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Stereotactic radiosurgery and combined immune checkpoint therapy with ipilimumab and nivolumab in patients with melanoma brain metastases: A retrospective monocentric toxicity analysis

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ABSTRACT

Purpose and objective: Adding stereotactic radiosurgery (SRS) to combined immune checkpoint therapy with ipilimumab and nivolumab (IPI + NIVO) has led to promising results for patients with melanoma brain metastases (MBM). This study retrospectively analyzes the toxicity profile depending on the timing of SRS with regard to IPI + NIVO.

Materials and methods: For this study, the clinical database was searched for all patients with MBM who were treated with SRS and IPI + NIVO. The patients were separated into three groups: group A completed IPI + NIVO (usually up to four cycles) >14 days before SRS, in group B IPI + NIVO was initiated>14 days after SRS, and group C received SRS concurrently to IPI + NIVO. Treatment related toxicity was obtained from clinical and neuroradiological records. Analyses were performed using the Fisher-Yates-test.

Results: 31 patients were assessed including six (19.4 %), seven (22.6 %) and 18 (58.1 %) patients, in groups A, B and C, respectively. Baseline prognostic markers between groups were balanced. In total, five (16.1 %) patients experienced neurological grade 3 toxicities related to SRS. All of these five patients were in group C, which was near-significantly correlated with a risk for grade 3 toxicities ($p = 0.058$). Post-hoc analyses showed that a maximum time period of seven days between SRS and IPI + NIVO was significantly correlated with grade 3 toxicity ($p = 0.048$).

Conclusion: Application of SRS to IPI + NIVO within a seven-day span was related to higher toxicity rates in this retrospective analysis. After previous studies focused on immune checkpoint monotherapies with SRS and

Abbreviations: AE, Adverse events; CTCAE, Common Terminology Criteria for Adverse Events; GPA, graded prognostic assessment; IPI, ipilimumab; MBM, Melanoma brain metastases; MRI, magnet resonance imaging; LDH, lactate dehydrogenase; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival; SRS, Stereotactic radiosurgery; SRT, Stereotactic radiotherapy; RN, radiation necrosis.

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declared it as safe, this study indicates that concomitant application of IPI + NIVO and SRS might increase side effects. Prospective validation is warranted to corroborate these findings.

Introduction

The introduction of immune checkpoint inhibitors is highly effective for the treatment of metastatic melanoma. In 2011, the CTLA4-inhibitor ipilimumab (IPI) has been the first checkpoint inhibitor to be approved by the food and drug administration in metastatic melanoma after Hodi and colleagues showed a significant overall survival (OS) benefit alone or in combination with a glycoprotein 100 peptide vaccine compared to the vaccine alone [1]. In the following years, the PD-1 inhibitors nivolumab (NIVO) (CheckMate 066) and pembrolizumab (KEYNOTE-006) could further improve survival rates [2,3]. The latest advance is the combination of IPI and NIVO (IPI + NIVO) which was superior to each respective monotherapy (CheckMate 067) [4]. Furthermore, this immune combination therapy showed impressive response rates in patients with melanoma brain metastases (MBM) in the CheckMate 204 trial. This trial analyzed 101 asymptomatic and 18 symptomatic patients treated with IPI + NIVO, and reported a clinical improvement, 36-months OS and PFS (progression-free survival), of 57.4 %, 54.1 % and 71.9 % for the asymptomatic patients, and 16.7 %, 18.9 % and 36.6 % for the symptomatic patients, respectively [5,6]. These two studies made combined IPI + NIVO the first-line treatment choice in patients with asymptomatic untreated MBM.

As stereotactic radiosurgery (SRS) presents a highly effective local treatment for MBM, its combination with checkpoint inhibitors is of particular interest [7–11]. IPI or NIVO alone is considered safe when being added to SRS and improves local and intracranial control and even OS for MBM [12–17]. OS could potentially be improved when local treatments (SRS and metastasectomy) were added, independent of the timing of the local treatment [18,19].

Except for a case report from 2020 reporting severe radiation necrosis (RN) when applying combined IPI + NIVO concurrently to SRS, few studies report on toxicity for this combination [20]. With grade 3 toxicity rates of around 50 % for IPI + NIVO alone [5,21] it might be possible that concurrent application to SRS leads to higher rates of RN or other grade 3 toxicities. As timing of local treatments does not seem to have an impact its success [18], it is important to know if SRS should be applied before, after or concurrently to IPI + NIVO to prevent unnecessary and, in some cases, life-threatening toxicity. To address this question, we retrospectively analyzed all patients with MBM at our center who received both SRS and IPI + NIVO with respect to toxicity and timing of both treatments.

