

Clinical Investigation

Control and Toxicity in Melanoma Versus Other Brain Metastases in Response to Combined Radiosurgery and PD-(L)1 Immune Checkpoint Inhibition



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Abstract

Purpose: Prior studies have mixed conclusions about the efficacy and central nervous system (CNS) toxicity profile of combining radiosurgery with anti-programmed cell death 1 (PD-1) immune checkpoint inhibition (ICI) for brain metastases. This study evaluates the safety and efficacy of combined radiosurgery and anti-PD-1 ICI for melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC) brain metastases (BM).

Methods and Materials: Forty-one patients with 153 radiation naïve melanoma BM and 33 patients with 118 BM of NSCLC and RCC origin from 2014 through 2019 received radiosurgery and either anti PD-1 receptor inhibition or anti PD-L1 inhibition targeting the PD-1 ligand with less than 4 months separating either therapy. Similar to Radiation Therapy Oncology Group 9005, high-grade CNS toxicity was defined as irreversible grade 3 or any grade 4/5 neurologic event. Salvage resection revealing necrosis and viable tumor was considered grade 4 toxicity and local failure. An increase in greatest cross-sectional diameter of 25% on contrasted magnetic resonance imaging was designated as a local failure.

Results: Median follow-up was 10 months (range, 1-41 months). Local control was estimated to be 90.3% at 1 year. Distant control was 38.8% at 1 year, and neither local nor distant control were significantly influenced by limiting steroids to the day of treatment ($P = .55$, $.52$ respectively). One-year freedom from high-grade toxicity was 90.4% for patients and 94.6% for tumors. Though melanoma

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Research data are not available at this time.

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accounted for 41 (55%) patients and 153 (56%) tumors, it accounted for all high-grade toxicities ($P = .03$). These patients had some combination of high tumor burden, aggressive steroid taper, and treatment with ipilimumab.

Conclusions: Stereotactic radiosurgery combined with anti-PD-1 ICI appears to result in a high rate of local tumor control and a low rate of high-grade CNS toxicity, comparable to historical series with radiosurgery alone. High-grade toxicity is more likely in melanoma than RCC and NSCLC. Coming prospective studies will shed light on further questions about treatment timing, steroids, and response. © 2020 Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Approximately 20% of patients with cancer will have brain metastases (BM). For many patients' BM secondary to melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC), historic median survival rates have been on the order of approximately 6 months.¹ Over the last decade, immune checkpoint inhibitors (ICI) have received much attention as effective agents against systemic metastases of melanoma, RCC, and NSCLC including metastases to the brain.² The use of programmed cell death 1 (PD-1) pathway inhibitors has become part of first line treatment in melanoma and NSCLC BM, with several trials showing improved tumor control and survival.^{3,4}

The rapid adoption of nivolumab and pembrolizumab in the treatment of metastatic disease has raised many questions on how to best combine ICI with radiosurgery for patients with BM. The early success of single agent anti-PD1 immunotherapy in melanoma has caused some to question the continued role of radiosurgery in BM.³ Others have pointed to a potential abscopal effect from synergistic irradiation combined with immunotherapy.⁵ Further, the proinflammatory nature of ICI has led some to delay radiation out of fear of increased high-grade toxicity.⁶

Although research into the safety, efficacy, and optimization of combination anti-PD-1 ICI and radiosurgery is still young, some trends have appeared. The combination's safety appears equal to or better than traditional chemo-RT regimens.⁷ Combination therapy seems to promote durable lesion control in melanoma and faster volumetric response in NSCLC metastases.^{8,9} Some data suggest that tumor control and response rates may be linked to timing of ICI relative to radiosurgery, with steroids possibly antagonizing the effect.⁶

Although these and other retrospective studies represent important steps forward in the treatment of BM with anti-PD-1 agents, they individually have limited scope and difficulty making statistically significant claims. Further studies are needed to optimize sequencing of combination anti-PD-1 ICI with radiosurgery for clinical practice. This retrospective study attempts to build on the aforementioned works by examining tumor control and specifically high-grade toxicity outcomes in these patients

as well as comparing melanoma to nonmelanoma primaries.

