



Evaluation of response to stereotactic radiosurgery in patients with radioresistant brain metastases

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Purpose: Renal cell carcinoma (RCC) and melanoma have been considered 'radioresistant' due to the fact that they do not respond to conventionally fractionated radiation therapy. Stereotactic radiosurgery (SRS) provides high-dose radiation to a defined target volume and a limited number of studies have suggested the potential effectiveness of SRS in radioresistant histologies. We sought to determine the effectiveness of SRS for the treatment of patients with radioresistant brain metastases.

Materials and Methods: We performed a retrospective review of our institutional database to identify patients with RCC or melanoma brain metastases treated with SRS. Treatment response were determined in accordance with the Response Evaluation Criteria in Solid Tumors.

Results: We identified 53 radioresistant brain metastases (28% RCC and 72% melanoma) treated in 18 patients. The mean target volume and coverage was 6.2 ± 9.5 mL and $95.5\% \pm 2.9\%$, respectively. The mean prescription dose was 20 ± 4.9 Gy. Forty lesions (75%) demonstrated a complete/partial response and 13 lesions (24%) with progressive/stable disease. Smaller target volume ($p < 0.001$), larger SRS dose ($p < 0.001$), and coverage ($p = 0.008$) were found to be positive predictors of complete response to SRS.

Conclusion: SRS is an effective management option with up to 75% response rate for radioresistant brain metastases. Tumor volume and radiation dose are predictors of response and can be used to guide the decision-making for patients with radioresistant brain metastases.

Keywords: Radiosurgery, Radioresistant, Renal cell carcinoma, Melanoma, Brain

Introduction

Brain metastasis is the most common intracranial malignancy in adults [1]. Up to 50% of patients with renal cell carcinoma (RCC) or melanoma develop brain metastases during the

course of their disease [2,3]. Standard treatment for patients with brain metastases includes external beam radiation therapy; however, RCC and melanoma brain metastases have been traditionally perceived to be 'radioresistant' to external beam whole brain radiation therapy (WBRT) compared to other

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histologies [4–7].

Stereotactic radiosurgery (SRS) has become a preferred treatment option in the initial management of patients with limited brain metastases. Randomized trials have demonstrated that SRS provides higher tumor control and preserves neurocognition compared to WBRT [8–11]. While radioresistant histologies, including RCC and melanoma, were underrepresented in these randomized trials, several retrospective studies have shown that radioresistant brain metastases have local control rates similar to those from non-radioresistant histologies when treated with SRS [12–16]. Unfortunately, these retrospective studies used outdated methodologies to assess local control, which may have contributed to the wide range of reported rates of local control from different institutions.

Since the definition of local control varies across studies, factors associated with improved local control in radioresistant brain metastases with SRS have not been established. In this study, we reviewed our experience with SRS in patients with radioresistant brain metastases from primary RCC and melanoma using a modern assessment technique to measure response rates and performed a detailed analysis of factors associated with response rate.

Materials and Methods

We conducted an IRB-approved retrospective cohort study including all patients with newly diagnosed brain metastases between 2009 and 2018 who underwent SRS at Acibadem Maslak Hospital (IRB No. 2019116). The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients treated with surgery and/or WBRT alone were excluded. Patients without radiographic follow-up and those who had re-irradiation with SRS were not included.

Demographic, clinical, and brain lesion information was collected, including age, gender, location of brain metastases, number of brain metastases, tumor size, tumor volume, addition of WBRT, prescription dose, coverage, and volume receiving a dose of at least 10 Gy and 12 Gy (V_{10Gy} and V_{12Gy} , respectively).

