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Original Research Article

Role of radiotherapy in extracranial metastatic malignant melanoma in the modern era

Ryan S. Youland [a], Miran L. Blanchard [a], Roxanna Dronca [b], Lisa Kottschade [b], Svetomir N. Markovic [b], Kenneth R. Olivier [a], Sean S. Park [a,*]

[a] Department of Radiation Oncology, Mayo Clinic, 200 First Street, Rochester, MN 55905, United States
[b] Division of Medical Oncology, Mayo Clinic, 200 First Street, Rochester, MN 55905, United States

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ABSTRACT

Background: To assess the role of radiotherapy in metastatic malignant melanoma (MM) patients in modern era.
Materials and methods: This is a retrospective study of MM patients treated with radiotherapy at Mayo Clinic from 1999 to 2014. Patients with pre- and post-treatment imaging studies (CT, MRI, and/or PET/CT) were assessed for metastasis failure (MF), regional/distant failure, and overall survival (OS).
Results: In 75 MM patients, 56 and 68 lesions were treated with conventional/hypofractionated radiotherapy (CHRT) and stereotactic body radiotherapy (SBRT), respectively. The median doses for CHRT and SBRT were 30 Gy and 50 Gy, respectively. 1-year MF was 17% (SBRT 6% vs CHRT 31%, $p < 0.01$). 1-year regional (5% vs 29%, $p < 0.01$) and distant progression (75% vs 89%, $p < 0.01$) were improved with SBRT. Median OS was 15.6 months (CHRT 7.0 vs SBRT 22.9, $p < 0.01$). Prognostic factors for OS included age $\leq$55 years (RR 0.25), oligometastatic disease (RR 0.34), SBRT (RR 0.38) and treating all lesions (RR 0.28, all $p < 0.01$).
Conclusions: SBRT for extracranial MM exhibited improved MF compared with CHRT, consistent with intracranial radiosurgery data. Though these data are retrospective and subject to selection bias, our findings support the prudent use of SBRT in a select group of favorable, oligometastatic MM patients, and should be discussed as an alternative to surgery and ablation.

Background

Malignant melanoma (MM) is known to be a relatively radioresistant cancer due to its high intrinsic capacity to repair sublethal DNA damage, which presents as a broad "shoulder" on cell survival curves [1,4,25]. Although *in vitro* cell survival studies have suggested that hypofractionated regimens may have an advantage over standard fractionation, [10,13,14] a randomized trial showed no difference in clinical outcomes between the two fractionation schemes [26]. Moreover, it has been shown that radioresistance increases as melanoma metastasizes [24]. Despite the concern for radioresistance, excellent metastasis control (MC) rates have been reported with stereotactic radiosurgery (SRS) for intracranial MM [18,19,23]. This study aimed to assess the efficacy of radiotherapy in the modern era and compared the outcomes between stereotactic body radiotherapy (SBRT) with conventional/hypofractionated radiotherapy (CHRT) for extracranial metastatic MM.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. Patients included in the analysis had a billing diagnosis of extracranial metastatic MM treated with radiotherapy at our institution between 1999 and 2014. Patients with at least one post-radiotherapy imaging study were included. The electronic medical record was used to capture clinical characteristics. CHRT was defined as 8 Gy or less delivered per fraction (range 1–20 fractions; 8–50 Gy), most commonly using three-dimensional conformal radiotherapy. SBRT was delivered in 1–5 fractions to 18–60 Gy via linear accelerator-based Volumetric Arc Therapy. Oligometastasis was defined as six or fewer metastatic lesions. Patients with a history of prior radiation therapy or an additional

* Corresponding author. Fax: +1 507 284 0079.
E-mail address: Park.Sean@Mayo.edu (S.S. Park).

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coexisting malignancy were not excluded. However, those undergoing reirradiation of the same lesion were excluded.