Methods and Materials

Patients

This single institution retrospective study assessed patients treated with radiosurgery and anti-PD-(L)1 ICI for NSCLC, RCC, and melanoma BM from 2014 to early 2019. Diagnosis was confirmed histologically. All patients had single fraction stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy (FSRT) in 5 fractions to BM not previously irradiated or resected. Patients with prior whole brain radiation therapy were excluded. Patients were included if they received at least 1 dose of either anti-PD-1 ICI targeting the PD-1 receptor or anti-PD-L1 ICI targeting the PD-1 ligand within 4 months of radiation and at least 1 follow-up contrasted brain magnetic resonance imaging (MRI). In prior studies of the safety of combinations of checkpoint inhibitors and radiosurgery the interval studied between therapies has varied from 2 weeks to 5.5 months or even any interval.¹⁰⁻¹³ In this study, we selected an interval of 4 months to capture the full acute toxicity window and allow for a long half-life with the potential that residual changes to the immune system may affect toxicity later than other therapies. Patient characteristics collected included driver mutation status (BRAF, ALK, EGFR); PD-L1 expression percentage (for NSCLC); absolute lymphocyte count; and Karnofsky performance status. The presence of cytotoxic T-lymphocyte-associated protein 4 inhibition (anti-CTLA-4 ICI) was also recorded. The study received institutional review board approval.

Radiosurgery

Patients were treated with either single fraction SRS or FSRT in 5 fractions based on physician preference. FSRT was generally considered when the tumor was over 3 cm in diameter or adjacent to very high-risk structures. Patients were immobilized using a thermoplastic mask. The contrasted computed tomography simulation was fused to a contrasted MRI for planning. Dose was prescribed

without planning target volume margin such that $\geq 99\%$ of the gross tumor volume received 100% of the prescription dose ($V100\% \geq 99\%$). SRS tumors received 16 to 22 Gy (median dose was 20 Gy) and FSRT tumors received 25 to 35 Gy. Dose was delivered in 2 to 4 single isocenter volumetric-modulated arc therapy arcs using either the Varian Edge Radiosurgery platform or the TruBeam STx and a 6 degree of freedom couch. Optical surface imaging was used to monitor patient positioning during treatment.

Systemic therapy

Patients received nivolumab, pembrolizumab, or durvalumab ICI within 4 months of radiation. Dose timing relative to SRS varied between patients. Most patients were on immunotherapy at the time of SRS or began therapy shortly afterward. A minority of patients finished their course of immunotherapy before SRS. Some patients with melanoma received combination ipilimumab and nivolumab. Although the ipilimumab schedule was recorded, it did not affect patient inclusion.

Corticosteroids, generally dexamethasone, were given to most patients after SRS at the discretion of the treating physician, with some receiving prolonged courses. The dose at the time of SRS and the schedule were recorded.

Endpoints and statistical analysis

Local progression was defined as a 25% increase in the longest diameter of a tumor on contrasted MRI in comparison to the planning MRI. To account for pseudo-progression caused by concurrent immunotherapy, local tumor progression was confirmed similar to the immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria.¹⁴ Per iRANO, confirmation of progression was required if immunotherapy was started ≤ 6 months prior and no new neurologic deficits attributable to progression were present. Confirmation required evidence of progression on 3-month follow-up MRI after the initial finding. Because these criteria could potentially exclude some true progression, we report local control rates both with and without additional iRANO-based exclusions.

Distant intracranial progression was defined as any new lesion appearing after radiosurgery on follow-up contrasted MRI. The iRANO imaging confirmation requirements for local progression were applied to distant progression as well.

Similar to the dose-limiting toxicity definition in Radiation Therapy Oncology Group 9005, high-grade toxicity was defined as irreversible grade 3 or any grade 4/5 neurologic events according to Common Terminology Criteria for Adverse Events version 4.¹⁵ Patients undergoing salvage resection with a pathologic mixture of

necrosis and viable tumor were scored as both grade 4 toxicity and local failure. Grade 5 toxicity is defined by death.

