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## Scientific Article

# Distant intracranial failure in melanoma brain metastases treated with stereotactic radiosurgery in the era of immunotherapy and targeted agents

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## Abstract

**Purpose:** Stereotactic radiosurgery (SRS) in combination with immunotherapy (IMT) or targeted therapy is increasingly being used in the setting of melanoma brain metastases (MBMs). The synergistic properties of combination therapy are not well understood. We compared the distant intracranial failure rates of intact MBMs treated with SRS, SRS + IMT, and SRS + targeted therapy.

**Methods and materials:** Combination therapy was defined as delivery of SRS within 3 months of IMT (anti-CTLA-4 /anti-PD-1 therapy) or targeted therapy (BRAF/MEK inhibitors). The primary endpoint was distant intracranial failure after SRS, which was defined as any new MBM identified on brain magnetic resonance imaging. Outcomes were evaluated using the Kaplan Meier method and Cox proportional hazards.

**Results:** A total of 72 patients with melanoma with 233 MBMs were treated between April 2006 and April 2016. The number of MBMs within each treatment group was as follows: SRS: 121; SRS + IMT: 48; and SRS + targeted therapy: 64. The median follow-up was 8.9 months. One-year distant intracranial control rates for SRS, SRS + IMT, and SRS + targeted therapy were 11.5%, 60%, and 10%, respectively ( $P < .001$ ). On multivariate analysis, after adjusting for steroid use and number of MBMs, SRS + IMT remained associated with a significant reduction in distant intracranial failure compared with SRS (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.29-0.80;  $P = .003$ ) and compared with SRS + targeted therapy (HR, 0.41; 95% CI, 0.25-0.68;  $P = .001$ ).

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Conflicts of interest: None.

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One-year local control for SRS, SRS + IMT, and SRS + targeted therapy was 66%, 85%, and 72%, respectively ( $P = .044$ ). On multivariate analysis, after adjusting for dose, SRS + IMT remained associated with a significant reduction in local failure compared with SRS alone (HR, 0.37; 95% CI, 0.14-0.95;  $P = .04$ ).

**Conclusions:** SRS with immunotherapy is associated with decreased distant and local intracranial failure compared with SRS alone. Prospective studies are warranted to validate this result.

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## Introduction

The incidence of cutaneous melanoma has steadily increased over the last 2 decades, with an estimated 87,110 adults to be diagnosed in 2017.<sup>1,2</sup> Approximately 50% of patients with melanoma either present with brain metastases or develop brain metastases during the course of their treatment.<sup>3</sup> More than 90% of patients with melanoma brain metastases (MBMs) will die from progression of their intracranial disease.<sup>4</sup> Compared with patients with brain metastases from breast or lung cancer, patients with MBMs have an almost 3-fold increased risk of neurologic death.<sup>5</sup>

Novel therapeutic agents such as immunotherapy (IMT) consisting of anti-CTLA-4 and/or anti-PD-1 therapy and targeted agents, consisting of BRAF and MEK inhibitors, have been shown to improve overall survival (OS) in patients with advanced melanoma, shifting the treatment paradigm away from conventional chemotherapy.<sup>6-9</sup> Single-arm, prospective studies examining the role of these agents in the setting of MBM have shown intracranial response rates varying from 5% to 39%.<sup>10,11</sup> Retrospective studies of the combined efficacy of SRS with either IMT or BRAF/MEK inhibitors have shown acceptable safety profiles<sup>10-12</sup> and have suggested that the timing of IMT with respect to SRS may differentially affect outcome.<sup>11,13</sup> However, only 1 study compared IMT and targeted therapy against one another in the setting of SRS for MBMs and did not find a difference in OS or distant intracranial failure.<sup>14</sup> Given the paucity of data on the relative efficacy of various combination regimens, we compared survival and distant intracranial failure outcomes of SRS alone, SRS + IMT (anti-CTLA-4 and anti-PD1 therapy), and SRS + targeted therapy (BRAF/MEK inhibitors) from a single institution.

