiletti DM, Lee CC, Kano H, et al. Stereotactic radiosurgery for brainstem metastases: an international cooperative study to define response and toxicity. *Int J Radiat Oncol Biol Phys*. 2016;96: 280-288.

34. Nakamura M, Nishimura H, Mayahara H, et al. Investigation of the efficacy and safety of CyberKnife hypofractionated stereotactic radiotherapy for brainstem metastases using a new evaluation criterion: 'symptomatic control. *J Radiat Res*. 2017; 58:834-839.

35. Brenner D, Martel M, Hall E. Fractionated regimens for stereotactic radiotherapy of recurrent tumors in the brain. *Int J Radiat Oncol BiolPhys*. 1991;21:819-824.

36. Shrieve DC, Kooy HM, Tarbell NJ, Loeffler JS. Fractionated stereotactic radiotherapy. *Important Adv Oncol*. 1996:205-224.

37. Shrieve DC. Basic principles of radiobiology applied to radiotherapy of benign intracranial tumors. *Neurosurg Clin N Am*. 2006;17:67-78.

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