Original Article

Stereotactic radiosurgery for single or oligometastatic brain lesions: A single institutional experience

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Abstract

Aim: Intracranial metastases are the most common neurologic complications of systemic cancer. Stereotactic radiosurgery (SRS) is a proven modality for treating single or oligometastatic brain lesions. In this retrospective study, we have analyzed patients data treated in our hospital with SRS.

Materials and Methods: The analysis included 52 patient's data treated between August 2010 and January 2018. These include the patients in the complete remission of the primary disease and have recurred in the brain with one to four metastases after a significant disease-free interval. Patient's case sheets and treatment planning system data were analyzed to collect the data for this study.

Results: Median follow-up was 10 months (range, 1–37 months). There were twenty cases of Ca (cancer) lung, 13 cases of Ca breast, 5 cases of Ca rectum, 4 cases of Ca endometrium, 2 case of Ca esophagus, and 1 case each of alveolar rhabdomyosarcoma of right parotid, Ca ovary, Ca vaginal vault, Ca lacrimal gland, Ca colon, Ca urinary bladder, and Ca prostate. These patients who had a recurrent disease in the brain were treated with doses ranging from 15 to 20 Gy in single fraction, 24 Gy in 3 fractions, 27 Gy in 3 fractions, or 30 Gy in 5 fractions. Median progression-free survival was 9 months, and median overall survival (OS) was 12 months in these patients.

Conclusion: Frameless SRS is an effective treatment of delivering high-dose radiation to patients who develop one to four brain metastasis with comparable median progression free and OS to the previously reported data.

Keywords: Frameless stereotactic radiosurgery, oligometastases, radiosurgery, stereotactic

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INTRODUCTION

Intracranial metastases are the most common neurologic complications of systemic cancer. In general, population-based studies from the past four decades suggest an incidence rate of approximately 10 per 100,000 population. A current estimate has been derived of 21,000–43,000 patients diagnosed with brain metastases per year in the United States. Application of autopsy and clinical data to the total number of cancer cases diagnosed in the United States suggests that over 100,000 patients develop brain metastases each year.[1] The most common site being the brain parenchyma; however, other sites such as the cranium, dura, or leptomeninges may be involved

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as well.[2] The management of metastatic brain lesions has undergone considerable evolution in the past several years. Conventionally, the management of solitary or multiple brain metastases has been whole-brain radiation therapy (WBRT).[3] WBRT relieves symptoms such as nausea, vomiting, headache, and/or neurological deficits which occurs due to the mass effect caused by the lesions and the surrounding edema. The symptomatic relief from headaches and motor loss ranged from 56% to 96% and from 46% to 77%, respectively. The median response duration varied from 1 to 8 months.[4] Pease *et al*. conducted a systematic review of WBRT and reported that neurological status response rates varied between 7% and 90%.[5]

Whole-brain radiation is relatively well tolerated, but it can cause a number of adverse effects, both over the short- and long-term. Neurocognitive effects are common late side effects in patients who have undergone WBRT. Neurocognitive degeneration induced by radiation therapy follows a biphasic pattern, initially starting with a transient decline in mental functioning at around 4–5 months posttreatment, followed by an improvement in neurocognitive functioning and then an ultimate irreversible return of impairment months to years later.[6]

In the past two decades, there has been a substantial improvement in systemic therapies which led at the improvement in the overall survival (OS). This has lead to techniques that aim to reduce the morbidity caused by WBRT and improve the quality of life. Stereotactic radiosurgery (SRS) has recently ascertained its role in treatment of brain metastasis. The evolution of imaging, radiation treatment planning, and delivery technology had to occur before several dedicated research groups were able to safely deliver SRS to patients with brain metastases.[7]

While SRS has been an established option in the treatment of 1–4 brain metastasis with an OS ranging from 8 to 16 months,[8] recent studies have shown as similar outcomes in patients having >10 brain metastasis treated with SRS who have a well-controlled extracranial disease.[9] In this retrospective single institutional study, we evaluated the progression-free survival (PFS) and OS.

MATERIALS AND METHODS

Patient characteristics

The patient characteristics for the study are mentioned in Table 1.

Table 1: Patient characteristics

Characteristics	Numbers
Number of patients	52
Number of metastatic brain lesions	87
Number of brain metastasis per patient (*n*)	
1	30
2	12
3	7
4	2
5	1
Age (years), median (range)	48.5 (31-81)
Primary lesion	
Lung	20
Breast	13
Rectum	5
Endometrium	4
Others	10
Sex	
Male	22
Female	30

Radiation therapy

Patients were immobilized using a thermoplastic mask (BrainLAB, Feldkirchen, Germany). Radiation treatment planning is performed on a planning computed tomography (CT) scan with a 1 mm slice thickness. A planning magnetic resonance imaging scan of brain with gadolinium contrast-enhanced T1 sequence is co-registered with the planning CT scan which would help in the target volume delineation. The gross tumor volume (GTV) for each brain metastasis was defined on gadolinium-enhanced magnetic resonance imaging (GdT1-MRI, Philips 1.5 T Achieva, Sense XL Torso coil). Treatment planning was performed with iPlan RT Image 4.1.3 (BrainLab, Feldkirchen, Germany). The planning target volume (PTV) was defined as GTV plus 1 mm. Radiation dose was prescribed to ensure coverage of at least 80% of the PTV with the prescribed dose. The target volume covered 100% of the prescribed dose. SRS was performed with a NovalisTx Radiosurgery LINAC with 6 MV photons. The patient positioning and verification was done using the BrainLAB ExacTrac X-ray 6D system.

