Patterns of Failure Outcomes for Combination of Stereotactic Radiosurgery and Immunotherapy for Melanoma Brain Metastases

Mohammed Abdulhaleem, MD[*], Hannah Johnston, MD[‡], Ralph D'Agostino Jr, PhD[§], Claire Lanier, MD[‡], Christina K. Cramer, MD[‡], Pierre Triozzi, MD[*], Hui-Wen Lo, PhD[‖], Fei Xing, PhD[‖], Wencheng Li, MD[¶], Christopher Whitlow, MD, PhD[#], Jaclyn J. White, MD[**], Stephen B. Tatter, MD, PhD[**], Adrian W. Laxton, MD[**], Jing Su, PhD[††], Michael. D. Chan, MD[‡], Jimmy Ruiz, MD[*]

[*]Department of Medicine, Hematology and Oncology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [‡]Department of Radiation Oncology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [§]Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [‖]Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [¶]Department of Pathology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [#]Department of Radiology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [**]Department of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [††]Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence: Mohammed Abdulhaleem, MD, Department of Medicine, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA. Email: mabdulha@wakehealth.edu

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BACKGROUND: Previous series have demonstrated central nervous system activity for immune checkpoint inhibitors (ICIs) and shown improved local control between stereotactic radiosurgery (SRS) and ICI for lung cancer brain metastases.
OBJECTIVE: To assess whether the addition of ICI to SRS for melanoma brain metastasis improves outcomes when compared with historical control group treated in the era before ICI availability.
METHODS: In this single institution retrospective series, outcomes of 24 patients with melanoma receiving concurrent ICI and SRS were compared with 111 historical controls treated before ICI era. Overall survival (OS) was estimated using the Kaplan-Meier method. Cumulative incidence of local and distant failures was estimated using a competing risk model that accounted for baseline differences using propensity score adjustments.
RESULTS: The median OS time was improved in patients receiving ICI compared with the historical control group (17.6 vs 6.6 months, hazard ratio [HR] = 0.056, $P = .0005$). Cumulative incidence at 1 year for local failure in the historical control and ICI groups was approximately 12.5% and 6.5%, respectively (HR = 0.25, $P = .19$), while cumulative incidence of distant brain failure in the historical control and ICI groups was approximately 48% and 28%, respectively (HR = 0.326, $P = .015$)
CONCLUSION: Distant brain failure and OS were improved in patients receiving concurrent ICI with SRS compared with historical controls. Local failure trended in the same direction; however, owing to small sample size, this did not reach statistical significance. While these data remain to be validated, they suggest that patients with brain metastasis may benefit from concurrent use of ICI with SRS.

KEY WORDS: Brain metastasis, Immunotherapy, Melanoma, Overall survival, Stereotactic radiosurgery

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Melanoma brain metastases represent approximately 15% of brain metastases and are the third most common type of brain metastases after lung and breast cancer metastases.[1] Melanoma brain metastases are particularly morbid given their propensity for hemorrhage,[2] their increased likelihood of local failure,[3] and their high rate of reseeding the brain over time.[4] Because of these factors, patients with melanoma have a higher rate of dying from brain metastases than brain metastases from other cancer primaries.[5]

There have been several advances in the management of melanoma over the past decade including the advent of multiple immunotherapy options.[6-8] These advances have improved overall survival in patients with metastatic melanoma, and this improvement has translated to melanoma patients with brain metastases. In fact, melanoma patients with brain metastases treated with immunotherapy not only have an improvement in overall survival but

ABBREVIATIONS: GK, gamma knife; **HR,** hazard ratio; **ICIs,** immune checkpoint inhibitors; **OS,** overall survival; **SRS,** stereotactic radiosurgery; **WBRT,** whole brain radiation therapy.

that survival difference is at least partially a result of decreased neurological death from improved brain metastasis control.[9]

Recent studies have suggested that immunotherapy and specifically immune checkpoint inhibitors (ICIs) can have activity within the central nervous system. Response rates for brain metastases for dual immunotherapy have been found to be 56% in a recent phase II study.[10] A recent study in patients with non–small-cell lung cancer revealed improved local control outcomes for brain metastases treated with concurrent stereotactic radiosurgery (SRS) and ICI compared with a historical population treated with SRS alone.[11] Moreover, ICI has previously been found to improve distant brain failure in patients with non–small-cell lung cancer.[12] Distant brain failure has historically been higher for patients with melanoma than other histologies.[2,13]

Owing to the advancing evidence for central nervous system activity of ICI and the unmet need for improved control of melanoma brain metastases, the present series sought to assess whether the combination of ICI and SRS improves local control over SRS alone in the melanoma population. This single institution retrospective review assesses outcomes of patients who were treated for newly diagnosed brain metastases from melanoma who received concurrent ICI and SRS as part of management strategy for new brain metastases. A historical control population derived from an era before ICI as standard of care therapy is used for comparison.

