Original Article

Timing and Type of Immune Checkpoint Therapy Affect the Early Radiographic Response of Melanoma Brain Metastases to Stereotactic Radiosurgery

Jack M. Qian, BS[1]; James B. Yu, MD[1]; Harriet M. Kluger, MD[2]; and Veronica L. S. Chiang, MD[1,3]

BACKGROUND: Growing evidence suggests that immunotherapy and radiation therapy can be synergistic in the treatment of cancer. This study was performed to determine the effect of the relative timing and type of immune checkpoint therapy on the response of melanoma brain metastases (BrMets) to treatment with stereotactic radiosurgery (SRS). **METHODS:** Seventy-five melanoma patients with 566 BrMets were treated with both SRS and immune checkpoint therapy between 2007 and 2015 at a single institution. Immunotherapy and radiosurgery treatment of any single lesion were considered concurrent if SRS was administered within 4 weeks of immunotherapy. The impact of the timing and type of immunotherapy on the lesional response was determined with the Wilcoxon rank-sum test, which was used to compare the median percent lesion volume change 1.5, 3, and 6 months after SRS treatment, with significance determined by $P = .0167$ according to the Bonferroni correction for multiple comparisons. **RESULTS:** Concurrent use of immunotherapy and SRS resulted in a significantly greater median percent reduction in the lesion volume at 1.5 (−63.1% vs −43.2%, $P < .0001$), 3 (−83.0% vs −52.8%, $P < .0001$), and 6 months (−94.9% vs −66.2%, $P < .0001$) in comparison with nonconcurrent therapy. The median percent reduction in the lesion volume was also significantly greater for anti–programmed cell death protein 1 (anti–PD-1) than anti–cytotoxic T-lymphocyte-associated protein 4 (anti–CTLA-4) at 1.5 (−71.1% vs −48.2%, $P < .0001$), 3 (−89.3% vs −66.2%, $P < .0001$), and 6 months (−95.1% vs −75.9%, $P = .0004$). **CONCLUSIONS:** The administration of immunotherapy within 4 weeks of SRS results in an improved lesional response of melanoma BrMets in comparison with treatment separated by longer than 4 weeks. Anti–PD-1 therapy also results in a greater lesional response than anti–CTLA-4 after SRS. ***Cancer* 2016;000:000–000.** © *2016 American Cancer Society.*

KEYWORDS: anti–cytotoxic T-lymphocyte-associated protein 4 (anti–CTLA-4), anti–programmed cell death protein 1 (anti–PD-1), brain metastases, immunotherapy, melanoma, stereotactic radiosurgery.

INTRODUCTION

Brain metastases (BrMets) historically develop in 10% to 40% of all cancer patients with metastatic disease.[1] Because survival is increasing in duration with the use of new systemic therapies such as targeted agents and immunotherapies, the incidence of BrMets is increasing also.[1] Understanding the efficacy of treatments for BrMets and their toxicities is, therefore, becoming increasingly important. Despite data showing that both targeted agents and immunotherapy agents can have therapeutic effects in the central nervous system,[2-4] the long-term control rates for these drugs remain unknown. Because of this, whole-brain radiation therapy, stereotactic radiosurgery (SRS), and surgical resection remain standard treatments for BrMets on account of their high rates of local treatment success.[5]

Radiation therapy, historically thought to be immunosuppressive because of its lymphotoxicity,[6] has more recently been shown to induce proinflammatory responses secondary to the modulation of antigen presentation and immune signaling pathways.[7] In the setting of systemic use of immune checkpoint inhibitors such as ipilimumab, pembrolizumab, and nivolumab against a variety of tumor types,[8] it remains unknown whether combining these agents with standard local treatment modalities might result in synergistic efficacy or toxicity. Given what could be synergistic mechanisms of action between immunotherapy and radiation therapy, it is reasonable to hypothesize that the combination could result in improved treatment outcomes.[9] Furthermore, it is unknown what the best timing might be for achieving maximal synergism and whether anti–cytotoxic T-lymphocyte-associated protein 4 (anti–CTLA-4) and anti–programmed cell death protein 1 (anti–PD-1) agents have different interactions with focal therapy.