Each metastatic lesion was assessed independently. Metastasis failure (MF) of the radiated lesion was assessed using all available post-radiotherapy imaging which included CT and/or MRI using RECIST criteria [5]. When available, PET/CT was preferred over other imaging modalities and PERCIST criteria were used for response evaluation [32]. Patients were classified as having a response if they had stable disease, a partial response or a complete response. Regional and distant failures were assessed by evaluating draining lymph node basins and distant anatomical regions, respectively. Survival data were obtained from the electronic medical record, which was updated by the social security death index if patients were otherwise lost to follow-up. For surviving patients, the date of last contact was used to define the patient's last follow-up date. Toxicity was prospectively collected in SBRT patients using CTCAE version 4.0 at the time of initial consultation, at the end of treatment, and during follow-up visits.

Single fraction equivalent dose (SFED) was calculated using established methods [21]. The Likelihood Ratio was used for comparison of characteristics between the two groups. The Kaplan-Meier method was used to calculate survival estimates, which were compared using the Log-Rank test. Prognostic factors were chosen for univariate analysis based on significance in prior studies. Multivariate analysis used the Cox proportional hazards model with prognostic factors found to be significant on univariate analysis. All statistical analyses were performed by a statistician from Mayo Clinic Cancer Center.

Results

Patient, Tumor, and treatment characteristics

A total of 124 lesions (56 CHRT and 68 SBRT) were treated in 75 patients. Median follow-up was 3.1 years (2.9 CHRT vs 4.9 SBRT). Patient, tumor, and treatment characteristics are summarized in Table 1. BRAF mutation status was available in 16 patients (56% were mutation-positive). The mean age of SBRT patients was older than CHRT (59.8 years vs 54.6 years, $p = 0.049$). A greater portion of SBRT patients had all sites of disease treated (65% vs 21%, $p < 0.01$), presented with oligometastatic disease (72% vs 54%, $p = 0.03$) and were treated with curative intent (66% vs 5%, $p < 0.01$).

The median doses for CHRT and SBRT were 30 Gy (range 8–50) and 50 Gy (range 18–60), respectively. The most common treatment regimens were 30 Gy in 10 fractions for CHRT and 50 Gy in 5 fractions for SBRT. The median SFED was 23.3 Gy overall (13.8 Gy for CHRT and 42.8 Gy for SBRT). Musculoskeletal (41% vs 22%, $p < 0.01$) and spine (30% vs 4%, $p < 0.01$) sites were more commonly treated with CHRT compared with SBRT. Conversely, a greater number of visceral metastases were treated with SBRT than CHRT: lung (25% vs 7%, $p < 0.01$) and liver (21% vs 2%, $p < 0.01$). A higher proportion of CHRT patients had recent chemotherapy within three months (55% vs 31%, $p < 0.01$) whereas more patients treated with SBRT had recent targeted or immunotherapy (69% vs 43%, $p < 0.01$).

Clinical outcomes

Complete response rates were higher after SBRT than CHRT (81% vs 13%, $p < 0.0001$). The rates of MF for all patients at 1 and 4 years were 17% and 20%, respectively. One- and 4-year MF rates were 6% and 10%, respectively, for SBRT patients, and 31% and 33%, respectively, for CHRT patients ($p < 0.01$; Fig. 1A). On univariate analysis, the use of SBRT ($p < 0.01$), curative treatment intent ($p < 0.01$) and treating all lesions ($p = 0.02$) were associated with improved MF (Table 2). Multivariate analysis was not performed due to a low number of events.

Regional failure was observed in 20 overall (4 SBRT and 16 CHRT; Fig. 1B). The rate of regional failure at 1 year 15% overall, 5% after SBRT and 29% after CHRT, and at 4 years was 16% overall, 6% after SBRT and 29% after CHRT ($p < 0.01$). Factors associated with a reduced risk of regional failure on univariate analysis (Table 2) included SBRT ($p < 0.01$), curative treatment intent ($p = 0.01$) and treatment of all lesions ($p = 0.02$). Multivariate analysis was not performed due to an insufficient number of events for a meaningful analysis.