## Methods and materials

### Patient population

Patients with intact MBMs who were treated with single-fraction SRS at Washington University in St. Louis between April 2006 and April 2016 were identified as part of a retrospective study that was approved by the institutional review board. Patients were included if they had at least 1 follow-up brain magnetic resonance imaging (MRI) scan. A total

of 233 MBMs in 72 patients met the inclusion criteria. Baseline patient, tumor, and treatment data were collected in a retrospective fashion.

### Radiosurgery

All patients underwent single-fraction SRS with Leksell Gamma Knife (Elekta Medical Systems, Stockholm, Sweden). Patients were treated with the Perfexion model Gamma Knife unless treated prior to April 2008, in which case a Model C unit was utilized. A high-resolution contrast-enhanced brain MRI and non-contrast-enhanced head computed tomography scan were obtained for treatment planning. A medical physicist, radiation oncologist, and neurosurgeon completed target delineation and treatment planning in concert. The prescription dose was based on recommendations from Radiation Therapy Oncology Group trial 90-05 with adjustments made at the discretion of the treating physician. In general, lesions measuring  $\leq 2$  cm were treated to 20 to 24 Gy, lesions 2.1 to 3 cm were treated to 18 Gy, and lesions  $> 3$  cm were treated to 15 Gy.

### Immunotherapy and targeted therapy

Combination therapy was defined as the delivery of SRS within 3 months of IMT (anti-CTLA-4/anti-PD-1 therapy) or targeted therapy (BRAF/MEK inhibitors). Patients who were not treated within 3 months of IMT or targeted therapy either received conventional chemotherapy or interleukin-2. IMT consisted of anti-PD-1 therapy, anti-CTLA-4 therapy, or a combination of both. In all cases, anti-PD-1 and anti-CTLA-4 therapy was either delivered before SRS and continued after SRS (concurrent) or delivered after SRS. Anti-PD-1 agents consisted of nivolumab, which was administered at 3 mg/kg every 2 weeks, or pembrolizumab, which was administered at 2 mg/kg every 3 weeks. Anti-CTLA-4 therapy consisted of ipilimumab, administered over 4 infusions every 3 weeks at 3 mg/kg or 10 mg/kg. Patients who received BRAF inhibitor (vemurafenib or dabrafenib) with or without MEK inhibitor (trametinib) harbored the V600E mutation. Vemurafenib was administered at 960 mg twice daily as a single agent. The BRAF/MEK inhibitor regimen consisted of dabrafenib 150 mg twice daily and trametinib 2 mg daily. BRAF/MEK inhibitors were held for 2 to 5 days prior to and after SRS.

## Patient follow-up

Patients were followed every 2 to 3 months with a brain MRI scan. All MRI images from the time of SRS to death or last follow-up were independently reviewed by 2 investigators (S.A. and C.A.).

## Outcome measures

The primary endpoint was distant intracranial failure, measured as the time from single-fraction SRS to the development of a new brain metastasis or last brain MRI scan. Distant intracranial failure was coded for each treated metastasis. Therefore, if a patient underwent 2 single-fraction SRS sessions, distant intracranial failure was coded separately for metastases treated during the first and second session. The treatment group for each metastasis was based on the type of therapy received within 3 months of SRS. OS was measured as the time from the first SRS to the time of death or last follow-up. When analyzing OS, treatment groups were based on the type of therapy received at first SRS. Local failure was determined for each MBM and was defined as an increase in the size of the treated metastasis at any time post-SRS, unless additional imaging studies or pathology from subsequent surgical resection noted radiation necrosis or pseudoprogression. This definition of local failure is consistent with that in our previously published work.<sup>15</sup>

## Statistical analysis

Frequency distributions between groups were assessed with Fisher's exact test for categorical variables and Wilcoxon rank sum for continuous variables. Prognostic factors were evaluated using the Kaplan Meier product-limit method and Cox proportional hazards regression model. Variables that were significant on Cox univariate analysis ( $P < .05$ ) were considered for Cox multivariate analysis. The cumulative incidence of distant intracranial failure was calculated using a competing risks model with death as a competing risk factor.