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Because of the increased efficacy of SRS in comparison with fractionated radiation, the majority of melanoma BrMets at our institution are treated primarily with radiosurgery whenever possible.[10] To explore the possible interaction between immunotherapy and radiation, we therefore performed a retrospective review of our melanoma BrMets patients who received both immune checkpoint therapy and SRS during their disease course, and we focused on how the timing and type of immunotherapy affected the lesional response.

MATERIALS AND METHODS

Study Design and Participants

All patients with melanoma BrMets treated with Gamma Knife SRS between 2007 and 2015 who also received either anti–CTLA-4 or anti–PD-1 immunotherapy were identified from an institutional review board–approved institutional database. Patients were excluded if they had leptomeningeal disease or no follow-up imaging after SRS. Individual lesions were also excluded from each patient's data if they were postoperative resection cavities or if the lesions were associated with extensive extralesional hemorrhaging. In patients who underwent SRS treatment more than once, each new lesion was studied independently and included in this study.

All patients were treated with the Leksell Perfexion Gamma Knife (Elekta Medical Systems, Inc). Lesions were treated to a median of 20 Gy (range, 12-24 Gy) to the tumor margin, with doses individualized with institutional standardized modifications of Radiation Therapy Oncology Group 90-05,[11] which take into account both the tumor volume and the number of lesions. Lower doses were prescribed for both an increasing tumor volume and an increasing number of lesions to be treated. Most patients treated with anti–CTLA-4 therapy received up to 4 doses of ipilimumab at either 3 or 10 mg/kg; several of these patients later received a re-induction course. Patients treated with anti–PD-1 therapy received pembrolizumab at a dose of either 2 or 10 mg/kg every 2 or 3 weeks or nivolumab at a dose of 3 mg/kg every 2 or 3 weeks. An examination of the number of days that elapsed between SRS and either the first or last dose of immunotherapy for each lesion (with lesions treated during immunotherapy assigned a value of 0) demonstrated a cluster of lesions around ± 4 weeks (Supporting Figure 1 [see online supporting information]). On this basis, immunotherapy and radiosurgery treatment of any single lesion were considered concurrent if SRS was administered within 4 weeks of the start or end of immunotherapy; all other lesions were defined as having had nonconcurrent treatment.

Three-dimensional, magnetization-prepared, rapid gradient echo, T1-weighted, gadolinium-enhanced magnetic resonance images with a 1-mm slice thickness of the whole brain were obtained on the day of SRS treatment and at each follow-up, as described in a previous publication from this institution.[12] To determine the lesional response, the maximal diameter of the T1 contrast-enhancing portion of each SRS-treated lesion was measured in 3 orthogonal planes at the time of treatment and at each follow-up by a single individual to reduce inter-reader measuring errors. Lesion volumes were calculated with the formula (length $\times$ width $\times$ height)/2, as previously published.[12] Data collection was censored for any single lesion if it required a local intervention, such as surgery, laser thermocoagulation, or salvage radiation, or if the patient received bevacizumab therapy. In addition, data collection was also terminated if the patient was switched from anti–CTLA-4 therapy to anti–PD-1 therapy during follow-up or vice versa. Volume changes at each follow-up were normalized to the baseline treatment volume. For a descriptive graphical analysis of temporal changes in volume, scans were grouped into intervals clustered at 1.5, 3, 6, 9, 12, 18, 24, and 36 months.

Statistical Analysis

Statistical analyses were performed with Stata (version 13.0; StataCorp, College Station, Texas). Baseline characteristics were compared with chi-square tests (for categorical variables) or an analysis of variance (for continuous variables). To determine the impact of the relative timing of therapies (concurrent vs nonconcurrent) and the type of immunotherapy (anti–CTLA-4 vs anti–PD-1) on the early lesional response, we used the Wilcoxon rank-sum test to compare the median percent volume change at follow-up between treatment cohorts at 1.5, 3, and 6 months, with significance determined by $P = .0167$ per the Bonferroni correction for multiple comparisons. These intervals were chosen a priori for clinical relevance and were based on our anecdotal experience that differences in treatment response between types of immunotherapy during those months may be most significant. We also used Kaplan-Meier methods to estimate overall survival per patient from the time of the first SRS treatment, and the log-rank test was used to compare median survival between different treatment groups.