All patients were treated with a robotic linear accelerator-based SRS, CyberKnife stereotactic radiosurgery unit (CyberKnife Inc., Sunnyvale, CA, USA). The target volumes were identified on magnetic resonance imaging (MRI) scans that were fused with treatment planning computed tomography (CT). The gross tumor volume (GTV) was delineated as contrast-enhancing tumor demonstrated on MRI. The planning target

volume (PTV) was generated by a uniform expansion of 1 mm from the GTV. Doses were prescribed to isodose lines that were 70%–90% such that 95% of the target volume (PTV) is conformally covered by 100% of the prescription dose. If there was a critical structure which constraint cannot be met than the PTV coverage allowed be compromised. AAPM TG 101 report was used for all plans and normal tissue dose constraints. For tumors <2 cm we tend to treat in 1 fraction, but for larger tumors (>2 cm) or tumors adjacent the critical structures such as brainstem the treatment is delivered in 3–5 fractions.

Patients received post-treatment MRI 4–6 weeks after SRS and were subsequently followed with imaging every three months. Tumor response was classified into categories (complete response, partial response, progressive disease, or stable disease) based upon the percent change in volume evaluated on MRI in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) [17].

The primary endpoint was to determine the occurrence of complete/partial response rate with SRS. To compare variables between the case and control group, chi-square test, Fisher exact test or t-test were used. Variables of interest were evaluated by univariate logistic regression. Survival analysis was evaluated with Kaplan-Meier survival analysis and log-rank test. We examined variables in the proportional hazard analysis (Cox model), to identify the independent predictors of survival. A p-value less than 0.05 was considered statistically significant.

Results

We identified 53 brain metastases from primary melanoma or RCC treated with SRS in 18 patients (7 females and 11 males) at our institution from 2009 to 2018. The primary tumor was melanoma in 13 patients (72%) and RCC in 5 patients (28%). Median follow-up was 10.4 months (range, 3.4 to 37.8 months). Median patient age was 52 years (range, 30 to 84 years). Median Karnofsky Performance Score was 90 (range, 80 to 100). The most common locations were frontal (34%) and parietal lobes (34%), followed by temporal (26%) and occipital lobes (6%). The mean prescription dose was 2,000 cGy (range, 1,000 to 2,700) in 1 to 5 fractions (median, 1 fraction). Treatment doses for most lesions were prescribed to isodose lines $\geq 80\%$. WBRT was received by 33% of the patients either before or after SRS (Table 1).

Overall survival was not significantly different in patients with complete/partial response versus progressive/stable

Table 1. Demographic and clinical characteristics of the patients included in the study (n = 18)

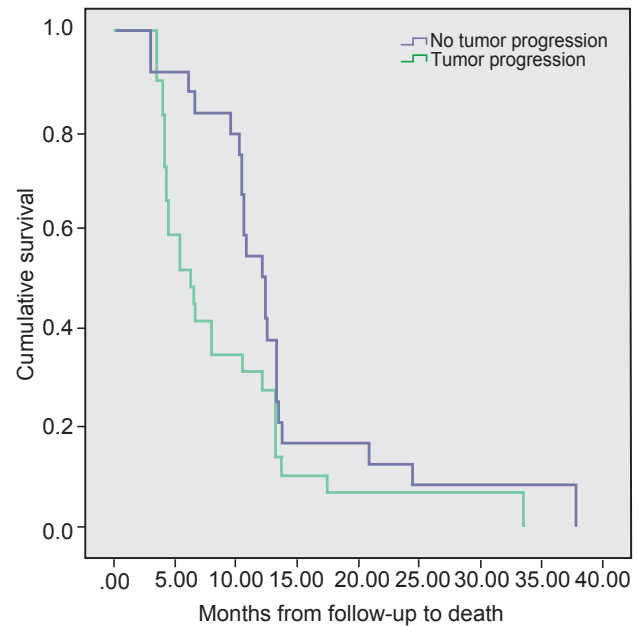
Characteristic	Value
Number of brain lesion	53
Age (yr)	52 (30–84)
Histology	
RCC	19 (36)
Melanoma	34 (64)
Location	
Lt. frontal	11 (21)
Rt. frontal	7 (13)
Lt. parietal	11 (21)
Rt. parietal	7 (13)
Lt. temporal	10 (19)
Rt. temporal	3 (7)
Lt. occipital	2 (3)
Rt. occipital	2 (3)
Radiation therapy	
WBRT	6 (33)
Dose (cGy)	3,000 ± 0
SRS	
Dose (cGy)	2,000 ± 487
PTV volume (mL)	6.2 ± 9.5
Coverage (%)	95.5 ± 2.9
V _{10Gy} (mL)	24.2 ± 31.7
V _{12Gy} (mL)	18.2 ± 25.2
SRS response	
Complete response	31 (58)
Partial response	9 (17)
Progressive disease	4 (8)
Stable disease	9 (17)

