

CLINICAL INVESTIGATION

Radiosurgery for melanoma brain metastases: the impact of hemorrhage on local control

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Objective: To investigate the influence of stereotactic radiosurgery on the risk of hemorrhage from brain metastases from malignant melanoma.

Methods: A cohort of 110 patients treated with stereotactic radiosurgery (SRS) for 358 melanoma brain metastases was identified. The incidence of hemorrhage before and after SRS was determined by review of serial MRI scans. Statistical analysis was performed to determine the influence of SRS on rate of hemorrhage. Overall survival (OS) and local control (LC) were assessed and prognostic factors, including hemorrhage pre- or post-SRS were analyzed.

Results: At presentation 83 of 358 (23.2%) melanoma metastases had hemorrhaged in 44 patients. Following SRS, 73 hemorrhages occurred in 358 treated tumors (20.4%). These rates were not significantly different; $p=0.362$, HR=0.846 (95% CI 0.591-1.211). The risk of post-SRS hemorrhage in patients was statistically significantly linked to previous hemorrhage. Fourteen of 65 patients (21.5%) who presented without hemorrhage prior to SRS subsequently demonstrated hemorrhage. Twenty-four of 44 patients (54.5%) who presented with hemorrhage went on to demonstrate further hemorrhage following SRS; $p=0.005$, HR 2.47 (95% CI 1.24-11.3). Mixed effects logistic regression modeling showed no influence of SRS on the risk of hemorrhage of a given lesion ($p=0.99$).

OS at 1 year was better for patients presenting with a single metastasis (41.2%) compared to multiple

metastases (20.3%, $p=0.009$). LC was 60.4% at 1 year following SRS. LC was significantly lower for metastases demonstrating hemorrhage either pre-SRS (51.7% vs 64.9%, $p=0.03$) or post-SRS (32.7% vs. 67.8%, $p<0.001$).

Conclusions: The current data show that SRS does not alter the risk of subsequent hemorrhage of treated metastases. However, hemorrhage may complicate follow-up assessment of response and LC following SRS. Careful assessment of imaging following SRS should include awareness that hemorrhage may mimic treatment failure in these patients.

Keywords: Brain metastases, hemorrhage, radiosurgery, melanoma

INTRODUCTION

In the United States, at least 170,000 and up to 500,000 patients develop brain metastases comprising 10 to 30% of cancer patients in the United States.¹⁻³ The incidence of brain metastases has been increasing partly due to improved imaging techniques as well as prolonged survival with effective systemic agents.⁴⁻⁶ Stereotactic radiosurgery (SRS) has provided an additional modality by which to treat patients with brain metastases and has been incorporated into randomized controlled trials.⁷⁻¹⁰ SRS

offers a conformal treatment option which may limit toxicities associated with whole brain radiotherapy in patients with brain metastases.⁷ Hemorrhagic brain metastases provide a particular challenge. The pre-treatment hemorrhage rate of melanoma brain metastases ranges from 9% to 30%.¹¹⁻¹⁵ Post-treatment hemorrhage has been noted in 15% to 25% of patients resulting in a craniotomy in 25% due to the hemorrhage.^{13,15} It is unclear whether SRS influences the risk of subsequent hemorrhage. In this report, we investigate the influence of SRS on the risk of hemorrhage from brain metastases from malignant melanoma.

PATIENTS AND METHODS

Between January 2000 and June 2011, 110 consecutive patients with 358 melanoma brain metastases were treated at the Huntsman Cancer Institute, University of Utah with SRS (Novalis, BrainLAB, Heimstetten, Germany) with available follow-up imaging. IRB-approved patient databases maintained by the Department of Radiation Oncology were used to identify the patients and provide clinical information for follow-up.

SRS treatment planning

The total dose delivered during SRS was dependent on the size of the metastatic lesions, as previously described by Shaw et al.¹⁶ Lesion diameter was determined as the diameter of a sphere that yielded the same volume as the measured lesion volume. In the majority of cases, dose was prescribed per RTOG 9005 guidelines, with lesions 3.01-4.00 cm in diameter treated to 15 Gy, lesions 2.01-3.00 cm treated to 18 Gy; however, variation did occur with lesions ≤ 2 cm, where in the earlier years of the study, these lesions were prescribed 20 Gy, and during the last year of the study they were prescribed 24 Gy. The prescription isodose line was identified utilizing a method previously described.¹⁷ Patients were treated with dynamic conformal arcs. Both frame-based and frameless techniques were utilized. Details regarding the frame-based technique have been previously reported.¹⁸ The frameless technique utilizes a thermal plastic mask in conjunction with the ExacTrac/Novalis image guidance system.¹⁹ This technique has been verified with quality assurance testing.²⁰ When treating a hemorrhagic lesion, the entire lesion was included in the target.