TABLE 1. Baseline Patient, Treatment, and Lesion Characteristics

Characteristic	Value
Patients (n = 75)	
Mean age at first SRS, y	62.5
Sex, No. (%)	
Male	51 (68)
Female	24 (32)
KPS, median (range)	90 (50-100)
Melanoma-specific GPA, median (range)	3 (0-4)
History of WBRT before SRS, No. (%)	5 (7)
Active systemic disease, No. (%)	61 (81)
Time from initial melanoma diagnosis to development of BrMets, median (range), mo	37.5 (0-318)
BRAF, No. (%)	
Mutated	22 (29)
Wild-type	30 (40)
Unknown/not tested	23 (31)
Prior chemotherapy, No. (%)	18 (24)
BRAF inhibitor, No. (%)	15 (20)
Immunotherapy type, No. (%)	
Anti–CTLA-4	54 (72)
Anti–PD-1	21 (28)
Lesions (n = 566)	
Lesion volume, median (range), mm^3	105.6 (4-27,482)
Dose, median (range), Gy	20 (12-24)
Timing of SRS, No. (%)	
Concurrent	313 (55)
Nonconcurrent	253 (45)
Length of follow-up after SRS, median (range), mo	6 (1-93)

Abbreviations: anti–CTLA-4, anti–cytotoxic T-lymphocyte-associated protein 4; anti–PD-1, anti–programmed cell death protein 1; BrMets, brain metastases; GPA, graded prognostic analysis; KPS, Karnofsky performance status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

RESULTS

Patient Demographics

A total of 75 patients with 566 SRS-treated melanoma BrMets were included in this study. Baseline patient, treatment, and lesion characteristics are listed in Table 1. The mean age at the time of treatment was 62.5 years, and 68% of the patients were male. The median Karnofsky performance status of the patients was 90 (range, 50-100), and the median melanoma-specific graded prognostic analysis was 3.0 (range, 0 to 4.0). Eighty-one percent of the patients had active extracerebral metastases at the time of their first SRS treatment. The median time from the initial diagnosis of primary melanoma to the development of BrMets was 37.5 months (range, 0-318 months). The median lesion size for the entire cohort was 105.6 mm^3 (range, 4-27,482 mm^3), and the median marginal dose for each lesion was 20 Gy (range, 12-24 Gy). The median length of imaging follow-up per lesion was 6 months (range, 1-93 months).

Thirty-three patients with 193 lesions had concurrent treatment with immunotherapy and SRS; 9 of these patients had multiple SRS treatments that were all concurrent with immunotherapy. Twenty-two patients with 91 lesions had nonconcurrent treatment; 9 of these patients had multiple SRS treatments that were all nonconcurrent. The remaining 20 patients with 282 lesions had both concurrent and nonconcurrent SRS treatments, with 120 (43%) of these lesions treated concurrently and 162 (57%) of these lesions treated nonconcurrently. In total, 313 lesions in 53 patients were treated concurrently, and 253 lesions in 42 patients were treated nonconcurrently. The baseline characteristics for these groups are shown in Table 2. For the nonconcurrent group, the median time between SRS and immunotherapy was 7.3 months (range, 1.5-41.6 months), with 195 lesions (77%) receiving immunotherapy before SRS and 58 lesions (23%) receiving immunotherapy after SRS.

Fifty-four patients (72%) received anti–CTLA-4 immunotherapy for a median number of 4 doses (range, 1-17 doses). Twenty-one patients (28%) received anti–PD-1 immunotherapy for a median number of 12 doses (range, 1-40 doses). Notably, 12 of these patients had previously received anti–CTLA-4 therapy. No patients received concurrent anti–CTLA-4 and anti–PD-1 therapy. Baseline characteristics for both groups are shown in Table 3. Although many of the standard demographics were similar between the 2 groups, lesions in the anti–PD-1 group tended to have larger baseline tumor volumes (median, 229.6 vs 85.7 mm^3; $P < .0001$), and these patients were prescribed lower SRS doses (median, 18 vs 20 Gy; $P < .0001$) and were more likely to have concurrent SRS treatment (lesions treated concurrently, 85% for anti–PD-1 vs 47% for anti–CTLA-4; $P < .0001$).