Distant failure was observed in 111 overall (58 SBRT and 53 CHRT; Fig. 1C). The rate of distant failure at 1 year was 81% overall, 75% after SBRT and 89% after CHRT, and at 4 years was 90% overall, 86% after SBRT and 95% after CHRT ($p < 0.01$). Factors associated with a lower risk of distant failure on univariate analysis (Table 2) included SBRT ($p < 0.01$), curative treatment intent ($p = 0.048$) and treatment of all lesions ($p < 0.01$). All three prognostic factors remained significantly associated with distant failure on multivariate analysis (Table 3).

Median overall survival (OS) was 15.6 months overall, 22.9 months after SBRT and 7.0 months after CHRT (Fig. 2A and B, $p < 0.01$). At 1 year, OS was 54% overall (79% after SBRT and 26% after CHRT, $p < 0.01$). Factors associated with improved OS on univariate analysis (Table 2) included oligometastatic disease ($p < 0.01$), use of SBRT ($p < 0.01$), SFED $\geq$45 Gy ($p = 0.02$), curative treatment intent ($p < 0.01$) and treatment of all lesions ($p < 0.01$). Notably, the use of recent systemic chemotherapy ($p = 0.07$) or targeted/immunotherapy ($p = 0.05$) were marginally associated with OS. On multivariate analysis, factors significantly associated with improved OS include age $\leq$55 years, oligometastatic disease, use of SBRT and treatment of all lesions (all $p < 0.01$, Table 3).

Toxicity

Toxicity data was obtained prospectively in patients receiving SBRT (Table 4). Acute pain and nausea were the most common toxicities recorded. Grade 2 or greater acute pain was noted in 9 (13%) and grade 2 or greater nausea was noted in 9 (13%). The most common late toxicities were pain and radiation pneumonitis. Grade 2 or greater late pain occurred in 4 (6%) and grade 2 or greater pneumonitis was noted in 2 (3%).

Discussion

This study examined patients with extracranial melanoma treated with SBRT compared with CHRT. Long-term MC after SBRT was excellent at 90%, which compared favorably to CHRT (67%). These outcomes are similar to previous reports of intracranial metastases treated with SRS.

The utility of SRS for MM brain metastases has been well established. Mori et al. retrospectively reported outcomes from 60 consecutive patients with a total of 118 melanoma brain metastases [19]. Single-fraction SRS was delivered to a mean dose of 16.4 Gy (range 10–20 Gy) to the margin (usually the 50% isodose line). Most (85%) additionally received whole brain radiotherapy (WBRT). Local control for evaluable tumors was excellent at 90%. A retrospective study from Powell et al. assessed outcomes after Gamma Knife radiosurgery for radioresistant malignancies (renal cell carcinoma, melanoma or sarcoma) treated to a median margin dose of 18 Gy (range 8–30 Gy) [23]. Nearly half (49%) also received WBRT. The authors reported excellent local control (94%) for patients with melanoma histology. A phase II, prospective study from the Eastern Cooperative Oncology Group (ECOG 6397)

Table 1
Patient, tumor, and treatment characteristics.