METHODS

Data Acquisition

This study was approved by our institutional review board. The Department of Radiation Oncology Gamma Knife Database was queried for all patients who received SRS for melanoma in the era of immunotherapy (2013 and beyond). Because of the interest in the role of immunotherapy in local control of brain metastases, patients who received immunotherapy concurrently (within 3 months of having SRS) were identified. Patients included in this study were also required to have a new diagnosis of brain metastases, and a new diagnosis of metastatic melanoma as the desire was to have the population not have distant prior exposure to immunotherapy (and thus have disease that has become resistant). All patients in the ICI group received only single agent immunotherapy. A historical control population from the era before upfront immunotherapy becoming the standard of care was selected to match the study population. Patients excluded from this study if they have received SRS 3 months apart from the initial diagnosis of brain metastasis.

Patients were considered to have oligometastatic disease if they had less than or equal to 5 nonbrain metastases without diffuse involvement of a single organ as previously described by Dingemans et al.[14] The lowest SRS dose was collected as a surrogate for volume because the dose prescribed was inversely related to the tumor volume.[13]

Stereotactic Radiosurgery

Patients were treated on the Gamma Knife Perfexion Unit (Elekta AB). Rigid headframe fixation was used for immobilization. Patients underwent a same-day high-resolution stereotactic 3T MRI brain (GE Healthcare). Treatment planning was performed on the GammaPlan Treatment Planning system (Elekta AB). Brain metastases were treated according to the radiation therapy oncology group 90-05 dosing guidelines.[15]

Patient Follow-up and Response Assessment

Patients underwent a follow-up MRI scan approximately 6 to 8 weeks after their initial SRS treatment and then every 3 months thereafter for the first 2 years after treatment. If, after 2 years, there was no tumor recurrence, imaging was spaced out to every 4 months for year 3 and every 6 months for years 4 and 5.

Local failure was determined either pathologically from a surgical sampling or by imaging criteria that are consistent with local tumor recurrence which has been previously published.[13] In short, in patients who did not have pathological confirmation of local recurrence, they were deemed to have evidence of imaging local recurrence if they had a 25% increase in the size of the lesion or serial increases in size with a corresponding increase in the perfusion signal on perfusion-weighted imaging. Distant failure was defined as a new metastasis outside of the prior gamma knife prescription volume. Toxicity was assessed using the common terminology criteria for adverse events v5.0 grading criteria.

Statistics

For survival analyses, time 0 was considered the day of SRS. Overall survival (OS) was estimated using the Kaplan-Meier method. CI of local failure and distant brain failure was calculated with a competing risk analysis through the Fine Gray Method using death as a competing risk.[16] Cohorts (historical control and ICI) were compared using descriptive statistics to determine statistical differences among groups. Chi-square analysis was used to compare categorical variables, while 2-sample tests were used to compare continuous variables. Statistical significance was defined as $P < .05$.

To account for any biases in baseline patient characteristics, a propensity score–adjusted approach was used to examine overall survival and the competing risk model for local recurrence and distant failure.[11,17] In the propensity score analysis, the propensity score was estimated for the conditional probability of being in the experimental group by including age, sex, race (White vs non-White), number of metastases at first SRS treatment, lowest marginal gamma knife dose, performance status, the scope of systemic disease, and brain surgery (yes/no) as covariates. Balance between groups was assessed after propensity score adjustment (Table 1). To account for nonrandomized nature of this study, the OS and competing risk models were fit to adjust for the propensity score.

All statistical analyses were performed using SAS v9.4 software.

Patient and Individual Consent

Consent was not required because no identifiable protected health information of any kind for any person was included in this series.

RESULTS

Patient Characteristics

Twenty-four consecutive patients with new brain metastases from melanoma were treated between November 2013 and May 2019 with concurrent ICI and SRS. All 24 patients received single-agent ICI with SRS. The historical control population was made up of 111 consecutive patients with new brain metastases from melanoma and who were treated between February 2000 and May 2011. Patients were censored at the time of the last MRI.