Early Lesional Response With Respect to the Timing of Treatment

As shown in Figure 1A, the median percent reduction in the lesion volume was significantly greater for the concurrent group than the nonconcurrent group at 1.5 (−63.1% vs −43.2%, $P < .0001$), 3 (−83.0% vs −52.8%, $P < .0001$), and 6 months (−94.9% vs −66.2%, $P < .0001$). On account of the differences between the groups in the prior treatment with chemotherapy, immunotherapy type, time to the development of BrMets from the initial melanoma diagnosis, and SRS doses, for sensitivity, we analyzed lesions in the subset of 20 patients with both concurrent and nonconcurrent SRS treatments because these patients could serve as their own controls. As expected, there were no longer differences in any baseline characteristics within this subset. Results are shown in Figure 1B, where the median percent reduction in the lesion volume remains significantly greater for the concurrent group than the nonconcurrent group at

TABLE 2. Baseline Patient and Lesion Characteristics by the Timing of Immunotherapy

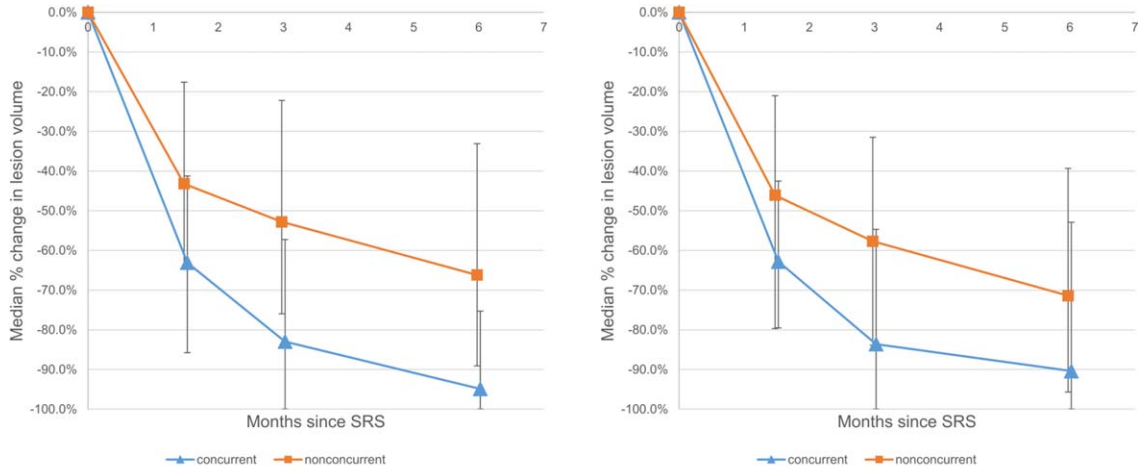
Patient Characteristic	Only Concurrent SRS (n = 33)	Only Nonconcurrent SRS (n = 22)	Both Concurrent and Nonconcurrent SRS (n = 20)	*P*
Mean age at first SRS, y	64.1	61.4	61.4	.6765
Sex, No. (%)				
Male	24 (73)	13 (59)	14 (70)	.555
Female	9 (27)	9 (41)	6 (30)	
KPS, median (range)	90 (70-100)	90 (60-100)	100 (50-100)	.218
Melanoma-specific GPA, median (range)	2 (1-4)	3 (0-4)	3 (0-4)	.580
History of WBRT before SRS, No. (%)	3 (9)	2 (9)	0 (0)	.378
Active systemic disease, No. (%)	29 (88)	16 (73)	16 (80)	.363
Time from initial melanoma diagnosis to development of BrMets, median (range), mo	26.1 (0-229)	66.2 (0-318)	51.5 (0-287)	.0128
BRAF status, No. (%)[a]				
Mutated	10 (30)	5 (23)	7 (35)	.601
Wild-type	17 (52)	7 (32)	6 (30)	
Prior chemotherapy, No. (%)	7 (21)	11 (50)	0 (0)	<.0001
BRAF inhibitor, No. (%)	6 (18)	3 (14)	6 (30)	.392
Type of immunotherapy, No. (%)				
Anti–CTLA-4	19 (58)	19 (86)	16 (80)	.043
Anti–PD-1	14 (42)	3 (14)	4 (20)	
No. of BrMets treated per SRS session, median (range)	3 (1-23)	3 (1-20)	4 (1-21)	.4981
Lesion Characteristic	**Only Concurrent SRS (n = 313)**	**Only Nonconcurrent SRS (n = 253)**	**—**	***P***
Lesion volume, median (range), mm^3	112 (4-10,370)	97.5 (4-27,482)	—	.3176
Dose, median (range), Gy	20 (12-24)	20 (12-24)	—	<.0001[b]