## Results

### Patient and melanoma brain metastases characteristics

Patient and MBM characteristics are listed in Table 1. The treatment groups were as follows: 121 MBMs (38 patients) were treated with SRS, 48 MBMs (18 patients) were treated with SRS + IMT, and 64 MBMs (16 patients) were treated with SRS + targeted therapy. Within the SRS + IMT group, 14 MBMs (29%) underwent SRS within 3 months

of both anti-PD-1 and anti-CTLA-4, 31 MBMs (65%) underwent SRS within 3 months of anti-CTLA-4 alone, and 3 MBMs (6%) underwent SRS within 3 months of anti-PD-1 alone. Patients were on anti-PD-1 and anti-CTLA-4 therapy for a median duration of 12.6 months (range, 0.23-25.9) and 2.1 months (range, 0.8-14.2), respectively. Within the SRS + BRAF/MEK-I group, 28 MBMs (44%) underwent SRS within 3 months of both BRAF-I and MEK-I therapy. Patients were on BRAF-I alone and BRAF-I + MEK-I for a median of 7.5 months (range, 1.13-13.9) and 11.2 months (range, 1.6-21.8), respectively. Patients who were treated with SRS + IMT were older than those who were treated with SRS or SRS + targeted therapy ( $P = .014$ ), had a lower number of repeat SRS sessions ( $P = .024$ ), and were more likely to be treated in a concurrent fashion ( $P < .001$ ). There were no differences between treatment groups in terms of Karnofsky performance status, Graded Prognostic Assessment score, dose, volume of each MBM, and total volume of MBM per SRS. A total of 61 patients (85%) underwent more than 1 follow-up brain MRI scan.

### Steroid use prior to stereotactic radiosurgery

Steroids were initiated prior to SRS in 21 cases. The majority of these patients ( $n = 19$ ) were administered dexamethasone in doses that ranged from 2 mg daily to 4 mg every 6 to 12 hours. One patient was taking 80 mg prednisone daily for dermatomyositis and another patient was taking 40 mg of prednisone daily for autoimmune colitis secondary to ipilimumab use.

### Distant intracranial failure and local failure

The rate of distant intracranial control at 1 year was higher in the SRS + IMT treatment group compared with the SRS and SRS + targeted therapy groups (60% vs 11.5% vs 10%,  $P < .001$ ; Fig 1). On multivariate analysis, SRS + IMT remained associated with a 52% reduction in risk of distant intracranial failure compared with SRS (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.29-0.80;  $P = .003$ ) and a 59% reduction in risk of distant intracranial failure compared with SRS + targeted therapy (HR, 0.41; 95% CI, 0.25-0.68,  $P = .001$ ; Table 2). When using death as a competing risk, the cumulative incidence of distant intracranial failures was also significantly reduced in the SRS + IMT treatment group compared with treatment without IMT (subhazard ratio, 0.51; 95% CI, 0.33-0.78;  $P = .002$ ). As a robustness check, the analysis was repeated after excluding patients who received whole brain radiation prior to the first SRS ( $n = 7$ ), and results remained unchanged (Suppl Fig S1).

On subgroup analysis, SRS within 3 months of both anti-PD-1 and anti-CTLA-4 ( $n = 14$ ) resulted in improved 6-month distant intracranial control compared with