TABLE 1. Patient Characteristics

Variables	Immunotherapy group (SD/%)	Historical control group (SD)	*P* value	*P* value after propensity score quintile adjustment
Age	62.2 (15.8)	57.8 (14.5)	.19	0.77
Sex (female vs male)	11 (45.8)	36 (32.4)	.24	0.08
Race (White vs non-White)	23 (95.8)	106 (95.5)	1.0	0.13
KPS	80.0 (8.3)	78.9 (7.7)	.54	0.75
Disease burden				
Widespread disease	11 (45.8)	60 (54.1)	.40 (widespread vs other)	0.56 (widespread vs other)
Oligometastases	8 (33.3)	39 (35.1)		
No metastasis[a]	5 (20.8)	12 (10.8)		
No. of metastases at SRS	4.96 (5.3)	2.41 (2.0)	.03	0.07
Lowest SRS margin dose	17.9 (16.5)	18.7 (18.1)	.23	0.77
Craniotomy (yes/no)	6 (25)	18 (16.2)	.38	0.53
Immunotherapy agents				
Pembrolizumab	15	N/A		
Ipilimumab	5			
Nivolumab	4			

KPS, knife dose, performance status; SRS, stereotactic radiosurgery.
[a]Patients had metastasis to the brain only without other systemic disease.

The median follow-up in the ICI group was 52 weeks vs 19 weeks for the historical group. Patients were censored from analyses (19 in the historical group and 5 in the ICI group) if they were lost to follow-up. Gamma knife (GK) failure events occurred in 18/111 in the historical group with mean time to failure was 8 months (2-25 months), while only 2/24 in the ICI group had GK failure with a mean of 10 months (4 and 15 months). Post-GK failure treatment in the historical group (total of 18 events) was 10 patients received craniotomy, 2 patients received whole brain radiation therapy (WBRT), 4 patients did not receive any treatment, 1 patient received chemotherapy, and 1 patient had unknown treatment. Post-GK failure treatment in the ICI group (total of 2 events) was 1 patient received craniotomy and 1 patient did not receive any treatment. Patient characteristics are summarized in Table 1. Balance on all baseline covariates was achieved after using the propensity score approach ($P > .8$ for all factors assessed).

Survival and Patterns of Failure

Kaplan-Meier method was used to estimate OS (Figure 1). The median OS time was improved in patients receiving ICI compared with the historical control group (approximately 17.6 months vs 6.6 months, hazard ratio (HR) = 0.22, log rank $P = .002$). Cumulative incidence of local failure (Figure 2) in the historical control group was 28.6% at 1 year, compared with 4.6% at 1 year in the ICI group (HR = 0.36, log rank $P = .36$). Cumulative incidence of distant brain failure (Figure 3) in the historical control and ICI groups was approximately 48% and 28%, respectively (HR = 0.41, $P = .07$).

To account for baseline differences between the ICI group and the historical group, a propensity score adjustment was performed. The results are summarized in Table 2. After adjusting for covariates by including the propensity score in the Cox proportional hazards regression models, there was a statistically significant improvement in overall survival (HR = 0.056, $P = .0005$), distant brain failure (HR = 0.326, $P = .015$), and a trend toward improved local control (HR = 0.25, $P = .19$) in patients treated with ICI.

Toxicity

Toxicity was assessed using the common terminology criteria for adverse events v5.0 grading criteria. Two of 24 patients in the ICI group experienced grade IV radiation necrosis (2 and 3 months after the original SRS procedures). Both of these patients required urgent resection of severe radiation necrosis, and both patients recovered function thereafter. No patients in the historical control group experienced grade IV radiation necrosis.