Abbreviations: anti–CTLA-4, anti–cytotoxic T-lymphocyte-associated protein 4; anti–PD-1, anti–programmed cell death protein 1; BrMets, brain metastases; GPA, graded prognostic analysis; KPS, Karnofsky performance status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
[a] Not all patients were tested for the BRAF status.
[b] Concurrently treated lesions had a lower distribution of marginal doses.

TABLE 3. Baseline Patient and Lesion Characteristics by the Type of Immunotherapy

Patient Characteristic	Anti–CTLA-4 (n = 54)	Anti–PD-1 (n = 21)	*P*
Mean age at first SRS, y	62.9	61.9	.7579
Sex, No. (%)			
Male	34 (63)	17 (81)	.134
Female	20 (37)	4 (19)	
KPS, median (range)	100 (50-100)	90 (70-100)	.259
Melanoma-specific GPA, median (range)	3 (0-4)	3 (1-4)	.331
History of WBRT before SRS, No. (%)	5 (9)	0 (0)	.149
Active systemic disease, No. (%)	46 (85)	15 (71)	.170
Time from initial melanoma diagnosis to development of BrMets, median (range), mo	38.9 (0-318)	27.8 (0-204)	.5225
BRAF status, No. (%)[a]			
Mutated	15 (28)	7 (33)	.399
Wild-type	17 (31)	13 (62)	
Prior chemotherapy, No. (%)	16 (30)	2 (10)	.067
BRAF inhibitor, No. (%)	8 (15)	7 (33)	.072
No. of BrMets treated per SRS session, median (range)	3 (1-20)	2 (1-23)	.1472
Lesion Characteristic	**Anti–CTLA-4 (n = 438)**	**Anti–PD-1 (n = 128)**	***P***
Lesion volume, median (range), mm^3	85.7 (4-27,482)	229.6 (4-10,370)	<.0001
Dose, median (range), Gy	20 (12-24)	18 (12-22)	<.0001
Timing of SRS, No. (%)			
Concurrent	204 (47)	109 (85)	<.0001
Nonconcurrent	234 (53)	19 (15)	

Abbreviations: anti–CTLA-4, anti–cytotoxic T-lymphocyte-associated protein 4; anti–PD-1, anti–programmed cell death protein 1; BrMets, brain metastases; GPA, graded prognostic analysis; KPS, Karnofsky performance status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
[a] Not all patients were tested for the BRAF status.



(A)

Time (months)	1.5	3	6
P value	<.0001	<.0001	<.0001

(B)

Time (months)	1.5	3	6
P value	.0057	.0001	.0046

Figure 1. Early lesional response with respect to the timing of immunotherapy for (A) the entire cohort and (B) the subset of patients with both concurrent and nonconcurrent SRS treatments. Error bars denote the interquartile range of the volume change at each time point. SRS indicates stereotactic radiosurgery.

1.5 (−62.8% vs −46.1%, $P = .0057$), 3 (−83.6% vs −57.7%, $P < .0001$), and 6 months (−90.4% vs −71.4%, $P = .0046$).

We additionally examined whether the sequence of therapies affected the results for concurrently treated lesions. One hundred twenty-two lesions were treated with SRS before immunotherapy was started, whereas 191 lesions were treated with SRS after immunotherapy was started. There was no difference at 1.5 (−64.9% vs −62.8%, $P = .53$), 3 (−82.0% vs −83.9%, $P = .93$), or 6 months (−92.0% vs −96.2%, $P = .23$).