	Total (N = 75)	CHRT (N = 37)	SBRT (N = 37)	*p*-Value
Age (mean, range in years)	57.5 (25–95)	54.6 (25–88)	59.8 (27–95)	0.049
Median follow-up (years)	3.1	2.9	4.9	
Lesions treated (n)	124	56 (45%)	68 (55%)	
Number of lesions treated				0.24
1	75 (61%)	37 (66%)	38 (56%)	
2	28 (23%)	11 (20%)	17 (25%)	
3	12 (10%)	5 (9%)	7 (10%)	
4	5 (4%)	2 (4%)	3 (4%)	
5	3 (2%)	1 (2%)	2 (3%)	
6	1 (1%)	0 (0%)	1 (2%)	
Site treated				
Musculoskeletal	38 (30%)	23 (41%)	15 (22%)	<0.01
Spine	20 (16%)	17 (30%)	3 (4%)	
Lung	21 (17%)	4 (7%)	17 (25%)	
Abdomen	19 (15%)	2 (4%)	17 (25%)	
Liver	15 (12%)	1 (2%)	14 (21%)	
Axilla	7 (6%)	7 (13%)	0 (0%)	
Thoracic/neck nodes	3 (2%)	1 (2%)	2 (3%)	
Orbit	1 (1%)	1 (2%)	0 (0%)	
Number of fractions (median, range)	5 (1–20)	5 (1–20)	3 (1–5)	<0.01
Total dose (median; Gy)	30 (8–60)	30 (8–50)	50 (18–60)	<0.01
SFED $\geq$ 45 Gy				<0.01
Yes	25 (20%)	0 (0%)	25 (37%)	
No	99 (80%)	56 (100%)	43 (63%)	
Treatment intent				
Curative	48 (39%)	3 (5%)	45 (66%)	<0.01
Palliative	76 (61%)	53 (95%)	23 (34%)	
All sites treated?				
Yes	56 (45%)	12 (21%)	44 (65%)	<0.01
No	68 (55%)	44 (79%)	24 (35%)	
Oligometastatic				
Yes	79 (64%)	30 (54%)	49 (72%)	0.03
No	45 (36%)	26 (46%)	19 (28%)	
Recent chemotherapy				
Yes	52 (42%)	31 (55%)	21 (31%)	<0.01
No	72 (58%)	25 (45%)	47 (69%)	
Recent targeted or immunotherapy				
Yes	71 (57%)	24 (43%)	47 (69%)	<0.01
No	53 (43%)	32 (57%)	21 (31%)	
Imaging modality				
PET/CT	94 (76%)	66 (97%)	28 (50%)	<0.01
CT	21 (17%)	2 (3%)	19 (34%)	
MRI	8 (6%)	0 (0%)	8 (14%)	
Bone scan	1 (1%)	0 (0%)	1 (2%)	

SFED, single-fraction equivalent dose; CHRT, conventional/hypofractionated radiotherapy; SBRT, stereotactic body radiotherapy; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

assessed patients with 1–3 intracranial brain metastases from renal cell carcinoma, melanoma or sarcoma [18]. No patients received WBRT and the SRS dose was 15–24 Gy, depending on tumor size. The rate of local failure after 6 months was 32%, with no reported differences in patterns based on histology. Our SBRT outcomes for extracranial MM compare favorably to these prior reports of treatment for intracranial metastases.

Many prior reports of patients with bone metastases from any histology have not shown a substantial difference in outcomes with conventional single-fraction compared with multi-fraction radiotherapy [11,15,29]. For example, in Radiation Therapy Oncology Group (RTOG) 97-14, patients with bone metastases from prostate or breast cancer were randomized to receive 8 Gy in one fraction or 30 Gy in 10 fractions [11]. There were no differences in symptom relief, though there was a higher rate of retreatment with the short-course regimen (18% vs 9%). A subsequent meta-analysis of 11 trials showed pain control in approximately 60% of patients regardless of the length of radiotherapy [31]. Higher rates of retreatment (21% vs 7%) and pathologic fracture (3% vs 1.5%) were seen in the short-course group. Notably, none of these studies used SBRT.

Prospective, non-randomized studies in patients with spinal metastases receiving SBRT have shown high rates of long-term pain control. Gerszten et al. reported long-term pain control in 86% of patients from a prospective cohort of 500 patients with spinal metastases treated with radiosurgery (mean dose 20 Gy) [8]. In the 38 patients with metastatic melanoma enrolled on the study, long-term pain control was achieved in 96% and radiographic control was achieved in 75%. A Phase I/II study from Chang et al. showed excellent 1-year freedom from tumor progression (84%) after SBRT for predominantly non-melanoma (97%) spinal metastases [2]. Thus, our reported MC of 90% after SBRT compares favorably to prior reports of patients treated with SBRT to the spine.