Statistical Package for the Social Sciences version 25 for Windows was used for statistical analysis and figures. Median survival was estimated using Kaplan-Meier analysis and compared between groups using the log rank test. R 3.6.1 was used for 1-year survival 95% confidence interval. Hazard ratios were calculated using Cox regression. Median follow-up was 10 months, ranging from 1 to 41 months.

Results

Patient and treatment characteristics

Forty-one patients with 153 melanoma BM and 33 patients with 118 NSCLC and RCC BM meeting the inclusion criteria underwent combination radiosurgery and anti-PD-(L)1 ICI. Two hundred nine tumors received SRS to a median dose of 20 Gy. Sixty-two tumors received FSRT to a median dose of 30 Gy. Melanoma tumors were on average larger than NSCLC and RCC tumors with average volumes of 1.7 cc and 0.7 cc, respectively ($P = .014$). Normal brain V12 and prescribed dose were not significantly different between groups ($P = .60$ and $P = .87$, respectively). Pembrolizumab was used slightly more often than nivolumab in patients with melanoma (22 vs 13). In patients with NSCLC/RCC, pembrolizumab and nivolumab were used evenly (16 vs 15). Twenty-three patients with melanoma (56%) received ipilimumab in addition to anti-PD-1 ICI. Only 3 patients (0.1%) received ipilimumab in other histologies. Patient and treatment characteristics are detailed in [Table 1](#).

Local tumor control

Only 21 tumors progressed locally after treatment resulting in a 90.3% (95% confidence interval, 86%-94.8%) freedom from local progression at 1 year. This is shown in [Figure 1](#). Including patients with potential pseudoprogression and only 1 follow-up MRI, this rate is 84.6%. Steroids prolonged >1 -day post-SRS did not appear to affect local control ($P = .52$, log rank), nor did tumor histology correlate with local control rates ($P > .20$, pairwise log rank).

Distant intracranial control

Thirty-nine patients experienced distant intracranial progression for an estimated 38.8% freedom from distant failure at 1 year, as shown in [Figure 2](#). As with local control, limiting steroids to the day of treatment did not correlate with prolonged distant control by log rank test

Table 1 Patient and treatment characteristics

Characteristics	Patients	Tumors
Total	74	271
Histology (%)		
Melanoma	41 (55%)	153 (56%)
NSCLC	24 (32%)	67 (25%)
RCC	9 (12%)	51 (19%)
Sex (m/f)	47/27	181/90
Race (white/black/other)	68/3/3	256/9/6
Age – median (range)	61 (32-84)	
Follow up – median (range)	10 (1-41)	7 (1-41)
Tumor dose (gy) – median (range)		
SRS		20 (16-22)
FSRT		30 (25-35)
Pretreatment lymphocyte count/uL	1332 (208-21,895)	1275 (208-21,895)
Tumor volume – median (range)		.15 cc (.01-31.57 cc)
Immunotherapy	Patients with melanoma	Patients with NSCLC/RCC
Nivolumab	13	15
Pembrolizumab	22	16
Pemb. & nivo. (not concurrent)	6	0
Durvalumab	0	2
Ipilimumab (%)	23 (56%)	3 (0.09%)

Abbreviations: FSRT = fractionated stereotactic radiation therapy; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SRS = stereotactic radiosurgery.

($P = .55$). Distant intracranial control was also examined in relation to ICI timing. Patients were compared in 3 groups: those receiving a final dose of ICI before SRS, those receiving ICI before and after SRS, and those starting ICI after SRS. There was no significant difference in distant control among the groups ($P = .57$).

High-grade toxicity

With only 6 patients experiencing an event, 90.4% of patients and 94.6% of tumors were free from high-grade toxicity at 1 year. The Kaplan-Meier estimates for freedom from high-grade toxicity are shown in Figure 3.

Toxicities were either irreversible grade 3 or grade 4 with no patients dying directly from treatment. Characteristics of these patients can be found in Table 2. Generally, patients experiencing high-grade toxicity had a combination of large tumor volumes (2.29-23.99 cc) and aggressive steroid tapers. Tumor volume carried a hazard ratio of 1.06 (1.01-1.12; $P = .02$).