Values are presented as median (range) or number (%) or mean ± standard deviation.

RCC, renal cell carcinoma; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; PTV, planning target volume.

disease (mean, 12.6 vs. 11.1 months; $p = 0.374$) (Fig.1). According to the Cox proportional hazards analysis, extracranial metastases on presentation (hazard ratio [HR] = 1.404, 95% confidence interval [CI], 1.169–1.639; $p = 0.003$) and the progression of the disease (HR = 1.023; 95% CI, 1.03–1.043; $p = 0.016$) had a significant impact on survival. However, neither patient's age (HR = 0.021; 95% CI, 0.006–0.036; $p = 0.156$) nor SRS response (HR = 0.635; 95% CI, 1.03–1.043; $p = 0.125$) had a significant impact on survival.

Forty lesions (75%) demonstrated a complete/partial

**Fig. 1.** Kaplan–Meier curve for overall survival from the time of stereotactic radiosurgery.

response and 13 lesions (24%) with progressive/stable disease. In patients with complete/partial response, age ($p = 0.752$), histologies ($p = 0.219$), location of the brain metastases ($p = 0.257$), and receipt of WBRT ($p = 0.908$) were not different than those with progressive/stable disease (Table 2). Mean target volume was significantly smaller in lesions with complete/partial response than that in lesions with progressive/stable disease (2.07 vs. 11.95 mL; $p < 0.001$). Lesions with complete/partial response received larger SRS doses (mean, 2,142 vs. 1,492 cGy; $p < 0.001$) and coverage (mean, 96% vs. 94%; $p = 0.008$) compared to those progressive/stable disease. There was no difference between the two groups for BED3 mean ($p = 0.460$) and BED10 mean ($p = 0.325$). In both groups, patients were more likely to receive single fractionated therapy; 11 lesions (84.6%) in the group with progressive/stable disease and 25 lesions (80.7%) in the group with complete/partial response ($p = 0.445$). At the time of SRS, 15 patients had extracranial metastases. There was no significant difference in the number of patients who presented with extracranial metastases between both groups ($p = 0.914$). Twelve patients received chemotherapy (either before and/or after SRS). Ten patients received immune checkpoint inhibitors. The number of patients receiving chemotherapy ($p = 0.239$) or immune checkpoint inhibitors ($p = 0.869$) was not significantly different between the groups.

Table 2. Demographic and clinical characteristics of patients with complete or no response