**Table 1** Patient and MBM characteristics

Patient/Tumor Characteristics	SRS	SRS + IMT	SRS + BRAF/MEK	P-value <sup>a</sup>
No. of Patients	38	18	16	
No. of MBMs	121	48	64	
Median age (range), y	56 (31-81)	61 (36-86)	52 (31-65)	.014
KPS at first SRS, n (%)				.628
60	1 (3)	0	0	
70	4 (11)	0	0	
80	13 (34)	4 (22)	5 (31)	
90	16 (42)	9 (50)	4 (25)	
100	4 (11)	5 (28)	7 (44)	
GPA at first SRS, n (%)				.876
1	5 (13)	1 (6)	1 (6)	
2	10 (26)	5 (28)	8 (50)	
3	13 (34)	7 (39)	6 (38)	
4	10 (26)	5 (0)	1 (6)	
Male: Female	31:7	12:6	6:10	1.0
Whole-brain radiation therapy prior to first SRS	3	1	3	1.0
Median dose (range), Gy	20 (11.2-24)	20 (15-24)	18 (16-24)	.119
Median volume (mm <sup>3</sup> ) per MBM (range)	362 (14-23,700)	329 (4-13,520)	112 (3-22,410)	.234
Median total volume (mm <sup>3</sup> ) per SRS (range)	2096 (88-36,695)	1415 (50-26,417)	931 (12-32,825)	.055
Median no. of MBMs per SRS (range)	3 (1-11)	4 (1-6)	4 (1-6)	.228
Median no. of SRS sessions per patient (range)	1 (1-3)	1 (1-2)	1 (1-4)	.024
Timing of IMT/BRAF/MEK-I, n (%)				< .001
Prior to SRS	N/A	0 (0)	9 (14)	
After SRS	N/A	3 (6)	13 (20)	
Concurrent SRS	N/A	45 (94)	42 (66)	
Steroid use prior to SRS				.416
Yes	22 (18)	7 (15)	17 (15)	
No	99 (81)	41 (85)	47 (73)	
Systemic disease prior to SRS, n (%)				.188
NED	3 (2)	7 (14)	15 (23)	
PD	68 (56)	27 (56)	21 (33)	
PR	5 (4)	1 (2)	14 (22)	
SD	45 (37)	13 (27)	14 (22)	

GPA, graded prognostic assessment; IMT, immunotherapy; KPS, Karnofsky performance status; MBM, melanoma brain metastasis; N/A, not available; NED, no evidence of disease; PD, progressive disease; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery.

<sup>a</sup> Comparison of IMT + SRS therapy to all other treatment groups.

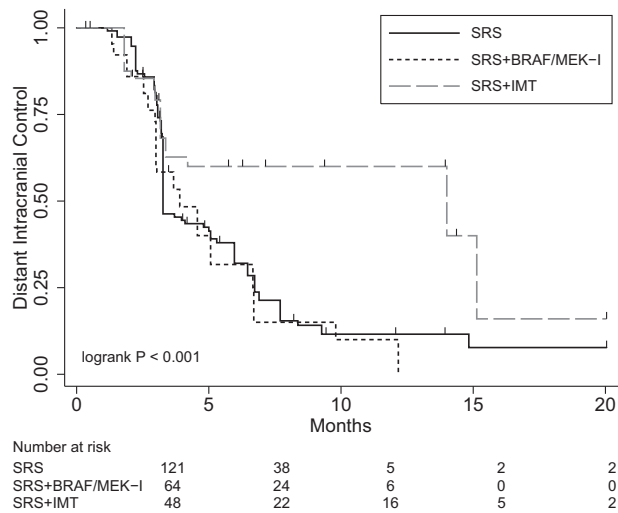
anti-PD-1 or anti-CTLA-4 alone (n = 34; 84% vs 50%;  $P = .016$ ). When stratifying the SRS + targeted therapy group on the basis of BRAF + MEK-I (n = 28) versus BRAF-I alone (n = 36), SRS within 3 months of BRAF + MEK-I resulted in improved 6-month distant intracranial control compared with BRAF-I alone (45% vs 21%;  $P = .011$ ).

The local control rate also differed significantly between treatment groups (SRS vs SRS + IMT vs SRS + targeted therapy: 66% vs 85% vs 72%;  $P = .044$ ; Fig 2). On univariate analysis, treatment group, number of MBMs, and dose were significantly associated with local control (Table 3). Dose, both as a continuous variable and dichotomized at 20 Gy, was significant on univariate analysis; however, dose >20 Gy was carried into the multivariate analysis due to its larger effect size. On multivariate analysis, SRS + IMT (compared with SRS alone) and dose >20 Gy remained significantly associated with a

decreased risk of local failure ( $HR_{SRS+IMT}$ , 0.37; 95% CI, 0.14-0.95;  $P = .04$ ;  $HR_{dose>20\text{ Gy}}$ , 0.22; 95% CI, 0.08-0.61,  $P = .004$ ).