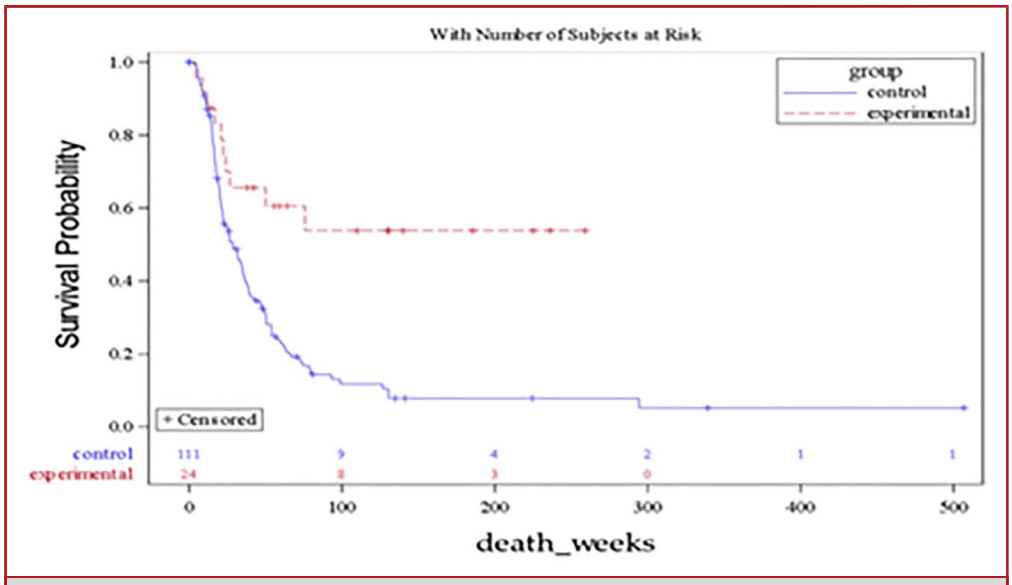

FIGURE 1. *Kaplan-Meier plots for overall survival of patients receiving concurrent immunotherapy as part of their systemic therapy regimen vs historical controls who did not receive immunotherapy.*

DISCUSSION

Immune checkpoint inhibitors have had an impact on multiple brain metastasis outcomes. A number of series have demonstrated improved overall survival in brain metastasis patients receiving immunotherapy.[9,10,18] The use of immune checkpoint inhibitors also seems to decrease brain metastasis velocity, the rate at which

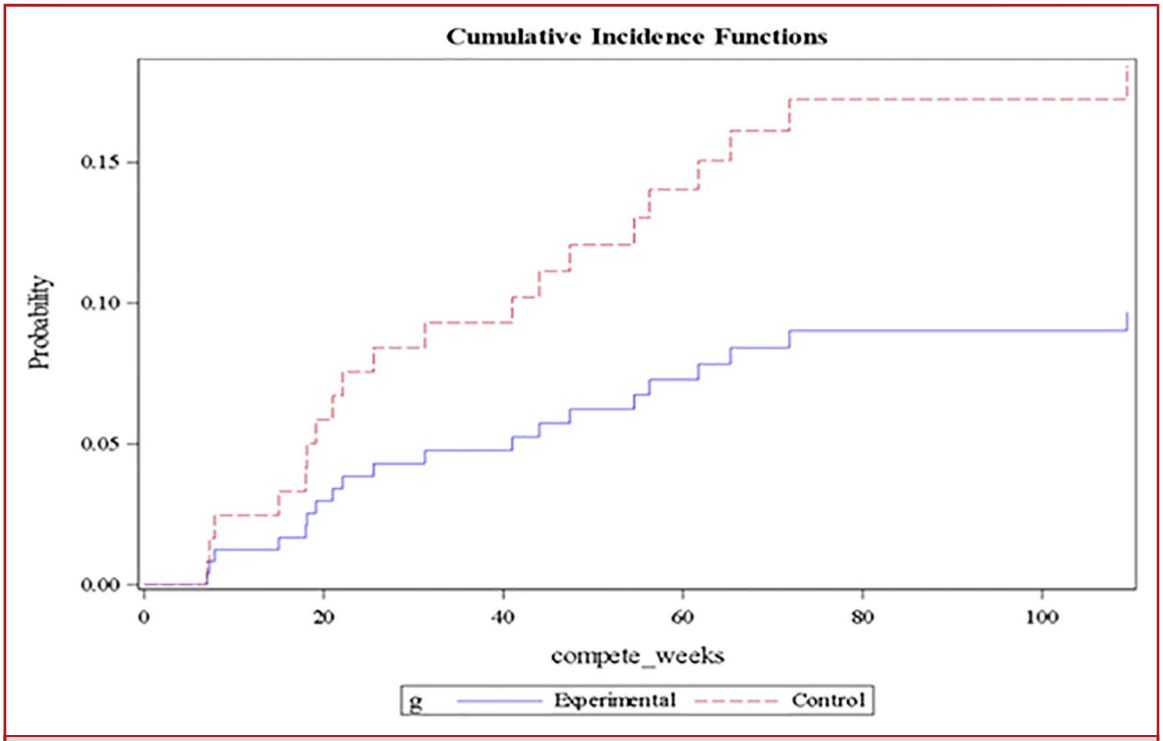

FIGURE 2. *Cumulative incidence plots for time to local failure using competing risk analysis comparing patient cohort receiving concurrent immunotherapy vs historical controls.*