Outcomes and definitions

Serial post-SRS, post-contrast T1-weighted MRI scans were analyzed. Evidence of hemorrhage was

based on non-contrast T1-weighted MRI sequences and diffusion-weighted MRI sequences in addition to radiology reports. Failure was defined as re-treatment of a given lesion or a sustained increase in the diameter sum of 20% following SRS. If re-treatment was not performed, and there existed a sustained increase in the diameter sum of 20%, a neurosurgeon (R.L.J.) reviewed the case to verify failure. The neurosurgeon established failure if the volume increase was clearly due to a progression of tumor rather than pure hemorrhage. Survival was defined as the time from SRS to death or the last clinical follow-up. The institutional follow-up policy includes an initial post-radiosurgery MRI scan at 4 to 6 weeks followed by surveillance MRI scans every 8 to 12 weeks thereafter.

Statistical analysis

Kaplan-Meier (K-M) analyses were used to describe the local control, freedom from hemorrhage and survival for the study cohort while the log-rank test was used to test the difference in local control and survival among subgroups defined by a single risk factor. A mixed effects logistic regression model was used to evaluate for a possible correlation between SRS of a given lesion and its risk for subsequent hemorrhage. A random effect was included to account for possible correlation between multiple lesions in the same patient. A p-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using Stata Version 11 (Stata Inc, College Station, TX) or R version 2.15.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between January 2000 and June 2011, follow-up imaging was available for 110 patients with 358 melanoma metastases treated with SRS at the Huntsman Cancer Institute at the University of Utah. Patient characteristics are displayed in Table 1. Most patients had RPA Class II disease (90.9%) and 46.4% presented with one brain metastasis. Most patients underwent a single course of SRS (64.5%) and WBRT was not utilized in 57.3% of patients. Planned WBRT was utilized in 27.2% of patients. The most common primary site was head and neck (33.6%). Salvage WBRT was utilized in 25.5% of cases. Metastasis characteristics are displayed in Table 2. The vast majority of metastases were less than 2 cm in size (80.7%).

Pre-treatment hemorrhage was noted in 21.8% of metastases. Following SRS, post-treatment hemorrhage

Table 1. Patient characteristics

		Patients	
		n	%
Total		110	
Age (yrs)(range)		55.9 (19.7 – 89.0)	
Gender	Male	76	69.1%
RPA	1	9	12.0%
	2	100	73.8%
	3	1	1.3%
Primary site	Head and neck	37	33.6%
	Trunk	29	26.4%
	Extremity	20	18.2%
	GI	3	2.7%
	GU	4	3.6%
	Unknown	17	15.5%
Single met initially	1	51	46.4%
#courses	1	71	64.5%
	2	28	25.5%
	3	6	5.5%
	4	1	0.9%
	5	2	1.8%
Pre-treatment hemorrhage		44	40.0%
Post-treatment hemorrhage		38	34.5%
WBRT	None	63	57.3%
	After SRS unplanned	28	25.5%

was noted in 20.7%. These rates were not significantly different ($p=0.362$, $HR=0.846$, 95% CI 0.591-1.211). The one year Kaplan-Meier rate of post-treatment hemorrhage was 32.6%. Utilizing a mixed effects logistic regression model to assess for a possible correlation between SRS and the risk of subsequent hemorrhage of a given lesion, we found no evidence for an influence of SRS on hemorrhage risk ($p=0.99$).

The Kaplan-Meier estimated 1-year overall survival was 30% and median survival was 7.5 months.

Patients with a single brain metastasis at presentation had improved 1 year actuarial overall survival (41.2% vs. 20.3%; $HR 0.60$, 95% CI [0.41-0.89]) (Figure 1). Overall survival was not influenced by hemorrhage either pre- or post- SRS.

Local control at 1 year following SRS was 60.4%. Metastases with pre-treatment hemorrhage had worse 1 year actuarial local control than those without pre-treatment hemorrhage (51.7% vs. 64.9%; $HR 1.90$, 95% CI [1.07-3.37]); $p=0.03$) (Figure 2). The