## Survival analysis

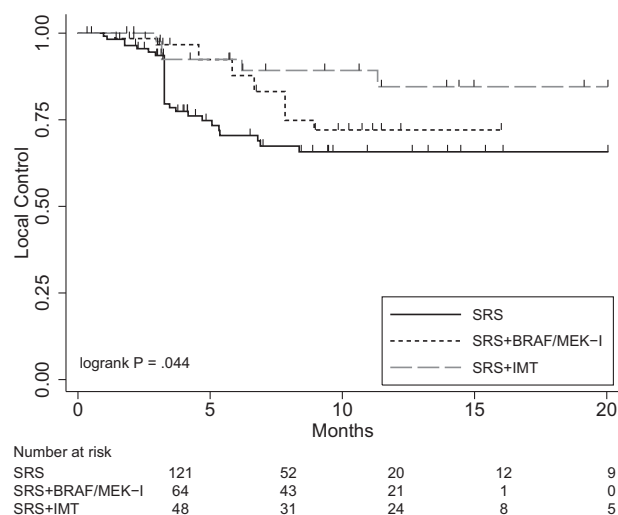
The median follow-up was 8.9 months for all patients and 12 months for patients who were alive at the time of analysis. For patients who were not alive at the time of the analysis, the median time between last brain MRI and death was 1.7 months. One-year OS was higher in patients who were initially treated with SRS + IMT during the first SRS session compared with patients who were treated without IMT (58% vs 31%,  $P = .016$ ; Fig 3). However, on multivariate analysis, only total volume of intracranial disease at first SRS and steroid use prior to first SRS remained significantly associated with OS (Suppl Table S1).



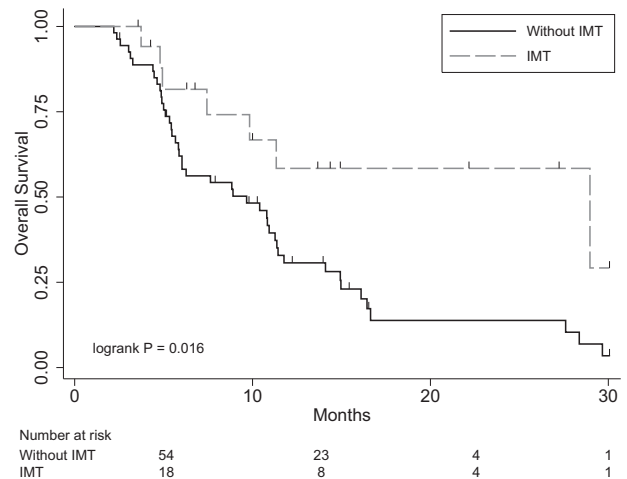
**Figure 1** Distant intracranial control of 233 melanoma brain metastases across 215 stereotactic radiosurgery sessions stratified by receipt of immunotherapy (anti-CTLA-4/anti-PD-1) or targeted therapy (BRAF/MEK-inhibitors).

**Toxicity**

Two patients developed seizures the day after SRS and required hospitalization. One of these patients was treated with SRS alone and the other was treated with SRS + BRAF-I. Pathology findings from emergent surgical resection in both cases confirmed metastatic melanoma with large areas of hemorrhage. Another patient developed headaches 5 months after SRS + BRAF-I, which persisted despite dexamethasone. MRI revealed hemorrhage in 2 MBMs, which required surgical resection. Pathology confirmed metastatic melanoma in 1 lesion and predominant radiation



**Figure 2** Local control of 233 melanoma brain metastases stratified by receipt of immunotherapy (anti-CTLA-4/anti-PD-1) or targeted therapy (BRAF/MEK-inhibitors).



**Figure 3** Overall survival in patients with melanoma brain metastases who were treated with or without immunotherapy during the first stereotactic radiosurgery.

necrosis in another. One patient who was treated with SRS + IMT underwent laser ablation of an MBM for presumed radiation necrosis. Biopsies were not obtained for pathologic review.