Early Lesional Response by Treatment Type

As shown in Figure 2A, the median percent reduction in the lesion volume was significantly greater for anti–PD-1 than anti–CTLA-4 at 1.5 (−71.1% vs −48.2%, $P < .0001$), 3 (−89.3% vs −66.2%, $P < .0001$), and 6 months (−95.1% vs −75.9%, $P = .0004$). Given the differences in the baseline tumor volumes and SRS doses between the 2 groups, for sensitivity, we analyzed a subset of lesions that were 10 mm or larger in diameter and received at least 16 Gy (Fig. 2B). One hundred five lesions met these criteria: 76 in the anti–CTLA-4 group and 29 in the anti–PD-1 group. In the subset analysis, the median percent reduction in the lesion volume remained significantly greater for anti–PD-1 than anti–CTLA-4 at 1.5 (−67.4% vs −39.4%, $P < .0001$), 3 (−75.4% vs −48.4%, $P = .0080$), and 6 months (−88.4% vs −71.3%, $P = .0154$).

We additionally examined whether prior therapy with anti–CTLA-4 affected the results for the anti–PD-1 patients. Twelve patients with 69 lesions had previously received anti–CTLA-4, whereas 9 patients with 59 lesions were anti–CTLA-4–naive. There was no consistent difference over time for the median percent reduction in the lesion volume at 1.5 (−70.4% vs −72.3%, $P = .68$), 3 (−90.0% vs −78.7%, $P = .0088$), and 6 months (−92.3% vs −96.6%, $P = .26$).

Combined Effect of Treatment Timing and Type on the Early Lesional Response

The effect of timing remained significant when we analyzed only lesions in the anti–CTLA-4 group. Concurrent treatment again demonstrated a significantly greater median percent reduction in the lesion volume at 1.5 (−58.3% vs −38.5%, $P < .0001$), 3 (−76.9% vs −52.5%, $P < .0001$), and 6 months (−94.2% vs −65.8%, $P < .0001$).

The effect of the treatment type was diminished when we analyzed only lesions treated concurrently, with a decrease in the magnitude of difference between anti–PD-1 and anti–CTLA-4 at 1.5 (−70.0% vs −58.3%, $P = .0761$), 3 (−89.8% vs −76.9%, $P = .0043$), and 6 months (−95.1% vs −94.2%, $P = .8086$).

Delayed Lesional Response

During follow-up, 39 lesions in 24 patients demonstrated regrowth to greater than 120% of the baseline volume. Ultimately, 11 lesions in 8 patients required surgical management, with 6 lesions resected and 5 lesions treated with