Materials and methods

All patients with MBM being treated with IPI + NIVO and irradiated at the University Hospital, LMU Munich, were included in our consecutive cohort and retrospectively analyzed. Patient characteristics (sex, age, time of primary diagnosis, time of diagnosis MBM, Eastern Cooperative Oncology Group (ECOG) performance status, graded prognostic assessment (GPA) [22]), disease related data (BRAF status, elevated lactate dehydrogenase (LDH) levels at time of radiation, localization of extracranial metastases, number and size of brain metastases), and treatment data (timing of IPI + NIVO treatment, further lines of systemic therapy, timing of SRS, dose of SRS, number of treated metastases, size of treated volume) were obtained from all patients.

Treatment

All patients received stereotactic radiosurgery with prescription doses of 18–20 Gy at the 80 % isodose line. IPI was administered with 3 mg/kg body mass together with NIVO with 1 mg/kg body mass every 3 weeks for 4 cycles; after that, with few exceptions, NIVO was administered separately with 240 mg every 2 weeks or 480 mg every 4 weeks.

Follow up

Clinical and imaging follow up examinations were evaluated retrospectively. Adverse events (AE) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0; in most cases, the grading was already systematically assessed by the treating physician, if not, grading was done retrospectively using the clinical databank. Follow up cranial MRI, which was regularly done every three months, was evaluated by two experienced neuroradiologists. The irradiated lesions were assessed concerning progressive disease, pseudoprogression, hemorrhage and RN. Hemorrhage was rated according to five grades: 0 = no bleeding; 1 = melanotic with possible bleeding; 2 = no space occupying hemorrhage; 3 = space occupying hemorrhage; 4 = radiation necrosis with hemorrhagic elements. RN was graded using CTCAE for “central nervous system necrosis”, and verified with Fluorethyl-l-tyrosin positrone emission tomography (FET PET) and/or biopsy. The timing of documented AEs and imaging changes was correlated and interpreted by two experienced clinicians.

Timing of SRS and IPI + NIVO

The patients were assigned into three groups depending on the time they received SRS in relation to the IPI + NIVO treatment which usually consists of four cycles: group A completed IPI + NIVO (usually up to four cycles) >14 days before SRS, in group B IPI + NIVO was initiated>14 days after SRS, and group C received SRS concurrently to IPI + NIVO. The time interval to SRS was defined as the time span in days before the beginning or after the end of the IPI + NIVO cycles, whereas parallel application was assigned with 0 days. Other than the usual 4 weeks chosen by most trials e.g. Kiess et al, the interval was chosen intuitively following the experience at the study center to detect possible changes within smaller intervals between treatments [16].

Statistics

Statistical analysis was performed using IBM SPSS Statistics version 28.0 (IBM, Armonk, New York, USA). Focusing on severe neurological toxicities (CTCAE grade 3 or higher) and newly detected space occupying hemorrhage or RN of irradiated MBM, the Fisher-Yates-test was used to detect differences between treatment groups. Kruskal-Wallis or Fisher-Yates tests were used to compare patient characteristics among all treatment groups. For survival analysis Kaplan-Meier-estimates were performed. The survival curves were compared using the log-rank test. A p value ≤ 0.05 was considered as statistically significant.

Results

In total, 31 eligible patients were identified (22 male, 9 female). Following the criteria described above, six (19.4 %) patients were allocated to group A, seven (22.6 %) into group B and 18 (58.1 %) into group C. Median ECOG performance status at time of applying SRS was 0 in all groups (range 0–2). Four (12.9 %) patients had MBM at first diagnosis of melanoma: zero (0.0 %), two (28.6 %) and two (11.1 %) in group A, B and C, respectively. Eleven (35.5 %) patients had elevated LDH at time of study SRS: four (66.7 %), three (43.0 %) and four (22.2 %) in group A, B and C, respectively. The groups did not differ significantly with regard to patient characteristics. Further patient characteristics can be found in Table 1.