**Discussion**

Our results yield 3 important findings. First, the combined treatment of SRS + IMT is associated with decreased distant intracranial failures compared with both SRS and SRS + targeted therapy. Even after adjusting for the number of MBMs, volume of intracranial disease, and steroid use prior to SRS, treatment with SRS + IMT was associated with a significant decrease in distant intracranial failure. Ahmed et al compared the outcomes of SRS + targeted therapy with those of SRS + IMT and SRS alone.<sup>14</sup> They also found that SRS + IMT was associated with improved distant intracranial control when compared with SRS alone but not when compared with SRS + targeted therapy. Their 1-year distant intracranial control rates of 5% versus 8% versus 20% for MBMs treated with SRS versus SRS + BRAF-I versus SRS + BRAF/MEK-I, respectively, are not very different from our rate of 11% for both SRS and SRS + targeted therapy.<sup>14</sup> However, our 1-year distant intracranial failure for SRS + IMT is higher than that reported by Ahmed et al. One explanation for this may be that the majority of patients in our study were treated with concurrent IMT, and all patients were continued on IMT after SRS. Kiess et al reported improved distant intracranial control rates for patients who received IMT after, rather than before, SRS.<sup>11</sup>

When interpreting our results, it is important to acknowledge the heterogeneity in the SRS + IMT treatment group. Twenty-nine percent of MBMs within this group underwent SRS within 3 months of both anti-PD-1 and anti-CTLA-4. The remaining MBMs were treated within 3

**Table 2** Univariate and multivariate analysis for distant intracranial failure

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Treatment Group				
SRS	1	.176	1	.317
SRS + BRAF/MEK-I	1.25 (0.90-1.74)	<.001	1.18 (0.89-1.84)	.003
SRS + IMT	0.42 (0.26-0.66)		0.48 (0.29-0.80)	
No. of MBM per SRS	1.12 (1.05-1.18)	<.001	1.09 (1.03-1.16)	.005
No. of SRS sessions	0.83 (0.61-1.14)	.246	–	
Volume (mm <sup>3</sup> ) <sup>a</sup>	1.16 (1.04-1.28)	.005	1.02 (0.90-1.16)	NS
Dose (cGy)	0.99 (0.98-0.99)	.019	1.00 (0.99-1.00)	NS
Sex				
Male	1	.693	–	
Female	1.07 (0.76-1.50)			
KPS at time of SRS				
60	1	.232	–	
70	0.33 (0.05-2.01)	.305	–	
80	0.48 (0.11-1.97)	.176	–	
90	0.38 (0.09-1.55)	.185	–	
100	0.38 (0.09-1.59)			
GPA at time of SRS				
1	1	.928	1.23 (0.70-2.16)	NS
2	1.01 (0.68-1.52)	.167	1.23 (0.68-2.24)	NS
3	0.74 (0.48-1.14)	.032	1.25 (0.54-2.88)	NS
4	0.49 (0.26-0.94)			
Age	0.99 (0.98-1.0)	.064	–	
Prior WBI				
No	1	.434	–	
Yes	1.18 (0.78-1.80)			
Steroid use prior to SRS				
No	1	<.001	1	.002
Yes	2.07 (1.42-2.99)		1.81 (1.25-2.64)	
Systemic disease				
NED	1	.507	–	
PD	0.85 (0.54-1.36)	.313	–	
PR	0.73 (0.39-1.35)	.522		
SD	0.85 (0.52-1.39)			

CI, confidence interval; GPA, graded prognostic assessment; IMT, immunotherapy; HR, hazard ratio; KPS, Karnofsky performance status; MBM, melanoma brain metastasis; NED, no evidence of disease; NS, not shown; PD, progressive disease; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery; WBI, whole-breast irradiation.