Follow-up

Patients were followed up initially after 8 weeks of SRS treatment and thereafter 3 monthly. A follow-up MRI of the brain is performed at the end of 6 months of treatment. Response assessment is made using Response Assessment in Neuro-oncology criteria.

PFS is defined as time to local failure, intracranial progression, or death. OS is defined as the time to death due to any cause.

Statistical analysis

PFS and OS were calculated using the Kaplan–Meier method using SPSS V19.0 IBM, CA-USA software and biostatistical assistance.

RESULTS

This retrospective analysis included 52 patients with 87 metastatic lesions treated between August 2010 and January 2018. There were twenty cases of cancer (Ca) lung, 13 cases of Ca breast, 5 cases of Ca rectum, 4 cases of Ca endometrium, 2 cases of Ca esophagus, and 1 case each of alveolar rhabdomyosarcoma of right parotid, Ca ovary, Ca vaginal vault, Ca lacrimal gland, Ca colon, Ca urinary bladder, and Ca prostate. The distribution of the lesions within the brain and the corresponding primaries of origin are depicted in Table 2.

Thirty-six of 52 (69.2%) patients were treated with single fraction of doses ranging from 15 to 20 Gy, 6/52 (11.5%) were treated for three fractions of doses ranging from 24 to 27 Gy, 2/52 (3.8%) patients were treated for four fractions to a dose of 28 Gy, and 4/52 (7.4%) patients were treated with five fractions of 30 Gy total dose. The median GTV volume was 4.95cc (range - 1.35 to 30.7cc).

Median follow-up was 10 months (range - 1 to 37 months). PFS and OS were estimated for every patient treated with SRS, and patients were censored when they died. The median PFS within the cranium estimated using Kaplan–Meier method was 9 months [Figure 1].

Twenty-two of 52 (42.3%) patients were dead at the time of analysis. The median OS was 12 months [Figures 1 and 2].

Patients were assessed for adverse effects using the CTCAE V4.0 during follow-up. All patients tolerated the treatment well. The most common adverse effect documented was fatigue, which was seen during the initial one or two follow-up post which no other adverse effects were reported.

DISCUSSION

Over the past two decades, various studies have demonstrated that frameless LINAC-based SRS offers

Table 2: Depicting the distribution of metastatic lesions within the brain and their corresponding primaries of origin

Site of lesion	Primary	*n*
Right frontal	Ovary	1
	Lung	4
	Breast	2
Left frontal	Lung	3
	Breast	2
	Prostate	1
Right parietal	Parotid	1
	Lung	4
	Breast	1
Left parietal	Breast	2
	Lung	8
	Esophagus	1
	Rectosigmoid	2
	Colon	1
Right temporal	Lung	3
	Vaginal vault	1
Left temporal	Lung	3
	Urinary bladder	1
Right occipital	Lung	3
	Lacrimal gland	1
Left occipital	Thyroid	1
Brain stem	Lung	3
Cerebellum	Lung	4
	Breast	5
	Rectum	3