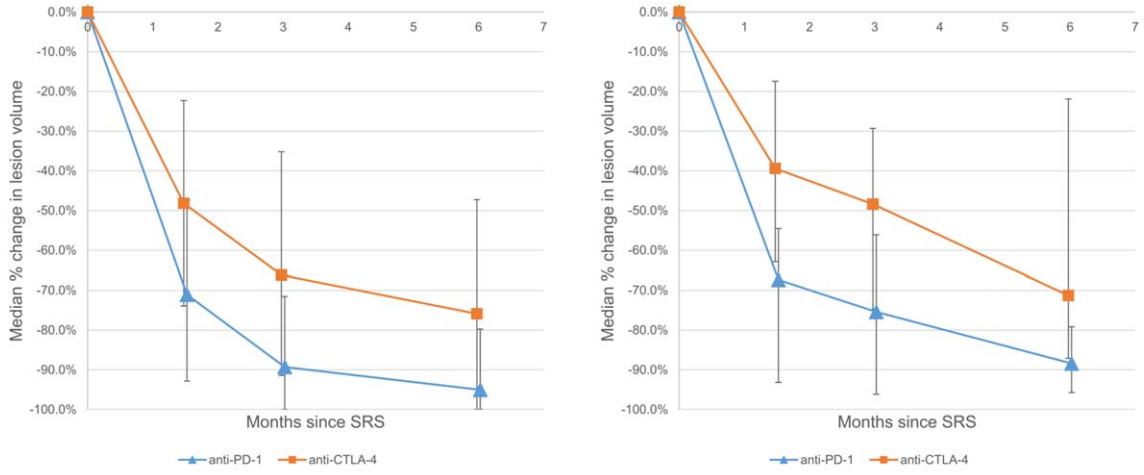


Figure 2. Early lesional response with respect to the type of immunotherapy for (A) the entire cohort and (B) the subset of patients with lesions at least 10 mm in diameter treated with at least 16 Gy. Error bars denote the interquartile range of the volume change at each time point. Anti-CTLA-4 indicates anti-cytotoxic T-lymphocyte-associated protein 4; anti-PD-1, anti-programmed cell death protein 1; SRS, stereotactic radiosurgery.

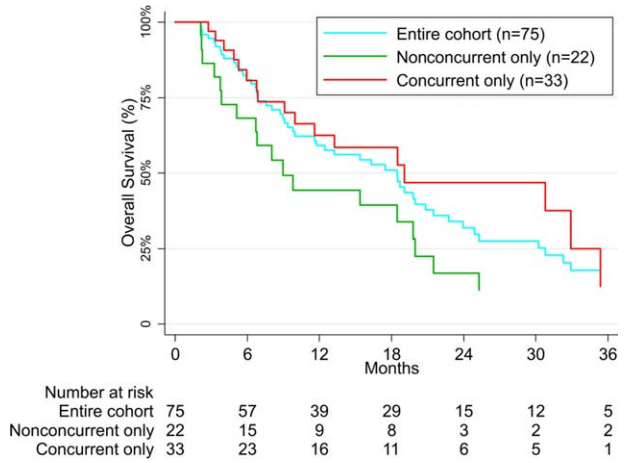


Figure 3. Kaplan-Meier curves illustrating the survival of the entire cohort as well as the patients who had only nonconcurrent or concurrent stereotactic radiosurgery treatments.

laser thermocoagulation. On pathology, all 11 lesions demonstrated features consistent with radiation necrosis; 3 lesions also contained some viable tumor. There were no significant differences in the regrowth incidence when we compared the treatment types and the relative timing of treatment.

Overall Survival

The median overall survival for all patients from the first SRS treatment was 18.5 months (range, 2.1-96.1 months; Fig. 3). Twenty-three of 75 patients (31%) were still alive at the time of the analysis with a median follow-up from the first SRS treatment of 15.5 months (range, 3.7-96.1 months). Of the patients who started on anti–CTLA-4 and had either only nonconcurrent SRS treatment (n = 19) or only concurrent SRS treatment (n = 19), the median overall survival was 8.0 months (range, 2.1-61.8 months) for nonconcurrent treatment and 19.1 months (range, 3.3-64.2) for concurrent treatment ($P = .0858$). When both anti–CTLA-4 and anti–PD-1 patients were included in the analysis, the median overall survival was 9.0 months (range, 2.1-61.8 months) for the 22 nonconcurrent-only patients and 19.1 months (range, 2.7-64.2 months) for the 33 concurrent-only patients ($P = .0691$).

DISCUSSION

Few data are available in the literature regarding the effect of the timing and type of immune checkpoint therapy on the outcomes of patients undergoing radiosurgical treatment for melanoma BrMets. Our study results suggest that 1) immunotherapy can have a synergistic effect with radiosurgery in the treatment of BrMets, even in those not known to have programmed death ligand 1 expression, and 2) the early lesional response is greater and more rapid with concurrent administration of immunotherapy and SRS. Notably, this timing effect remained significant even when we examined a subset of patients who had both concurrent and nonconcurrent therapy.