Median follow up after study-SRS was 33.2 months (95 % CI 27.3–58.9 months). Median OS since diagnosis of MBM was 23.8 months in total: 13.9 months (95 % CI 11.4–16.3 months) in group A and not reached in groups B and C. Median OS since study-SRT was overall 20.2 months, 11.6 months for group A and could not be reached in group B and C. Median intracranial progression free survival (iPFS) was 4.9 months for the entire cohort (95 % CI 0.0–10.4): 2.5 months (95 % CI 2.4–2.5), 14.4 months (95 % CI 7.1–21.7) and 4.2 months (95 % CI 1.2–7.2) in group A, B, and C, respectively. There was no significant difference between the respective survival rates. Local control after SRS was high (93.5 % at 1y), and median intracranial control was 55.4 % at 1y without significant group differences. Further information regarding patients' outcomes can be found in Fig. 1.

In total, ten (32.3 %) patients reported CTCAE grade 3 neurological toxicities, five (16.1 %) of which were related to SRS. Of the latter five patients two (40.0 %) had RN and three (60.0 %) space-occupying hemorrhage. Regarding the symptoms of these five patients three (60.0 %) had a seizure, one (20.0 %) of them showed severe symptoms of increased intracranial pressure, and one (20.0 %) patient had a seizure and hemiparesis. Notably, all patients with SRS-related CTCAE grade 3 toxicities were in group C, 80 % of these with increased edema, and therefore 27.8 % of all group C patients experienced respective toxicities. Furthermore, pseudoprogression occurred in 44.4 % of patients in group C, compared to 16.7 % (group A) and 28.6 % (group B). When considering the exact SRS timing in patients who experienced toxicities, all of them received SRS within a seven-day interval prior to or after an IPI + NIVO cycle. The relationship between the SRS-related CTCAE grade 3 toxicities and group C was near-significant ($p = 0.058$). When comparing patients who received SRS and an IPI + NIVO cycle within a seven-day time span with all other patients, the relationship to CTCAE grade 3 toxicities showed statistical significance ($p = 0.048$). Further results regarding follow up can be found in Table 2.

Discussion

Evidence on combined IPI + NIVO immunotherapy and SRS concerning synergistic toxicities in MBM is scarce up to now as the presumed safety of adding SRS to IPI + NIVO is mainly based on publications analyzing the toxicity of combining SRS to each agent separately [14,23,24].

Our results strongly suggest an association between timing of SRS and toxicity during treatment with IPI + NIVO. In fact, all five patients with therapy related AEs received SRS within seven days prior to or after an IPI + NIVO cycle. A strength of this study is that only melanoma patients with IPI + NIVO and SRS as radiation modality were included, in comparison to other studies, in which various treatments were mixed.

Concerning monotherapy, some studies reported interesting results on IPI and SRS. Diao et al described the combination of SRS and IPI as overall safe in a monocentric retrospective evaluation [23]; they observed a significantly improved tumor reduction, however noted significantly higher rates of hemorrhage and symptomatic imaging changes when applying SRS concurrently to IPI (defined as within 4 weeks) [23]. Cohen-Inbar et al also observed an influence of timing when comparing SRS before or during IPI (group A) with SRS after IPI (group B) [25]: group A showed a significantly longer local recurrence-free duration but also significantly more post therapeutic perilesional edema [25]. A similar improvement of intracranial control and iPFS with a higher RN occurrence for applying SRS and IPI concurrently was described by Skrepnik et al. [26]. Another study by Olson et al reported improved OS in a small retrospective cohort of 27 patients for concurrent or prior administration of SRS and IPI (23.4 vs 10.4 months) [27]. Obviously, all of these experiences were retrospectively designed studies with rather small cohorts. However, timing seems to have a certain influence for SRS and IPI with regard to control and toxicity. Therefore, it may be speculated that timing also has an impact on IPI + NIVO and SRS. Similar to these observations on IPI and SRS, the present study showed a higher rate of CTCAE grade 3 AEs for concurrent

Table 1
Patient characteristics.