<sup>a</sup> Volume (mm<sup>3</sup>) is log transformed and represents total volume of intracranial disease at a given SRS treatment.

months of single-agent anti-PD-1 (6%) or anti-CTLA-4 (65%). Although our study numbers are small, on subgroup analysis, distant intracranial control was higher when both anti-PD-1 and anti-CTLA-4 were delivered within 3 months of SRS compared with either agent alone. This is consistent with data from Checkmate 067, which showed improved progression-free survival in patients who received both anti-PD-1 and anti-CTLA-4 compared with anti-CTLA-4 alone. However, it should be noted that patients with brain metastases were excluded from this study. Studies with large numbers of MBMs are needed to determine whether the benefit of improved distant intracranial control is limited to patients who receive both anti-PD-1 and anti-CTLA-4 therapy in a concurrent or sequential fashion.

There is also some degree of heterogeneity within the SRS + targeted therapy group. Forty-four percent of MBMs within this group underwent SRS within 3 months of BRAF-I + MEK-I, and the remaining MBMs underwent SRS within 3 months of BRAF-I alone. On subgroup analysis, SRS within 3 months of both BRAF + MRK-I was associated with improved distant intracranial control compared with BRAF-I alone. This is consistent with several randomized control trials that showed improved progression-free survival in patients with advanced melanoma who underwent combination BRAF-I + MEK-I compared with BRAF-I alone.<sup>8,16</sup>

Second, similar to distant intracranial control, local control was superior in MBMs that were treated with SRS + IMT compared with SRS alone, after adjusting for



**Table 3** Univariate and multivariate analysis for local failure

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Treatment Group				
SRS	1	.176	0.51 (0.26-1.01)	.054
SRS + BRAF/MEK-I	0.63 (0.32-1.23)	.028	0.37 (0.14-0.95)	.040
SRS + IMT	0.34 (0.13-0.89)			
No. of MBM per SRS	1.15 (1.04-1.28)	.007	1.07 (0.96-1.20)	NS
Volume (mm <sup>3</sup> )	1.12 (0.95-1.32)	.175	–	
Size >3 cm				
No	1	.062		
Yes	2.42 (0.96-6.14)			
Total Volume (mm <sup>3</sup> ) <sup>a</sup>	1.08 (0.89-1.31)	.422	–	
Dose (Gy)	0.75 (0.66-0.85)	< .001	–	
Dose >20 Gy				
No	1	.005	1	.004
Yes	0.23 (0.08-0.64)		0.22 (0.08-0.61)	
Gender				
Male	1	.436	–	
Female	1.27 (0.69-2.35)			
KPS at time of SRS				
100	1	.120	–	
90	1.95 (0.84-4.53)	.125	–	
80	2.02 (0.82-4.96)	.725	–	
70	1.45 (0.18-11.88)		–	
60	No events			
GPA at time of SRS				
1	1	.532	–	
2	1.33 (0.54-3.26)	.556	–	
3	0.73 (0.27-2.03)	.353	–	
4	1.68 (0.56-5.0)		–	
Age	1.01 (0.99-1.02)	.530	–	
Prior WBI				
No	1	.697	–	
Yes	0.81 (0.29-2.28)			
Steroid prior to SRS				
No	1	.843	–	
Yes	1.09 (0.46-2.58)			
Systemic disease				
SD	1	.775	–	
PR	0.85 (0.27-2.63)	.129	–	
PD	1.68 (0.85-3.27)			
NED	No events			

CI, confidence interval; GPA, graded prognostic assessment; IMT, immunotherapy; HR, hazard ratio; KPS, Karnofsky performance status; MBM, melanoma brain metastasis; NED, no evidence of disease; NS, not shown; PD, progressive disease; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery; WBI, whole-breast irradiation.

<sup>a</sup> Volume (mm<sup>3</sup>) is log transformed and represents total volume of intracranial disease at a given SRS treatment.

dose. Qian et al showed that SRS within 4 weeks of IMT resulted in a greater reduction of MBM volume at 1.5 and 6 months compared with SRS delivered more than 4 weeks from IMT.<sup>13</sup> A greater response rate was also observed in patients who were treated with anti-PD-1 therapy compared with patients who were treated with anti-CTLA-4 therapy. We did not have a sufficient number of patients who were treated within 4 weeks of SRS to study the relationship between timing of IMT and local or distant control.