Four of the 6 patients with high-grade toxicity presented with focal motor deficits corresponding to tumor location. One patient had global motor deficits, and the final patient experienced significant cognitive disturbance. All 6 patients required substantial increases in dexamethasone to 4 mg every 6 to 8 hours. Four of the 6 required resection.

Interestingly, all high-grade toxicity events occurred in patients with melanoma. No grade 3 or higher toxicities occurred in patients with RCC or NSCLC. This difference was significant ($P = .033$) when comparing

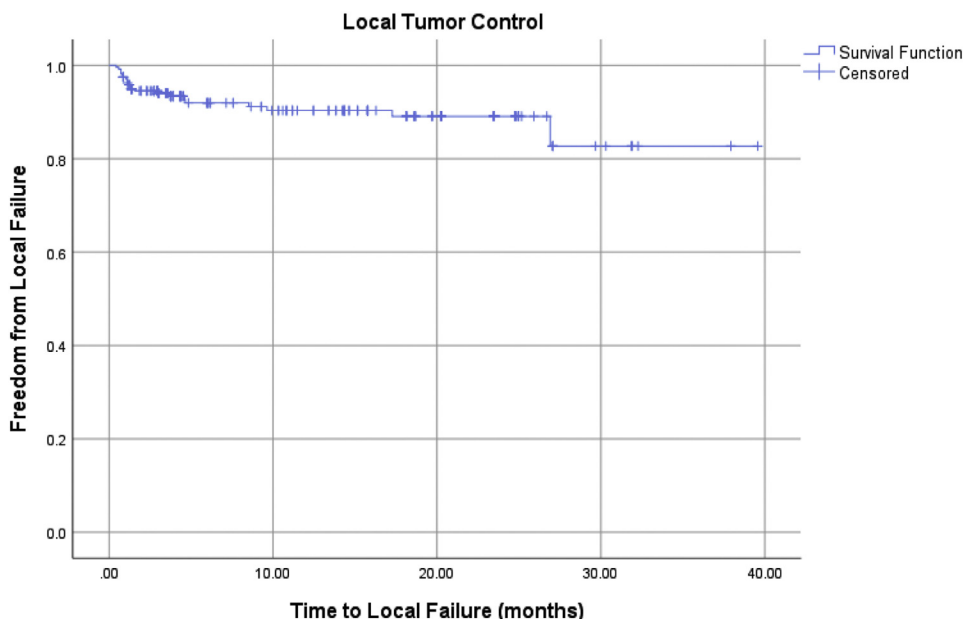


Figure 1 Kaplan-Meier estimate of local tumor control. One-year freedom from local failure was 90.3%.