Table 2. Metastases characteristics

	Metastases	
	n	%
Total	358	
Median follow-up (months)	3.8	
Median dose (Gy)(range)	20 (12-24)	
Size	<2 cm	289 80.7%
	2 to 3 cm	52 14.5%
	>3 cm	17 4.7%
Pre-tx hemorrhage	Yes	78 21.8%
	No	270 75.4%
	Unknown	10 2.8%
Post-tx hemorrhage	Yes	74 20.7%
	No	284 79.3%
Local failures		79 22.1%
Response to local failures	Crani	30 38.0%
	WBRT	9 11.4%
	Re-SRS	7 8.9%
	Supportive	33 41.8%
Response to post-treatment hemorrhage	Crani	15 20.3%
	WBRT	4 5.4%
	Re-SRS	1 1.4%
	Supportive	54 73.0%

crude post-treatment hemorrhage rate was 20.7% of metastases. The 1 year actuarial hemorrhage free survival was 67.9%. Metastases achieving a complete response following SRS (n=62) had a lower rate of hemorrhage post-SRS than those not achieving complete response (HR 0.19, p=0.02). Metastases with post-treatment hemorrhage had worse 1 year actuarial local control than those without post-treatment hemorrhage (32.7% versus 67.8% (HR 3.48; 95% CI [1.94-6.25], p<0.001))(Figure 3). Craniotomy was performed in 20.3% of those lesions while no intervention was performed in 73.0% of lesions after post-treatment hemorrhage.

DISCUSSION

Historical data have shown that fractionated whole brain radiation therapy for melanoma brain metastases leads to no neurological improvement in 60% of cases for whom the median survival is 17 days.²¹ WBRT alone has been well documented as relatively ineffective at achieving local control in patients with metastatic melanoma leading to the suggestion that it is a “radioresistant” histology.²²⁻²⁸ SRS has improved the local control of melanoma cerebral metastases though it is controversial as to whether melanoma brain metastases have poorer local control following SRS treatment than non-

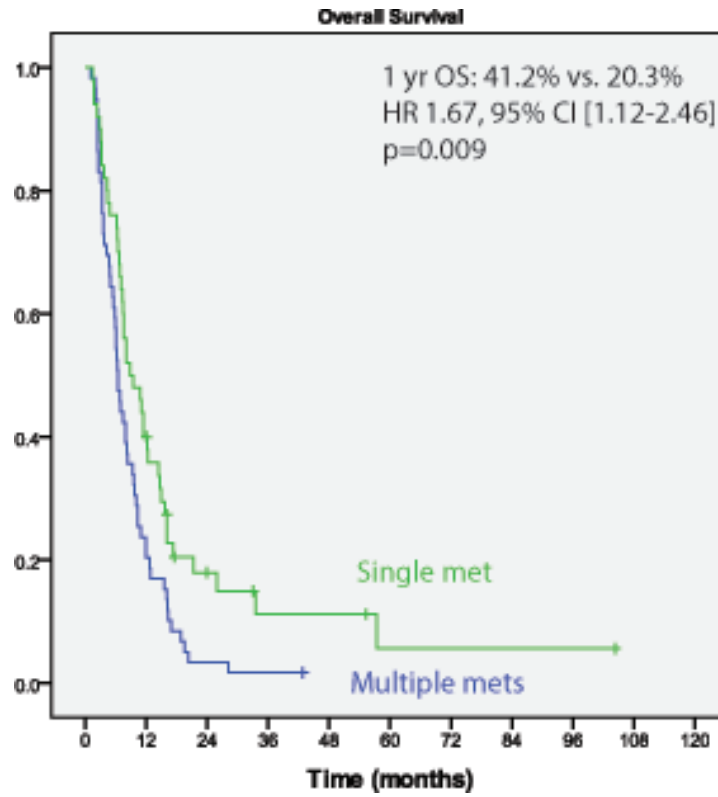


Figure 1. Overall survival is improved in patients with a single brain metastasis (p=0.009)

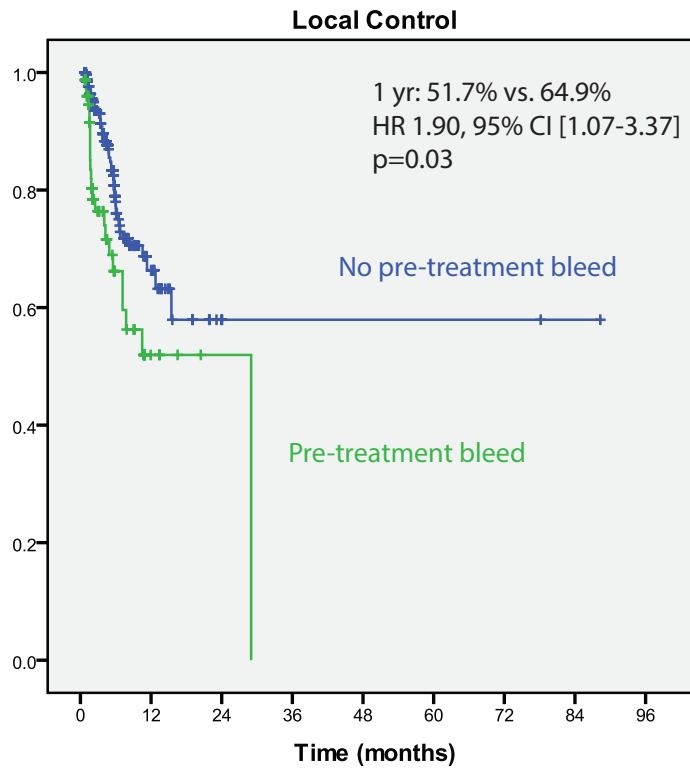


Figure 2. Local control is worse for metastases with pre-treatment hemorrhage (p=0.003)