There is a paucity of available literature reporting outcomes after SBRT in patients with extracranial MM outside the spine. A

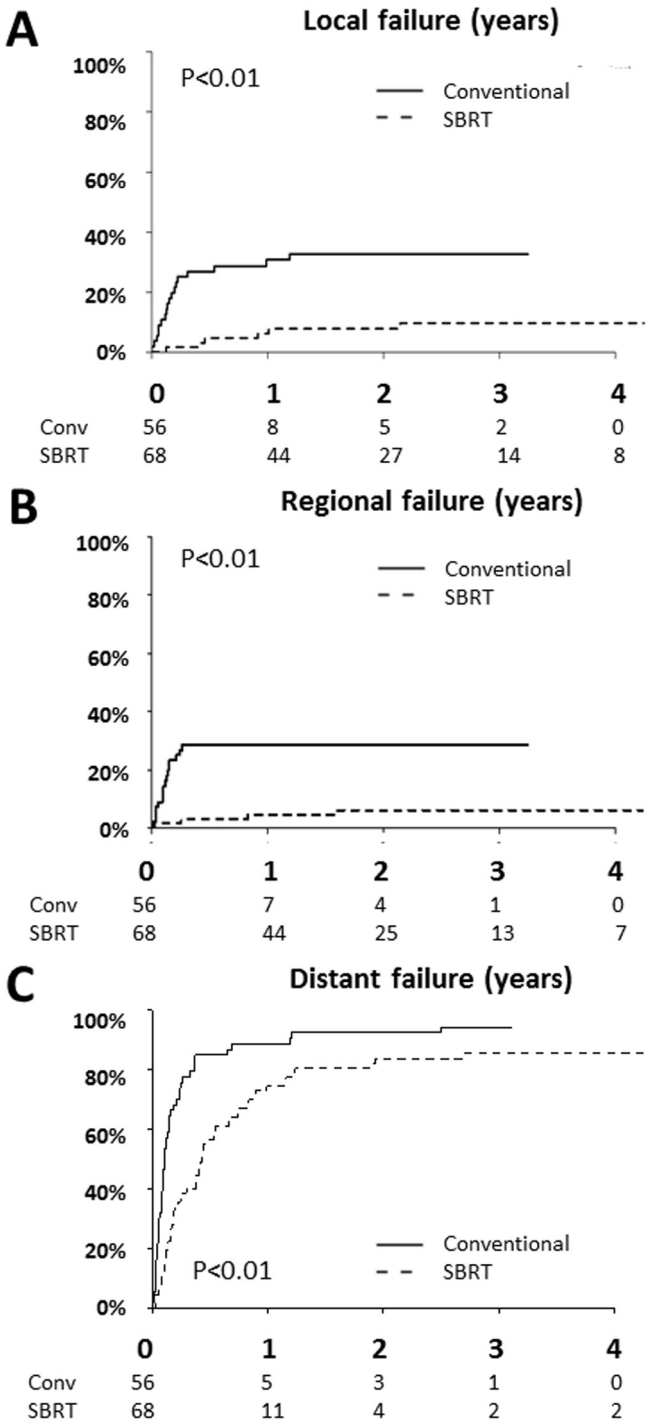

Fig. 1. Kaplan–Meier curves for local failure (A), regional failure (B) and distant failure (C). Conventional/hypofractionated radiotherapy is depicted by a solid black line and stereotactic body radiotherapy (SBRT) is depicted by a dashed black line.

Table 2
Univariate analysis of prognostic factors.

	Risk Ratio	95% CI	*p*-Value
Local progression			
Age >55 years	1.09	0.49–2.42	0.83
Oligometastatic	0.62	0.28–1.37	0.24
SBRT?	0.23	0.09–0.56	<0.01
SFED ≥45 Gy	0.15	0.02–1.07	0.06
Recent chemotherapy	1.14	0.52–2.52	0.74
Recent immunotherapy	0.60	0.27–1.32	0.20
Curative intent	0.15	0.03–0.50	<0.01
All lesions treated	0.34	0.14–0.84	0.02
Regional progression			
Age >55 years	0.44	0.18–1.09	0.08
Oligometastatic	0.66	0.27–1.57	0.34
SBRT?	0.18	0.06–0.52	<0.01
SFED ≥45 Gy	0.41	0.10–1.64	0.20
Recent chemotherapy	2.19	0.90–5.32	0.08
Recent immunotherapy	0.47	0.19–1.13	0.09
Curative intent	0.16	0.04–0.65	0.01
All lesions treated	0.27	0.09–0.79	0.02
Distant progression			
Age >55 years	1.08	0.70–1.64	0.74
Oligometastatic	1.37	0.74–2.56	0.32
SBRT?	0.43	0.23–0.79	<0.01
SFED ≥45 Gy	0.92	0.57–1.48	0.72
Recent chemotherapy	1.06	0.70–1.60	0.77
Recent immunotherapy	0.78	0.51–1.18	0.23
Curative intent	0.55	0.31–0.99	0.05
All lesions treated	0.39	0.23–0.68	<0.01
Overall survival			
Age >55 years	2.56	1.58–4.15	<0.01
Oligometastatic	0.53	0.29–0.98	0.04
SBRT?	0.34	0.18–0.62	<0.01
SFED ≥45 Gy	1.47	0.69–3.22	0.34
Recent chemotherapy	1.50	0.93–2.43	0.10
Recent immunotherapy	1.37	0.82–2.29	0.23
Curative intent	1.48	0.75–2.92	0.25
All lesions treated	0.31	0.15–0.64	<0.01