Third, combination therapy, as delivered in our patient population, appears to be well tolerated with no unanticipated neurotoxic events. There were only 2 cases of radiation necrosis and 2 cases of seizures secondary to hemorrhagic MBMs that required emergent surgery. Given that MBMs have a 10% probability of hemorrhage after SRS, this would not be considered unusual.<sup>17</sup> Others have reported acceptable toxicity profiles when combining SRS with BRAF-I or IMT.<sup>18-20</sup> Due to the low number of events, a formal analysis of predictors for neurotoxicity was not possible.

Although 1-year OS was greater in patients who were initially treated with SRS + IMT compared with those who were treated without IMT, this benefit did not hold on multivariate analysis when accounting for total volume of intracranial disease and steroid use. A review of the literature demonstrates mixed results, with some retrospective studies demonstrating a favorable association between SRS + IMT and OS and others finding no association.<sup>14,20,21</sup> Inconsistencies may be due to the fact that not all retrospective studies control for variables such as tumor volume or steroid use in their multivariate model.

Evasion of the immune system is a known hallmark of metastatic disease, and there is an emerging hypothesis that coadministration of radiation and IMT may enhance the immune system's response to cancer.<sup>22</sup> This hypothesis stems from the observation that radiation, particularly in high doses, upregulates inflammatory cytokines that promote tumor lymphocyte infiltration and presentation of neoantigens in the tumor microenvironment, thereby increasing the immunogenicity of tumors.<sup>23,24</sup> This effect, coupled with anti-CTLA-4 and anti-PD-1 therapy, may result in a heightened immune response to cancer cells.<sup>25,26</sup>

Our results add credence to this hypothesis because MBMs that were treated with SRS and anti-CTLA-4/anti-PD-1 therapy had improved distant intracranial control compared with patients who did not receive IMT. However, given the retrospective nature of this study, robust prospective studies are needed to formally test the presence of a synergistic effect between SRS and IMT. Such prospective studies are already underway with 4 actively enrolling trials combining IMT and SRS for MBMs (ClinicalTrials.gov identifiers: NCT01703507, NCT1950195, NCT01689974, NCT02107755). However, questions still remain regarding the sequence and time interval between the 2 therapies, whether steroids can be administered without decreasing efficacy of IMT, and how and when to measure response to therapy.

The limitations of this study include its retrospective nature, small patient numbers, and heterogeneity within treatment groups. Our results should be interpreted with the understanding that 29% of MBMs within the SRS + IMT group were treated with both anti-PD-1 and anti-CTLA-4, and 44% of MBMs within the SRS + targeted therapy group were treated with both BRAF-I and MEK-I. Although patients do cross over from 1 drug class to another and such crossovers could potentially confound our results, there was no difference in the proportion of patients who remained on IMT or targeted therapy until the date of last follow-up or distant intracranial failure. Therefore, differences in the crossover rates between treatment groups are unlikely to explain the difference in outcomes.

Additional limitations to this study include the fact that the primary endpoint and the time interval between systemic therapy and SRS were not prespecified. A 3-month time interval was chosen on the basis of our patient population and its use in prior studies.<sup>14</sup> Selection biases may

also influence the results of our study because patients who require steroids for symptom management may be less likely to be treated with IMT. To reduce the influence of such biases, we controlled for steroid use in our multivariate analysis. Toxicity may also be underreported because toxicity data were collected in a retrospective fashion.

## Conclusion

Despite the study limitations, our data represent one of the few published series comparing outcomes of SRS versus SRS + targeted therapy versus SRS + IMT in intact MBMs and provides insight into combination therapy that warrants prospective validation. Because the majority of patients with MBMs die from progression of intracranial disease, there may be opportunities to improve outcomes through optimal combinations of SRS and IMT.

## Supplementary data

Supplementary material related to this article can be found at <https://doi.org/10.1016/j.adro.2017.07.003>.

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