Characteristic	PD/SD	CR/PR	p-value
Age (yr)	53.10 ± 12.66	52.00 ± 12.05	0.752
Histology			0.219
RCC	5 (22.73)	12 (38.71)	
Melanoma	17 (77.27)	19 (61.29)	
WBRT	11 (50.00)	16 (51.61)	0.908
Location			0.257
Lt. frontal	5 (22.72)	6 (19.35)	
Rt. frontal	2 (9.09)	5 (16.13)	
Lt. parietal	5 (22.72)	6 (19.35)	
Rt. parietal	4 (18.18)	3 (9.68)	
Lt. temporal	3 (13.64)	7 (22.58)	
Rt. temporal	3 (13.64)	0 (0)	
Lt. occipital	0 (0)	2 (6.45)	
Rt. occipital	0 (0)	2 (6.45)	
Number of lesions			0.445
Single	20 (90.91)	25 (80.65)	
Multiple	2 (9.09)	6 (19.35)	
SRS dose (cGy)	1,492.3 ± 357	2,141.9 ± 388	<0.001
V _{10Gy} (mL)	21.36 ± 14.55	26.14 ± 39.74	0.593
V _{12Gy} (mL)	14.80 ± 12.00	20.64 ± 31.42	0.412
Coverage (%)	94.37 ± 3.35	96.44 ± 2.10	0.008
Target volume (mL)	11.95 ± 12.30	2.07 ± 3.16	<0.001
Tumor size (cm)			<0.001
<1	9 (40.91)	28 (90.32)	
>1	13 (59.09)	3 (9.68)	
Immune checkpoint inhibitor	6 (20)	4 (18.18)	0.869
Chemotherapy	18 (58.06)	17 (77.27)	0.239
Extracranial metastases on presentation	25 (80.65)	18 (81.82)	0.914
BED10	53 ± 24.47	58 ± 14.70	0.325
BED3	134 ± 69.74	147 ± 45.04	0.460

Values are presented as mean ± standard deviation or number (%).

RCC, renal cell carcinoma; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; BED, biologically effective dose.

Discussion and Conclusion

Within a cohort of patients with radioresistant brain metastasis treated with SRS, we noted two main findings: the majority of patients had complete/partial response, and clinical factors such as tumor volume, SRS dose, and coverage are associated with complete/partial response.

In our series, complete/partial response was observed in 75% of the lesions treated with SRS. While this is within the range of other retrospective studies, it is unclear whether the response rates observed in these studies were complete/

partial [18-21]. Unfortunately, these retrospective studies used outdated ambiguous methodologies to assess local control, such as only measuring a single dimension or not even elaborating on their criteria for what was considered to be local control, making it difficult to generalize reported outcomes. In contrast to these studies, we utilized the standardized RECIST criteria to determine the tumor response to SRS. Furthermore, all patients included in our study were followed closely with surveillance brain MRIs every three months and symptomatic radiation necrosis was not observed.

In addition to investigating the treatment response rate, we

also sought to determine factors associated with complete/partial response. One of the key findings of our study is that smaller tumor volume is a positive predictor of complete/partial response to SRS. This was also supported by prior studies [12,19,21-24]. Furthermore, our results also support the use of a higher SRS dose in brain metastases with melanoma or RCC, as reported in prior studies [24,25]. Based on the data from retrospective studies, the addition of WBRT did not consistently provide local control and survival benefit for radioresistant histologies [19-21,24,26-28]. Our results also suggest that the addition of WBRT did not provide significant improvement in response rate. Furthermore, higher coverage was associated with complete response in patients with radioresistant histologies.

In our study, there was no difference in survival in patients who achieved complete/partial response to SRS compared to those progressive/stable disease. Survival is a complex endpoint in patients with brain metastases and is influenced by factors such as performance status, age, number of metastases, primary diagnosis, and presence of extracranial metastases [29]. The extracranial metastases on presentation and the progression of the disease has a significant effect on survival in our study. SRS response rate may be more clinically relevant as improvement in systemic therapies continue to prolong survival in patients with radioresistant metastatic disease.

Limitations of our study include its retrospective design with inherent confounding factors and the clinical heterogeneity of patients with brain metastases. Another limitation of our study is that we did not examine the impact of systemic therapy, which could independently affect outcomes. The presence of additional unobserved confounding covariates may contribute to response rate, even with statistical methods that attempt to reduce the impact of selection bias on outcomes.

Compared to previous work, the added strengths of our study were the utilization of contemporary RECIST criteria to determine the response rate. In conclusion, SRS is an effective management option with up to 75% response rate for radioresistant brain metastases. Tumor volume and radiation dose were predictors of response and can be used to guide decision-making for patients with radioresistant brain metastases.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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