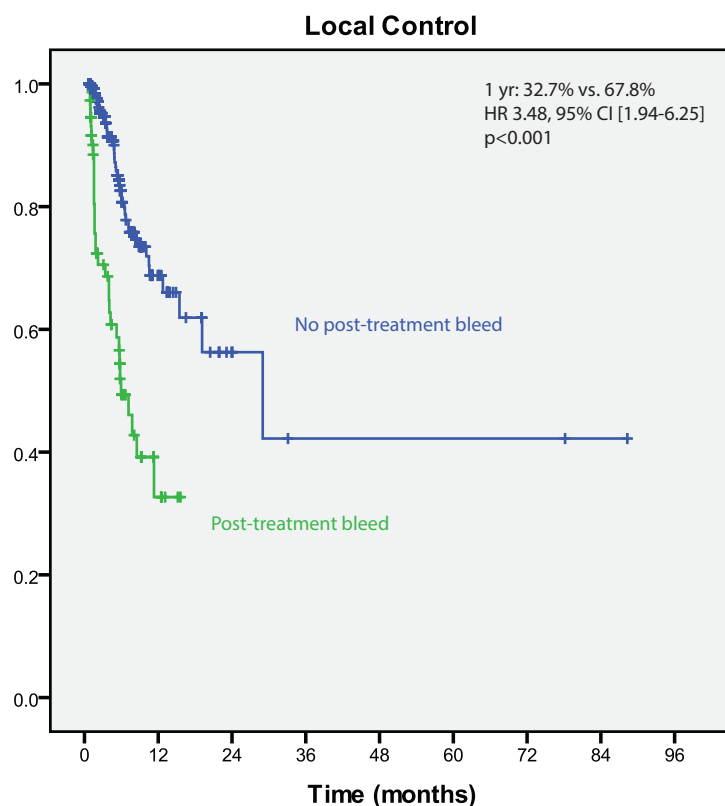


Figure 3. Local control is worse for metastases with post-treatment hemorrhage ($p < 0.001$)

melanoma brain metastases. Some retrospective studies have shown a lower rate of local control for melanoma brain metastases²⁹⁻³³ though others have shown no difference in local control rates of melanoma relative to other histologies.³⁴⁻³⁹ We report a 1 year local control rate for melanoma metastases following SRS of 60.4%.

We report a pre-treatment hemorrhage incidence of 21.8% compared with a post-treatment hemorrhage incidence of 20.7%. We also report no correlation between the use of SRS and hemorrhage risk of a treated lesion. This is consistent with the existing literature. Redmond et al.¹⁵ reported their institutional experience in treating melanoma brain metastases with Gamma Knife. They reported a pre-treatment hemorrhage rate of 23.7% and post treatment hemorrhage rate of 15.2%. They also conclude that Gamma Knife does not appear to increase the rate of hemorrhage.

We found that metastases with pre-treatment hemorrhage have worse local control than those without pre-treatment hemorrhage. This is consistent with previous studies of hemorrhagic brain metastases treated with SRS in which pre-treatment hemorrhage and size correlated with worse local control.^{13, 29, 38} This may be due to a larger target (and subsequently lower dose deliv-

ered). In this report, we also note a higher likelihood for developing post-treatment hemorrhage if pre-treatment hemorrhage is noted. Previous studies have not demonstrated a relationship between pre-treatment hemorrhage and post-treatment hemorrhage.¹⁵

This analysis is limited by the single-institution retrospective design which predisposes it to selection biases. The limited median follow-up related to the patient population is a further drawback. Moreover, the patient population is restricted to those with follow-up imaging lending itself to further selection bias. There is no “control” group of patients with untreated intracranial melanoma metastases to ascertain a baseline risk of hemorrhage over time. As such, a random effects logistic regression model was utilized to estimate the influence of the given treatment (i.e., SRS) on hemorrhage risk using a given metastasis as its own control.

In summary, we report no influence of SRS on the risk of hemorrhage in melanoma brain metastases. Pre-treatment hemorrhage as well as post-treatment hemorrhage correlates to poorer local control within this subset of patients. Hemorrhage must be taken into account when reporting local control data following SRS for melanoma brain metastases.

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