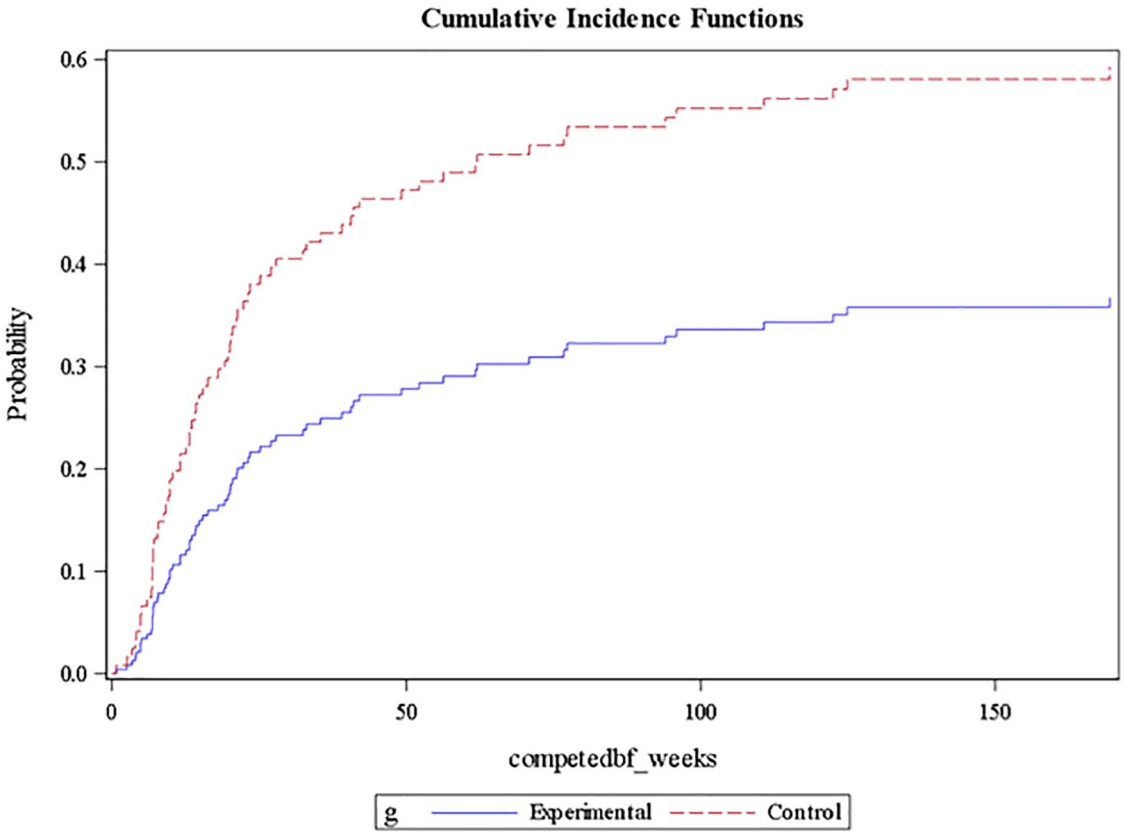

FIGURE 3. *Cumulative incidence plots for time to distant brain failure using competing risk analysis comparing patient cohort receiving concurrent immunotherapy vs historical controls.*

cancer reseeds the brain.[19] Several reports have suggested that the use of immune checkpoint inhibitors in combination with SRS may increase the likelihood of toxicity of SRS, including the likelihood of post-treatment edema, pseudoprogression, and radiation necrosis[20,21]; although despite this risk, patients are still less likely to die of central nervous system-related causes when treated with SRS and immunotherapy.

The present series adds to the increasing amount of data that there may be improved local control with the combination of SRS and immune checkpoint inhibitors for melanoma brain metastases. Although the classic dogma has been that the blood brain barrier prevents efficient penetration of systemic therapy into the central nervous system to affect adequate treatment of brain metastases, there are emerging data that some systemic therapies

TABLE 2. Propensity Score–Adjusted Models for Overall Survival, Local Control, and Distant Brain Failure

	Overall survival		Local control (accounting for competing risk of death)		Distant brain failure (accounting for competing risk of death)	
Variable	**Hazard ratio (CI)**	***P* value**	**Hazard ratio (CI)**	***P* value**	**Hazard ratio (CI)**	***P* value**
Propensity score adjusted	0.056 (0.01-0.30)	.0005	0.25 (0.021-1.06)	.19	0.326 (0.098-0.9)	.015
Propensity score unadjusted (concurrent immunotherapy group)	0.22 (0.102-0.47)	.002	0.36 (0.078-1.68)	.36	0.41 (0.20-0.84)	.07

