4

Combined Stereotactic Radiosurgery and Immune Checkpoint Inhibitors for the Treatment of Brain Metastasis

Ahmet Kucuk[1] • Erkan Topkan[2] • Nulifer Kılıc Durankus[3] • Sukran Senyurek[3] • Eyub Yasar Akdemir[3] • Duygu Sezen[3] • Yasemin Bolukbasi[3] • Ugur Selek[3] • Berrin Pehlivan[4]

[1]Mersin City Education and Research Hospital, Radiation Oncology Clinics, Mersin, Turkey; [2]Baskent University Medical Faculty, Department of Radiation Oncology, Adana, Turkey; [3]Koc University, School of Medicine, Department of Radiation Oncology, Istanbul, Turkey; [4]Department of Radiation Oncology, Bahcesehir University, Istanbul, Turkey

Author for correspondence: Erkan Topkan, Baskent University Medical Faculty, Department of Radiation Oncology, 01120, Adana, Turkey. E-mail: docdretopkan@gmail.com

Cite this chapter as: Kucuk A, Topkan E, Durankus NK, Senyurek S, Akdemir EY, Duygu S, Bolukbasi Y, Selek U, Pehlivan B. Combined Stereotactic Radiosurgery and Immune Checkpoint Inhibitors for the Treatment of Brain Metastasis. In: Sergi CM, editor. *Advancements in Cancer Research*. Brisbane (AU): Exon Publications; Online first 03 Jan 2023. p. 57–74

Doi: https://doi.org/10.36255/treatment-brain-metastasis

Abstract: Metastasis of solid tumors to the brain occurs in about 30% of cases. Surgery and whole-brain radiotherapy have been the standard treatments with very limited success rates. As a result of the unsatisfactory local control and long-term survival outcomes, stereotactic radiosurgery has been used as an alternative to surgery and whole-brain radiotherapy, or to improve the outcomes in conjunction with other treatments. However, stereotactic radiosurgery does not produce the desired survival results despite the striking increases in local control rates, primarily because of deaths attributed to extracranial systemic disease progression or unavoidably fatal distant brain recurrences. Lately, immunotherapy has become

In: Sergi CM, editor. *Advancements in Cancer Research*. Exon Publications, Brisbane, Australia. ISBN: 978-0-6453320-9-4. Doi: https://doi.org/10.36255/advancements-in-cancer-research

a part, or mainstay, of treatment algorithms for many cancer types. Several authors have proposed the integration of stereotactic radiosurgery and immunotherapy for the treatment of brain metastasis. This chapter evaluates the efficacy and safety of combining novel immunotherapeutics with traditional stereotactic radiosurgery for the treatment of brain metastasis.

Keywords: combination therapy for brain metastasis; immune checkpoint inhibitors for brain metastasis; immunotherapy for brain metastasis; stereotactic radiosurgery for brain metastasis; stereotactic radiosurgery

INTRODUCTION

Brain metastasis occurs in 30–40% of adult patients with solid cancers (1, 2). Lung cancers (small and non-small cell), malignant melanoma (MM), renal cell carcinoma (RCC), and breast cancer are the most common causes of brain metastasis (3). Chemotherapy, surgery, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), targeted therapies, and immunotherapy are used to treat brain metastasis (4, 5). SRS is used more frequently in clinical practice because it produces better results with less toxicity than WBRT (6) (Figure 1). The main mechanisms by which the ionizing radiation used in WBRT functions are double-strand DNA damage, 'oxygen fixation' of the damage, and the production of cytotoxic free radicals in tumor cells. When ionizing radiation is used in the form of high-precision SRS, it affects the local and systemic immune responses against the tumor cells by inducing immunogenic cell death, improving neoantigen presentation, and activating cytotoxic T-cells (7). In comparison to conventional WBRT, SRS offers better local control rates with a lower risk of neurocognitive decline (8). Given this foundational understanding, several authors recently discussed their experiences using various combinations of immune checkpoint inhibitors (ICIs) and SRS in patients who presented with brain metastasis from various cancers. As a result, it has been proposed that immunoradiotherapy may facilitate a higher local control and an antitumor systemic response by activating the adaptive immune system through T-cells (7). The goal of the current chapter is to summarize our current knowledge on the role of combined SRS and ICIs for the treatment of brain metastasis.