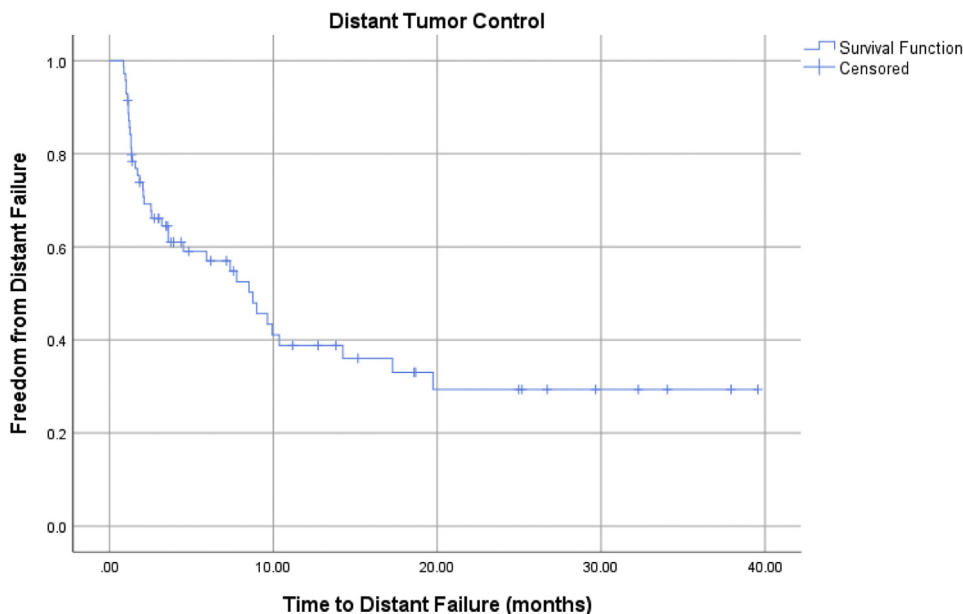


Figure 2 Kaplan-Meier estimate of time to distant intracranial failure post stereotactic radiosurgery (SRS). One-year freedom from distant failure was 38.8%.

melanoma against RCC and NSCLC using the log rank test. The Kaplan-Meier estimates are shown in Figure 4. Timing of ICI relative to SRS did not seem to influence toxicity (log rank $P = .52$). Three patients received SRS during a course of ICI with doses of immunotherapy both before and after SRS. The other 3 began ICI after SRS.

Discussion

Although combination radiosurgery and anti-PD-(L)1 checkpoint inhibition have received much attention in the treatment of BM, no prospective studies and only a handful of retrospective studies have reported data on safety and efficacy of combination treatment.¹⁶ The unprecedented intracranial activity of ICI combined with a fear of increased high-grade toxicity based on the proinflammatory nature of ICI has caused several trials to move and delay radiation in favor of immunotherapy alone for asymptomatic tumors.^{3,17,18} Therefore, we retrospectively analyzed response and high-grade toxicity rates in patients treated at our institution with concurrent SRS and PD-1/PD-(L)1 ICI for BM. We found 90% of tumors were controlled at 1 year with under 10% of patients experiencing a high-grade toxicity. The events that did occur were solely in melanoma metastases. This is probably in part due to the larger average tumor volume seen in melanoma in this data set. Several other expected risk factors for toxicity were prominent. All patients with high-grade toxicities were undergoing an aggressive steroid taper specifically to avoid interactions with the immunotherapy. All events

occurred in patients with heavy intracranial tumor burden. Interestingly, 5 of the 6 patients (83%) with high-grade toxicities received ipilimumab though only 56% of patients with melanoma received ipilimumab overall. The overall heterogeneity of anti-PD-1 ICI choice was reflected in the 6 patients with high-grade toxicity. Three patients received nivolumab. Two received pembrolizumab, and 1 received both at separate points in the disease course.

Combination SRS anti-PD-1/PD-(L)1 ICI therapy appears to durably control target lesions. In our study, an estimated 90% of metastases were locally controlled at 1 year. Similar studies have found the same high rates of local control.¹⁹⁻²¹ One 2017 retrospective study of combined SRS and ipilimumab in melanoma BM found very high local control of 94.8%. This is close to our experience, though patients received CTLA-4 ICI in this study instead of PD-1 ICI.¹⁹ Another 2016 retrospective estimated local control for melanoma BM receiving combined SRS and PD-1 ICI to be 85% at 1 year.²⁰ Although this does mirror our experience, it should be noted that this study was an early experience including only 26 patients. These data compare favorably with previously reported local tumor control with radiosurgery alone. Although local control of BM with radiosurgery alone varies based on many factors such as dose and tumor volume, studies have seen 1-year rates anywhere from 45% to 85%.^{22,23} In a 2019 retrospective study from Wake Forest of combination therapy versus SRS alone for NSCLC and melanoma BM, combined SRS with ICI resulted in 1-year local control of 91% whereas SRS alone produced 96%.²¹ This difference was not statistically significant ($P = .17$). ICI choice in this