Propensity score model covariates included age, sex, race, number of metastases, lowest GK dose, KPS, disease burden, and craniotomy.

may cross sufficiently to make a therapeutic difference.[22] Both cytotoxic chemotherapy[23] and small molecule targeted agents[24,25] have been found to increase local control when delivered concurrently with stereotactic radiosurgery for brain metastases. A recent series of patients with non–small-cell lung cancer brain metastasis treated with SRS showed that the use of concurrent immune checkpoint inhibitors dramatically improved local control of brain metastases.[11] A recent report from New York University shows that in patients with melanoma, a significantly higher proportion of patients experience local failures if they have not received immunotherapy.[26] Because local failures tend to be fairly rare events after SRS, it may take the combined results of multiple series to validate these results. However, because local failure has historically been a rare event after SRS, single institution series may be underpowered to answer this question alone.

Melanoma brain metastases have classically been a difficult histology to manage because of the high rate of distant and local failure after SRS. The use of ICI has previously demonstrated benefits of decreased distant brain failure after SRS in patients with melanoma.[26,27] This is likely due to improved control of extracranial disease. It has previously been unclear when the proper time for using WBRT would be for patients with melanoma, particularly given the concern for balance between the cognitive toxicity of WBRT[28] and the question of overwhelming distant brain failure from melanoma's characteristic high brain metastasis velocity.[29,30] Moreover, melanoma has been classically considered a radioresistant histology, which makes it more resistant to WBRT alone,[31] and even has a higher local failure rate with SRS alone.[32] The advantage of having a systemic agent that has activity within the brain is that it potentially adds to both local and regional control after SRS while avoiding the toxicity of WBRT. Thus, WBRT can be reserved for salvage of numerous metastases or when cancer has become resistant to immunotherapy.

A particularly useful population for which this improved local control may ultimately be applied in future clinical trials is those patients who have had a resected brain metastasis. A standard treatment option after such a metastasectomy has been cavity-directed radiosurgery, for which multiple randomized trials have shown to be a feasible and effective technique.[33,34] However, the local control in this population is less than what is seen with surgery followed by WBRT. However, WBRT carries the risk of the aforementioned cognitive toxicity. Having a systemic agent that adds to the likelihood of local control can potentially be quite useful. Unfortunately, the present series was underpowered to detect a difference in local control in this subpopulation. Only 1 of 18 local failures in the historical control population represented a cavity failure, while there were no cavity failures in the ICI cohort.

The novelty of the present series is rooted in its confirmation for a melanoma-specific population that the benefits seen with immunotherapy regarding overall survival, distant brain failure, and local failure of SRS. Brain metastases are increasingly being treated as histology-specific conditions, and for patients with melanoma, this condition has a history of death from neurological causes. Although the role of the present series may be somewhat confirmatory, there is not yet a broad literature for melanoma brain metastases showing these findings. Moreover, the clinical applicability of these findings is quite significant because patients with melanoma often have multiple options for management of systemic disease from BRAF inhibitors to observation (in cases of no detectable extracranial disease). The present data support that in patients with melanoma brain metastases, the use of immunotherapy is likely beneficial regarding survival and control of intracranial disease.

Limitations

There are several limitations to this study. This study is a retrospective analysis and is therefore subject to selection bias. In addition, the sample size of patients treated with immunotherapy is limited, and this study was assessing for differences in a relatively rare event in local failure. After propensity score adjustment of our analyses, differences in both distant failure and local failure between the I/O treated population and the historical controls became nonstatistically significant. This is likely an issue of being underpowered. We wanted the population to be a pure population of patients treated with I/O given concurrently with SRS and served to exclude some of the patients who received I/O at other time points. In addition, owing to a corruption in the treatment planning database, we were unable to determine exact tumor volumes from the historical data set. As such, the lowest volume dose was used as a surrogate for tumor volume, although this is an inexact estimation.

CONCLUSION

Despite the limitations, this study represents a validation within a different histology that the combination of immune checkpoint inhibitors and SRS can improve local control otherwise afforded by SRS alone. The next step would likely be to integrate this combination into clinical trials with the express goal of improving the therapeutic ratio for melanoma brain metastases.

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Disclosures

Dr Chan is a speaker for the Elekta SBRT course and receives an honorarium from Monteris for speaking. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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