Immunotherapy and targeted therapy are grouped together. SBRT, stereotactic body radiotherapy; SFED, single-fraction equivalent dose.

Table 3
Multivariate analysis of prognostic factors.

	Risk Ratio	95% CI	*p*-Value
Distant progression			
All lesions treated	0.44	0.26–0.76	<0.01
Curative intent	0.48	0.27–0.86	0.01
SBRT?	0.38	0.22–0.65	<0.01
Overall survival			
Age >55 years	3.95	1.99–7.87	<0.01
Oligometastatic	0.34	0.16–0.73	<0.01
SBRT?	0.38	0.19–0.74	<0.01
All lesions treated	0.28	0.12–0.64	<0.01

SBRT, stereotactic body radiotherapy.

prior study by Stinauer et al. included 17 patients with metastatic melanoma, which demonstrated that an aggressive SBRT regimen with a single-fraction equivalent dose of at least 45 Gy is most effective in achieving local control [30]. This favorable dose escalation response data is consistent with the report by Olivier et al. suggesting that doses above 30 Gy were associated with more durable palliation and longer survival in patients with metastatic melanoma [20]. Our excellent MC suggests that a high biological dose can overcome the radioresistant nature of MM histology. Although it is clear that the patients receiving SBRT had more favorable clinical characteristics with a smaller disease burden and more comprehensive treatment of all sites of disease, more had visceral disease than those receiving CHRT. Without prospectively balancing the groups, it is difficult to elicit the true influence of SBRT on survival outcomes. It is possible that superior MC can translate into improved OS in appropriately selected patients. This notion is supported by our association of SBRT with improved OS on multivariate analysis. However, until a randomized, phase III trial is performed comparing SBRT with CHRT in extracranial metastatic MM, our findings must be interpreted with caution and should be viewed as hypothesis-generating.

The abscopal effect, defined as an unexpected distant tumor response after radiotherapy, was not seen in the current cohort.