		All (n = 31)	Group A (n = 6)	Group B (n = 7)	Group C (n = 18)	Difference between groups
Sex	**male**	22 (71.0 %)	5 (83.3 %)	4 (57.1 %)	13 (72.2 %)	
	female	9 (29.0 %)	1 (16.7 %)	3 (42.9 %)	5 (27.8 %)	p = 0.653*
Median age at study-SRS (years)		55 (range 22–74)	61 (range 39–72)	55 (range 38–71)	52 (range 22–67)	p = 0.664**
Median ECOG performance status at study SRS		0 (range 0–2)	0 (range 0–1)	0 (range 0–2)	0 (range 0–1)	p = 0.955**
Median GPA-Index		2.5 (1.5–3.5)	2 (range 1.5–2.5)	2.5 (range 1.5–3.5)	2.5 (range 1.5–3)	p = 0.177**
Median GPA estimated survival (months)		12.1 (range 8.3–34.1)	8.3 (range 8.3–15.8)	12.1 (range 8.3–34.1)	15.8 (range 8.3–15.8)	p = 0.170**
BRAF mutation	**yes**	19 (61.3 %)	3 (50.0 %)	4 (57.1 %)	12 (66.7 %)	
	no	12 (38.7 %)	3 (50.0 %)	3 (42.9 %)	6 (33.3 %)	p = 0.889*
Brain metastases at primary diagnosis	**yes**	4 (12.0 %)	0 (0.0 %)	2 (28.6 %)	2 (11.1 %)	
	no	27 (87.1 %)	6 (100.0 %)	5 (71.4 %)	16 (88.9 %)	p = 0.459*
Median LDH at study-SRS (U/l)		239.5 (range 142–2310)	292.0 (range 177–2310)	275.5 (range 170–600)	218.0 (range 142–1404)	p = 0.470**
Patients with elevated LDH at study-SRS (above 250 U/l)	**yes**	11 (35.5 %)	4 (66.7 %)	3 (43.0 %)	4 (22.2 %)	
	no	13 (41.9 %)	1 (16.7 %)	3 (43.0 %)	9 (50.0 %)	
	not available	7 (22.6 %)	1 (16.7 %)	1 (14.3 %)	5 (27.8 %)	p = 0.163*
Median number of irradiated metastases		2 (range 1–10)	3 (range 1–7)	1 (range 1–3)	2 (range 1–10)	p = 0.127**
Median volume of each PTV		0.9 (range 0.1–11.3)	0.9 (range 0.2–5.2)	1.5 (range 0.8–8.9)	0.8 (range 0.1–11.3)	p = 0.412**
Median PTV sum (cc)		2.9 (range 0.5–13.2)	2.8 (range 0.5–13.2)	2.6 (range 0.8–8.9)	3.8 (range 0.5–11.3)	p = 0.970**
Median number of extracranial sites at study-SRS		1 (range 0–4)	1 (range 1–3)	1 (range 0–3)	2 (range 0–4)	p = 0.568**
Extracranial metastases at diagnosis MBM	**yes**	25 (80.1 %)	6 (100.0 %)	4 (57.1 %)	15 (83.3 %)	
	no	6 (19.4 %)	0 (0.0 %)	3 (42.9 %)	3 (16.7 %)	p = 0.159*

Group A: IPI + NIVO finished > 14 days before SRS; Group B: IPI + NIVO started > 14 days after SRS; Group C: SRS ≤ 14 days to IPI + NIVO.
* Fisher-Yates test; ** Kruskal-Wallis test.
IPI + NIVO: combined immunotherapy of ipilimumab and nivolumab; SRS: stereotactic radiosurgery; LDH: lactate dehydrogenase; GPA: Graded prognostic assessment; ECOG: Eastern Cooperative Oncology Group; MBM: melanoma brain metastases; PTV: planning target volume.