Although much remains unknown about the effect of immunotherapy on BrMets as well as its interaction with radiation therapy, our findings are consistent with the current literature. Preclinical studies have suggested that concurrent treatment is most effective.[7] To date, only a small number of retrospective clinical studies have examined timing with respect to the combination of SRS and immunotherapy for melanoma BrMets. Although most of these studies had small patient numbers and failed to identify any significant effect of timing on outcomes,[13-15] in 2015, Kiess et al[16] reported that among 46 patients, those treated with SRS before or during ipilimumab had increased overall survival in comparison with those treated with SRS after ipilimumab. They also noted a trend toward higher rates of local control with concurrent treatment versus nonconcurrent treatment. Schoenfeld et al[17] also found in a small series of 16 patients that SRS before ipilimumab was associated with increased survival in comparison with SRS after ipilimumab. Jiang et al[18] subsequently reported in abstract form that in a larger cohort of 71 patients, those who received SRS within 5.5 months of their last dose of ipilimumab had significantly improved intracranial control in comparison with those who received SRS after 5.5 months; however, they did not find a difference in overall survival. Although our study was not designed to look at survival, a subanalysis of our data also suggests a trend toward increased survival with concurrent treatment, although this did not reach statistical significance.

Local control rates have reportedly been high for melanoma BrMets treated with both SRS and anti–CTLA-4 therapy as well as SRS and anti–PD-1 therapy.[14-16] However, to our knowledge, no study has attempted to compare anti–PD-1 and anti–CTLA-4 to each other directly in this setting. Our data suggest that, compared with anti–CTLA-4 and SRS, anti–PD-1 and SRS may result in greater and more rapid lesion shrinkage in the initial months after SRS, even after we control for the baseline lesion size and the SRS dosing. However, these results may have been influenced by a disproportionate number of lesions in the anti–PD-1 group also having concurrent treatment with SRS. When we examined only lesions that were treated concurrently, the effect of anti–PD-1 on early lesional response was diminished, and it remained significant only at the 3-month time point. It is possible, however, that the lower numbers of lesions and patients in this subgroup resulted in an analysis underpowered to detect smaller differences between anti–PD-1 and anti–CTLA-4.

The limitations of this study include its retrospective nature and relatively low number of patients, particularly in the nonconcurrent subset of patients receiving anti–PD-1. Also, although we attempted to address several additional questions in secondary analyses, including the effect of the treatment sequence and the effect of prior anti–CTLA-4 use on outcomes for anti–PD-1 and SRS, the lower numbers of patients and lesions available for these subgroups may have produced underpowered analyses and obscured potential differences. In addition, we recognize our use of the early lesional response as a surrogate for treatment efficacy has limitations. Although some studies have suggested that a significant early lesional response to SRS translates into prolonged local control,[19,20] ultimately, our results still need to be correlated with more traditional measures of clinical outcomes. Future studies could also examine the treatment response on the basis of changes in other magnetic resonance sequences and look at tumor hemorrhage, vascularity, cellularity, or perilesional edema. Finally, because of the median survival of 18 months for our study patients, the role that immunotherapy may play in the development of radiation necrosis also needs to be determined.

In conclusion, we find that immune checkpoint therapy administered within 4 weeks of SRS (either before or after SRS) results in an improved lesional response of melanoma BrMets in comparison with immunotherapy and SRS used more than 4 weeks apart. Anti–PD-1 immunotherapy may also have a greater effect on the lesional response than anti–CTLA-4 in this setting. Although anti–CTLA-4 and anti–PD-1 have distinct mechanisms of action, a comparison of monotherapies may become less relevant as oncologists move toward combination therapy.[21] However, the mechanism by which concurrent immunotherapy increases the effect of radiation remains unknown, and it is unclear whether this effect is isolated to melanoma or perhaps could be applied to other cancer types that also develop BrMets. Further testing and validation of these results in larger prospective studies and in other cancer types are warranted. In addition, the number of doses of immunotherapy concurrent with radiosurgery needs to be studied to determine whether this paradigm could be used to improve the results of other radiotherapy treatments.

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AUTHOR CONTRIBUTIONS

Jack M. Qian: Study design, data collection, analysis and interpretation of the data, statistical analysis, drafting of the manuscript, critical revision of the manuscript, and approval of the final version. **James B. Yu**: Analysis and interpretation of the data, statistical analysis, critical revision of the manuscript, and approval of the final version. **Harriet M. Kluger**: Critical revision of the manuscript and approval of the final version. **Veronica L. S. Chiang**: Study design, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript, and approval of the final version.

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