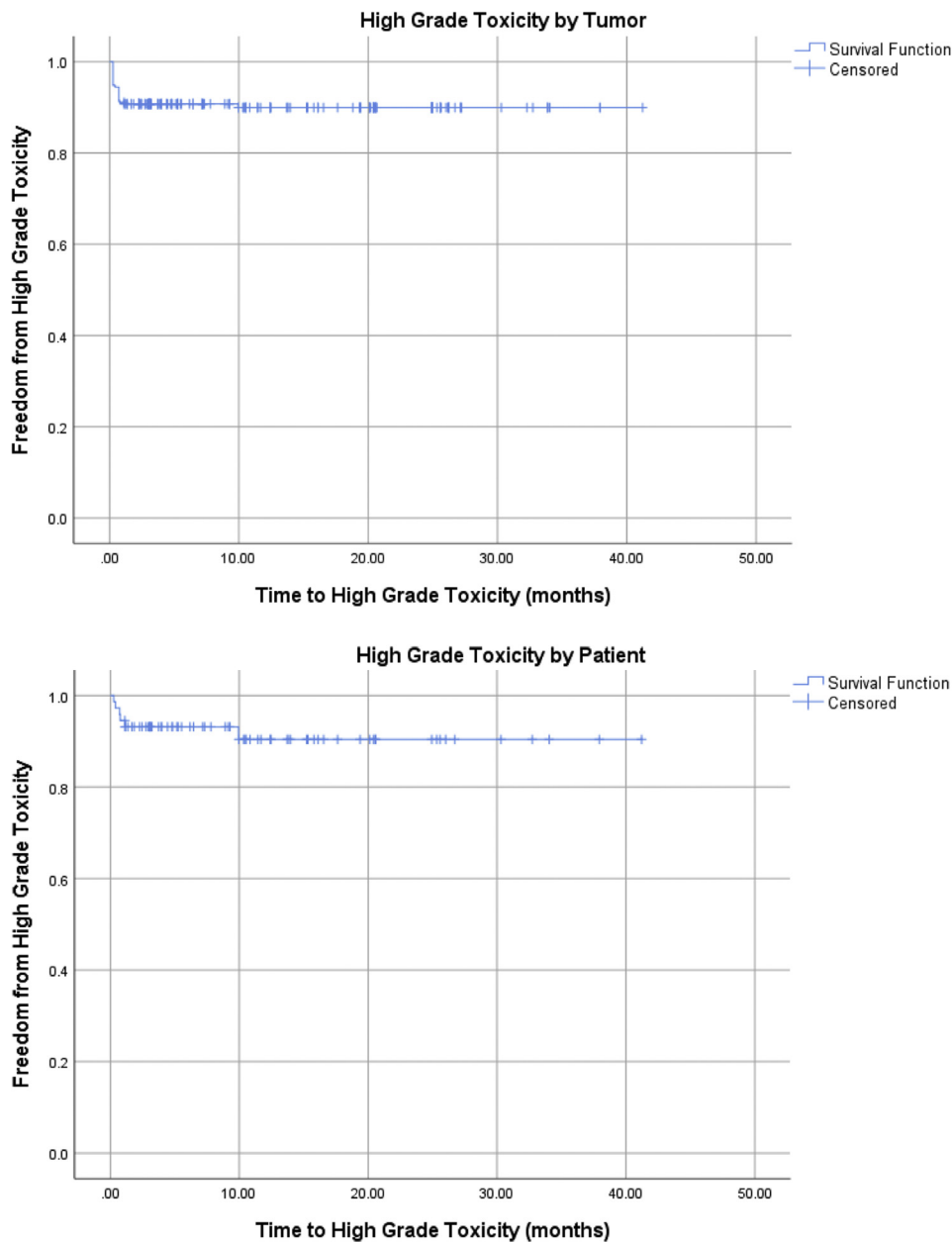


Figure 3 Estimated freedom from toxicity shown per tumor and per patient. Both had over 90% freedom from high-grade toxicity at 1 year.

study was heterogeneous, with 15% of patients only receiving CTLA-4 ICI whereas all patients in the current study received PD-1 ICI +/- CTLA-4. Both this study and the current study found similar rates of local control. Local tumor control with combination SRS and ICI in our study and several others appears to compare favorably to previous reports of SRS alone.