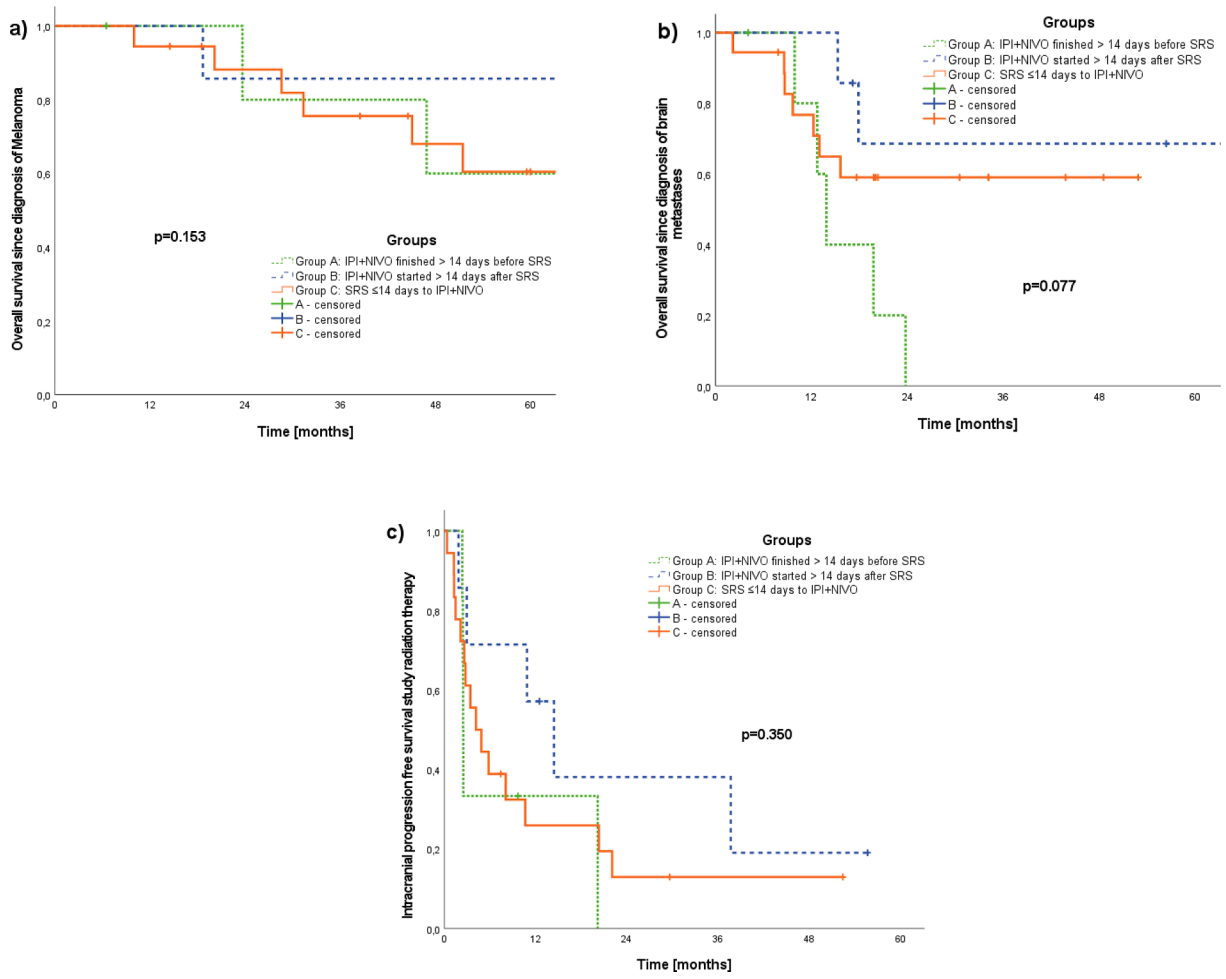

Fig. 1. Kaplan-Meier survival curves of patients with melanoma brain metastases. Group A (n = 6): combined immunotherapy of ipilimumab and nivolumab (IPI + NIVO) finished >14 days before stereotactic radiosurgery (SRS); Group B (n = 7): IPI + NIVO started >14 days after SRS; Group C (n = 18): SRS ≤ 14 days to IPI + NIVO a) Overall survival since first diagnosis malignant melanoma b) OS since diagnosis melanoma brain metastases c) Intracranial progression free survival since study-SRS.

Table 2
Follow up results.

	All (n = 31)		Group A (n = 6)		Group B (n = 7)		Group C (n = 18)	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
SRS of new brain metastases	5	19.4 %	1	16.7 %	2	28.6 %	3	16.7 %
Salvage WBRT	4	12.9 %	1	16.7 %	2	28.6 %	1	5.6 %
Salvage WBRT + SRS of new brain metastases	2	6.1 %	1	16.7 %	0	0.0 %	1	5.6 %
Local progressive disease	2	6.5 %	1	16.7 %	0	0.0 %	1	5.6 %
Intracranial progressive disease	22	71.0 %	4	66.7 %	5	71.4 %	13	72.2 %
Neurological AEs CTCAE°3 (total)	10	33.3 %	2	14.3 %	1	3.2 %	7	38.9 %
Neurological AEs CTCAE°3 (related to study-SRS)	5	16.1 %	0	0.0 %	0	0.0 %	5	27.8 %