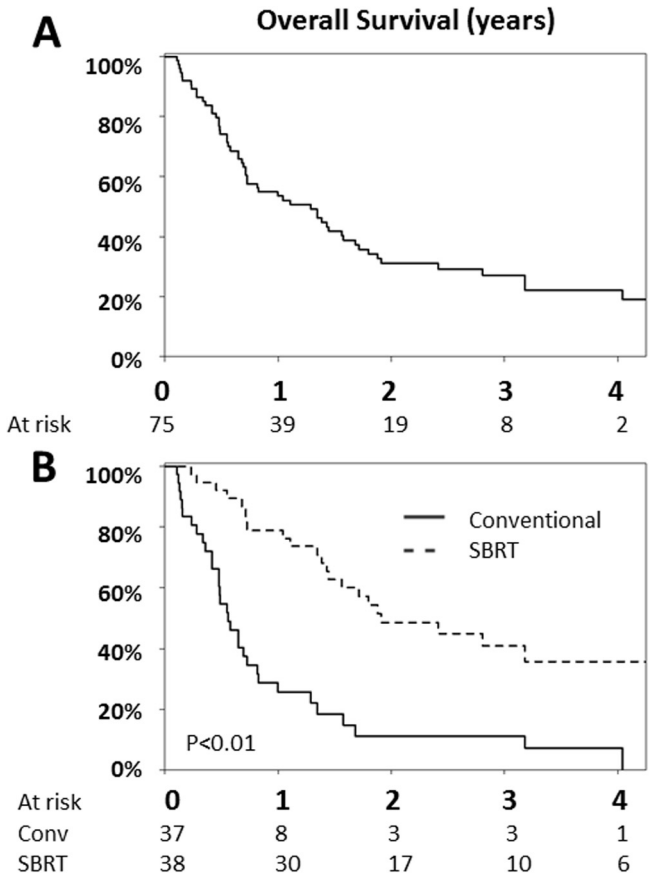

Fig. 2. Overall survival for the entire cohort (A) and broken down by treatment type (B). Conventional/hypofractionated radiotherapy is depicted by a solid black line and stereotactic body radiotherapy (SBRT) is depicted by a dashed black line.

Though it is thought to be rare, the abscopal effect has been reported in patients treated for metastatic MM [9,16]. The abscopal effect is thought to be mediated by immune system activation, which may be enhanced by ipilimumab [22,28]. The use of systemic therapy was not associated with improved outcomes in our study. This is inconsistent with randomized, phase III studies demonstrating modest improvements in outcomes with various systemic agents [3,6,12,17]. This may be due to the retrospective nature of this study, which could be confounded by unreported variables. It is also notable that the immunotherapy treatments used in this study (i.e. GM-CSF) predates the PD-1-based therapy that is commonly used today. Ultimately, our study was not designed to evaluate the efficacy of systemic therapy, so the lack of benefit seen in our patients may not be generalizable to all metastatic melanoma patients.

Because of the retrospective nature of this study, it has several limitations. The treatment groups were not balanced with respect to prognostic factors. A more favorable group of patients were typically selected to receive SBRT and all potential favorable characteristics were not likely quantified and entered into our multivariate analysis. One specific omission is the performance status of patients before treatment, which was not available for analysis. Many prognostic classification systems in metastatic disease rely heavily on performance status [7,27]. Thus, it is difficult to exclude the influence of confounding variables on survival outcomes for the patients reported in this series. In addition, we do not have data assessing longitudinal symptomatic improvement with treatment. Our group is planning for a future study to compare the relative efficacy of symptomatic control in patients treated with SBRT and CHRT. Lastly, no prospective toxicity data from CHRT patients are available for analysis and would be a useful addition to this study. Ultimately, future prospective trials are needed to validate the findings reported in this study.

In conclusion, this retrospective study of patients with extracranial MM reports excellent MC and minimal toxicity after SBRT, which is concordant with intracranial SRS outcomes. This study suggests that SBRT treatments in a select group of oligometastatic patients may result in improvements in OS by optimizing MC and treating all MM lesions. Prospective studies are needed to assess the true efficacy of SBRT compared with CHRT in patients with MM.

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Conflict of interest

No actual or potential conflicts of interest pertaining to this study exist for the authors.

Table 4
Toxicity data.

Acute	None	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pain	57	2	8	1	0	0
Nausea	57	2	6	3	0	0
Esophagitis	66	1	1	0	0	0
Peripheral neuropathy	66	0	0	2	0	0
Vertebral compression fracture	66	0	0	2	0	0
Edema	68	0	0	0	0	0
Fatigue	67	1	0	0	0	0
Anorexia	67	0	1	0	0	0
Gastric ulcer	67	0	0	0	1	0
Sepsis	67	0	0	0	1	0
Mucositis	68	0	0	0	0	0
Pericarditis	67	0	1	0	0	0
Rib fracture	67	0	1	0	0	0
Late						
Pain	62	2	4	0	0	0
Pneumonitis	64	2	2	0	0	0
Portal hypertension	65	0	0	3	0	0
Fracture	67	0	1	0	0	0
Bowel perforation	67	0	0	0	1	0
Gastric ulcer	67	0	1	0	0	0

Ethical considerations

All work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctro.2017.09.002.

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