One proposed benefit to combining radiosurgery with ICI is the potential for enhanced antigen presentation and immune system priming. Furthermore, it is unknown whether treatment of the central nervous system will induce an improvement in extracranial disease control, but limited case series suggest this may be the case despite the brain being thought of as an immune

sanctuary.²⁴ One of the benefits of anti-PD-1 therapy is that the monoclonal antibodies do not have to cross the blood-brain barrier. It is only the peripherally activated T-cells that must cross for the ICI to have an effect on the central nervous system. It has been hypothesized that concurrent radiation releases new tumor antigens and disrupts the blood-brain-barrier to increase the possibility for an extracranial immune response.²⁵ It has also been shown that nivolumab can penetrate the cerebrospinal fluid at effective concentrations, allowing for possible intracranial antigen response.²⁶ Some have called these effects an “in situ vaccine.”²⁷ To that end, we examined the distant intracranial control in our patients. Kaplan-Meier 1-year freedom from distant progression was

Table 2 Characteristics of patients experiencing high-grade toxicity*

Grade	Histology	Dose (Gy) & schedule	# Targets	Largest tumor volume (cc)	Ipilimumab	Dex. dosage before toxicity	Toxicity resection required
3 Motor weakness and vertigo → fall	Melanoma	30 FSRT	1	23.99	Yes-started 3 months after RT	12 mg with taper	No
4 Motor weakness → fall	Melanoma	20 SRS	4	4.21	Yes-stopped 8 months before RT	12 mg with “aggressive” taper to 8 mg	Yes
3 Motor weakness	Melanoma	18 SRS	14	2.29	Yes-day of RT	4 mg with taper to 2 mg	No
4 Motor weakness	Melanoma	30 FSRT	8	19.67	Yes-started 14 days post RT	8 mg day 1 with next day resection	Yes
4 Motor weakness, seizures	Melanoma	17 SRS	2	11.97	Yes – but 2 years post RT	8 mg with taper	Yes
4 Cognitive disturbance	Melanoma	30 FSRT	1	5.49 with significant prior edema	None	>2 mg aggressive wean to 2 mg	Yes

Abbreviations: FSRT = fractionated stereotactic radiation therapy; RT = radiation therapy; SRS = stereotactic radiosurgery.

* Melanoma, extensive tumor burden, and aggressive steroid weans predominated.

39%. This is in comparison with the overall 6-month distant control rate of 48% reported previously in a similar study of combined anti-PD-1 ICI and SRS for NSCLC BM.²⁸ Although this study was early and therefore only had 17 patients, it did find that distant failures did not occur in patients receiving ICI before SRS. In contrast, our study did not find any correlation between ICI timing and distant intracranial control rates. The previously mentioned study comparing SRS alone with combination therapy in NSCLC and melanoma BM found distant intracranial control of 46% in those receiving

combination therapy and 66% in those receiving only SRS.²¹ Although SRS alone seemed to produce better distant control, neurologic death was far more likely in those treated with SRS alone versus combination therapy. These results mirror our reported distant control rate of 39%. Without immunotherapy, studies of BM treated with SRS have found rates of distant intracranial control on the order of 11%-48%, although some studies have found melanoma is an independent risk factor for distant brain progression.²⁹⁻³¹ Again, combination SRS and ICI seems to perform in the middle to upper end of distant control