Group A: IPI + NIVO finished > 14 days before SRS; Group B: IPI + NIVO started > 14 days after SRS; Group C: SRS ≤ 14 days to IPI + NIVO.
IPI + NIVO: combined immunotherapy of ipilimumab and nivolumab; SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy; AE: adverse event; CTCAE: common terminology criteria for adverse events version 5.0.

administration of SRS and IPI + NIVO (here defined as SRS during or 14-days before or after IPI + NIVO).

Toxicity specifically regarding IPI + NIVO and SRS has not been analyzed in any other study, so far. The rationale of adding SRS to the systemic treatment with IPI + NIVO is mainly based on the fact that SRS has shown to have a synergistic effect on brain metastases when added to IPI or NIVO, and that the combination of IPI and NIVO has a strong benefit for patients with MBM [12,28,32]. The treatment effect of IPI + NIVO for MBM has been explored in several large trials, mostly, however, lacking detailed information regarding radiotherapy or toxicity. A retrospective study by Qian et al. (n = 110; 35 (31.8 %) non-small cell cancer and 75 (61.8 %) melanoma patients) concluded that concurrent immune checkpoint inhibition (IPI or NIVO alone, and IPI + NIVO) and brain irradiation (SRS/SRT or WBRT) was associated with improved response of brain metastases [29]; but notably, only 28 (25.5 %) patients received combined IPI + NIVO, 16 of them (14.5 %) sequentially and 12 (10.9 %) concurrently to radiotherapy [29]. Local therapy (defined as SRS or surgery) was superior when combined with IPI + NIVO in a retrospective study of 380 patients by Amaral et al. [18]: This analysis, however, does not differentiate between surgery and SRS; furthermore,

timing of local treatment was analyzed with regard to OS but not in relation to toxicity [18]. In a large randomized trial with 1,296 untreated MBM patients, of which 314 received IPI + NIVO, Larkin et al reported that 21 % of this group received subsequent radiotherapy during the 5-year follow up, but, again, without any remark on radiotherapy-specific toxicity [30]. Long et al showed an advantage of IPI + NIVO compared with NIVO alone for MBM in a randomized phase II trial, but only included 8 patients with SRS within a small additional non-randomized cohort [21]. Only two patients received radiotherapy prior to IPI + NIVO in Checkmate 204, which compared 101 asymptomatic with 18 symptomatic MBM patients in an open-label phase II study and showed an advantage especially for asymptomatic patients [5,6]. Therefore, despite available large cohorts, none of these studies gave real answers to SRS-related toxicity and timing in relation to IPI + NIVO.

Obvious limitations of our study are the relatively small cohort and its retrospective character. Additionally, a certain selection bias has to be taken into account since patients who received SRS and IPI + NIVO concurrently possibly had more rapidly progressing disease. Nevertheless, patient characteristics (Table 1) and outcomes (Table 2) of the groups did not differ greatly, making them comparable to a certain degree. Neither initial ECOG score, nor total irradiated volume, nor number of extracranial metastatic sites and number and volume of brain metastases differed among these three groups. Yet, a selection bias cannot be excluded.

Overall, the present study is the first analysis addressing toxicity specifically for IPI + NIVO and SRS. Despite of the advantages of the combination of IPI + NIVO and SRS, too close application of SRS and IPI + NIVO seems to increase the risk of higher-grade AEs. Obviously, this observation needs to be confirmed in larger cohorts and, ideally, prospective studies. However, we advise caution when applying SRS within seven days of an IPI + NIVO cycle at least for patients with large MBM or lesions at critical locations, who have a higher risk for RN or hemorrhage. Another option might be applying hypofractionated SRT regimens to reduce the risk of side effects [31].

Conclusion

SRS combined with immune checkpoint inhibitors has shown to be an effective treatment for patients with MBM. However, applying SRS to MBM within seven days prior to or after combined IPI + NIVO administration was related to significantly higher rates of CTCAE grade 3 AEs in this retrospective cohort of 31 patients. Caution when concomitantly applying IPI + NIVO during SRS may be advisable. However, further prospective data is warranted before any ultimate advice can be given.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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