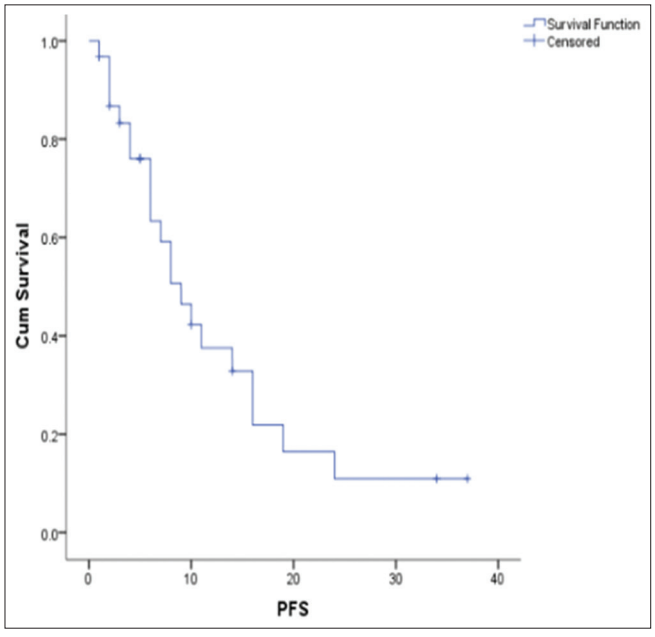

Figure 1: Kaplan–Meier curves depicting the median progression-free survival

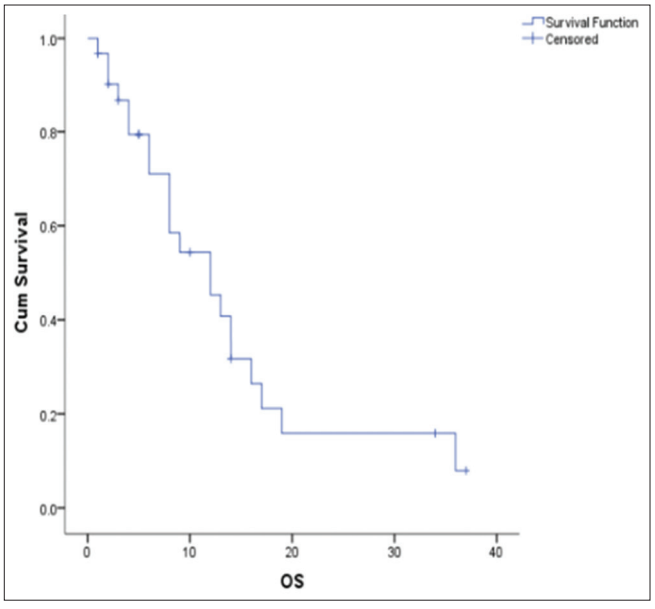

Figure 2: Kaplan–Meier curves depicting the median overall survival

a good intracranial PFS and a comparable OS among patients treated for brain metastases. The American Society of Radiation Oncology guidelines recommend SRS as an alternative treatment to surgery for a single lesion <3 cm in size in good prognosis patients.

In a study by Bhatnagar *et al*.,[10] the median PFS was 9 months and OS was 8 months. Kocher *et al*.[11] in a randomized study reported ninety patients treated using SRS alone and 61 of them had single brain metastases. Local control rates were 75% at 12 months and 69% at 24 months. Marcrom *et al*.[12] demonstrated a 12-month local control of 86%. Tumors which were <3 cm in diameter showed an improved 12-month local control of 95% compared with 61% in tumors, which are ≥3 cm ($P < 0.001$). The Kaplan–Meier estimate of 12-month local control was 91% in tumors treated with 30 Gy and 75% in tumors treated with 25 Gy ($P = 0.015$). Tumor diameter ≥3 cm demonstrated in an increase in the local failure, and a 30 Gy prescription resulted in a decrease in the local failure on multivariate analysis (hazard ratio [HR]: 8.11 [range, 2.09–31.50; $P = 0.003$] and HR, 0.26 [range, 0.07–0.93; $P = 0.038$]). Central nervous system toxicity of Grade 4 occurred in four patients (6%) requiring surgery, and no patient experienced irreversible Grade 3 or 5 toxicity. Increasing tumor diameter was associated with increased toxicity risk (HR, 2.45 [range, 1.04–5.742; $P = 0.04$]).

Yamamoto *et al*.[13] published an observational study of 1194 patients with 1–10 brain metastases and Karnofsky Performance Status ≥70 treated with SRS. Median OS after SRS was 10.8 months (95% confidence interval [CI], 9.4–12.4) in patients with two to four metastases and 10.8 months (95% CI, 9.1–12.7) in patients with five to ten metastases (HR 0.97; 95% CI, 0.81–1.18; $P = 0.78$; $P_{\text{noninferiority}} < 0.001$). Treatment-related adverse events were not different in patients with more than five metastatic lesions to those with less than five metastatic lesions (9% vs. 9%; $P = 0.89$). In this study, patients with one brain metastasis had significantly better median OS (13.9 months) than the patients with 2–4 (10.8 months; $P = 0.0004$) or 5–10 (10.8 months; $P = 0.019$) brain metastases.

The reported local tumor control rates are 90%–94% for brain metastases from breast cancer and 81%–98% for brain metastases from lung cancer in another study. In conventionally radioresistant brain metastases, local tumor control rates after radiosurgery are 73%–90% for melanoma and 83%–96% for renal cell cancer.[14] A three-arm prospective randomized trial compared gamma knife radiosurgery alone, WBRT alone or the combination of both in patients with brain metastases of various primary histologies. The local control was 87%, 91%, and 62% for gamma knife, gamma knife + WBRT, and WBRT alone, respectively, suggesting that the outcome of the two radiosurgery arms was superior.[15]

Our study has demonstrated clinical outcomes with a median PFS of 9 months and median OS of 12 months, which is comparable to the previously published data.

CONCLUSION

The results presented in this study prove that LINAC-based frameless SRS using Brain Lab Mask and ExacTrac 6D system is a safe, highly effective, and well-tolerated modality of treatment for oligometastatic brain lesions. The local control and the OS are comparable to the outcomes reported in literature.

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Conflicts of interest
There are no conflicts of interest.

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