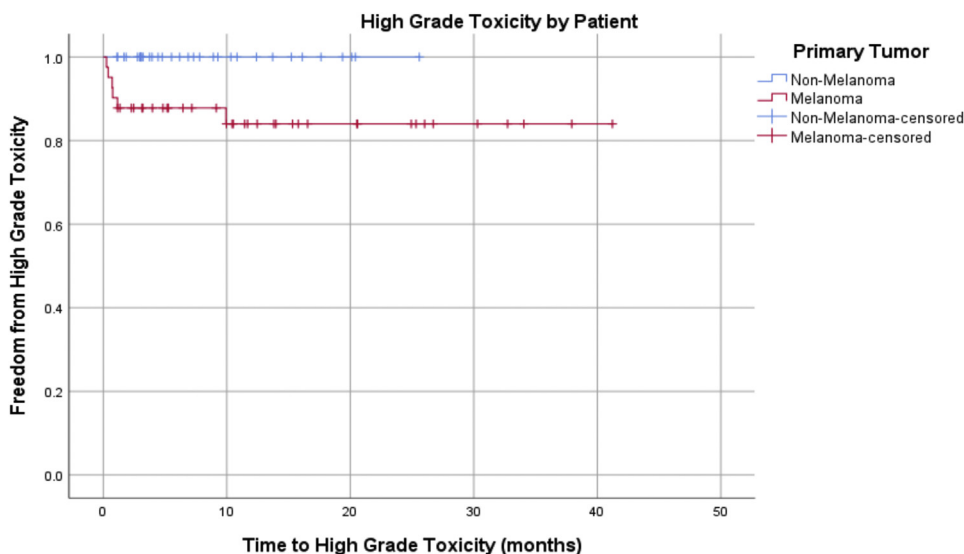


Figure 4 Kaplan-Meier estimates of time to high-grade toxicity comparing melanoma with all others. All events occurred in melanoma brain metastases (BM).

rates seen in SRS alone. One-year distant control approaching 40% to 50% is promising, but this concept needs additional study to identify which factors predict for improved distant intracranial control.

One of the ongoing fears surrounding concurrently administering ICI and SRS is a perceived propensity for high-grade toxicity. Previous studies have reported mixed findings to that end. Most studies have shown rates of radionecrosis on the order of 6% to 8%, with most under 10%.^{32,33} One retrospective study saw radionecrosis in only 3.2% at 1 year for patients who received SRS within 1 half-life of ICI.⁶ It should also be noted that 1 2016 study saw radionecrosis in 37.5% of patients treated with combination SRS and ICI.³⁴ This retrospective of patients from 2006 to 2012 reported increased risk of radionecrosis in patients treated with an unspecified ICI compared with cytotoxic and targeted therapies. They also included breast and colorectal tumors, which the present study does not. Although other studies have used radiographic radionecrosis as a surrogate for clinical toxicity, the present study focused on the most clinically meaningful higher grade clinical events (irreversible grade 3 or greater). We believe this is an important distinction as it attempts to better include toxicity events that might most heavily influence clinical decision making. Our incidence of high-grade toxicity was 9.6% at 1 year. Additionally, all high-grade events in this study occurred in melanoma metastases. Taken together, these rates are very similar to the 8% incidence of radionecrosis seen at 1 year in Radiation Therapy Oncology Group 9005 without immunotherapy, suggesting comparable risk profiles.¹⁵ Based on these data, the incidence of toxicity severe enough to alter treatment decisions is comparable with or without ICI. It should be noted that tumors with increased mass effect and edema after radiosurgery and ICI may be undergoing an inflammatory process that is distinct from histologic necrosis. “Adverse radiation effect” is an alternative term for this process, although whether the process that occurs with radiation alone versus radiation plus ICI is identical is unknown.³⁵

Conclusions

In this retrospective study of melanoma, NSCLC, and RCC BM, combination radiosurgery and anti-PD-1/PD-(L)1 ICI resulted in excellent local control with rates of high-grade toxicity on par with radiosurgery alone. Patients who did experience high-grade toxicity all had melanoma with no high-grade events seen in patients with NSCLC or RCC. A larger data set with future analysis will be required to confirm that this observation is independent of other known factors predictive of high-grade toxicity, such as tumor volume. These results add to the growing body of retrospective work supporting the efficacy and safety of combining radiosurgery and ICI.

In contrast to many studies, the focus on high-grade toxicity in this retrospective study provides an important profile of the toxicities severe enough to influence clinical decision making. Many conflicts remain unsolved in the literature. It is clear that prospective trials are needed to illuminate many questions about toxicity, progression, and local control in NSCLC and melanoma BM.³⁶ One such trial, the Anti-PD-1 Brain Collaboration + Radiotherapy Extension study, is examining survival in melanoma BM treated using nivolumab/ipilimumab with 1 arm receiving only salvage therapy and the other receiving SRS initially with immunotherapy. Estimated study completion is August 2024.³⁷ Another trial will examine how dose fraction influences toxicity in melanoma and patients with NSCLC BM treated with concurrent radiation and pembrolizumab. Recruiting is active and study completion is estimated for October 2021.³⁸ Further progress through additional prospective studies is required to illuminate current debates and guide clinical decisions.

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