IMMUNE CHECKPOINT INHIBITORS

Immune cells, such as macrophages, natural killer cells (NKc), dendritic cells, T-lymphocytes, and B-lymphocytes, are frequently engaged in the antitumoral immune response. T-cells bear the greatest antitumor immune workload. The balance between stimulatory and inhibitory (immune-checkpoint) signals governs the final vehemence and efficiency of immune responses triggered by T-cell recognition of specific antigens. (9, 10). Tumors and peripheral tissues can also trigger an immune response, as can the lymph nodes. T-cells remain unresponsive unless they recognize matching antigens via their receptors. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are

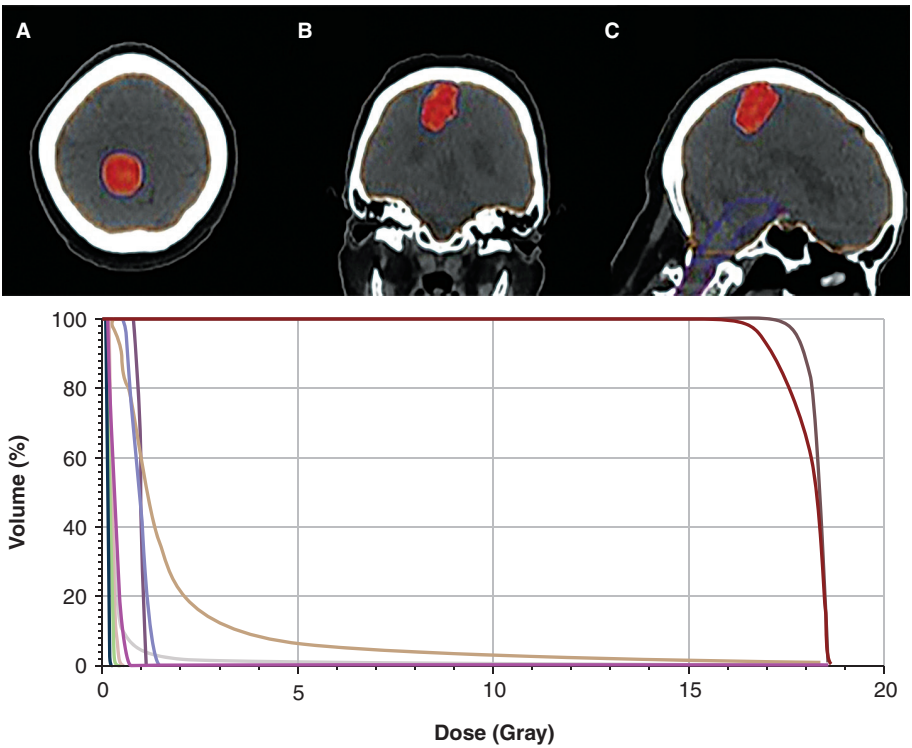

Figure 1. A typical linear accelerator based stereotactic radiosurgery plan and related dose-volume histogram for a patient with single brain metastasis. A: Axial; **B:** Coronal; **C:** Sagittal view.

the two immune checkpoints that have been most successfully targeted in the context of cancer immunotherapy, both being inhibitory receptors in controlling the immune response at various levels using different mechanisms. The antibodies, ipilimumab (IPI) for CTLA-4, and nivolumab (NIVO) and pembrolizumab (PEMBRO) for PD-1 receptor, block these inhibitory receptors on T-cells and are effective against tumors and are thus frequently used in the treatment of a range of cancers. This highly specialized activity blocks the transmission of the "off" signal, enabling the T cells to kill cancer cells.

INTERACTIONS BETWEEN THE IMMUNE SYSTEM AND RADIOTHERAPY

The biological effects of ionizing radiations are primarily caused by DNA damage. Double-strand DNA damage results in cell death if it is not properly repaired. Various studies investigating the impact of radiotherapy (RT) on the immune system over the last two decades indicated that local RT increased systemic immune response through antitumoral immune stimulant actions. Following RT, high levels of tumor-associated antigens are released from necrotic and apoptotic

tumor cell debris. Dendritic cells then present these antigens to CD8+ cytotoxic T cells. The immune system is turned on to fight tumor cells all over the body when these antigens are recognized (11). Results from preclinical and clinical studies corroborated this crucial information by demonstrating that therapeutic radiation, especially when combined with ICIs, significantly increased systemic immune response, which led to immunogenic tumor cell death (12–15). Additional crucial information on the significance of RT doses and fractionation, as well as the ideal timing of RT that exerts maximum antitumor immune stimulation, were revealed by research examining the interactions between RT and the immune system. Schaue et al. examined the effects of the total dose, the dose per fraction, and the number of fractions of RT on the RT-induced immune response and the outcomes in a mouse melanoma model (16). According to the authors, tumor growth was effectively inhibited by single fraction doses of radiation, and successful local control rates were correlated with the radiation dose and the quantity of tumor-reactive T cells. ICIs can be administered prior to, during, or after the SRS. Concurrent use of both modalities was defined in most studies as the administration of ICIs 2 to 4 weeks before or after the SRS provided the best local control and overall survival outcomes. Based on this clinical evidence, it is currently recommended that the time between SRS and ICIs does not exceed four weeks (17, 18). It should be noted, however, that different ICIs may have sequence-dependent distinct efficacy in relation to their administration timing relative to the SRS.

CLINICAL EVIDENCE FOR COMBINATION THERAPY

Clinical trials examining various combinations of SRS and ICIs in patients with brain metastasis have been supported by hypothetical and preclinical evidence demonstrating a synergistic relationship between SRS and ICIs. However, there is still debate regarding the best sequence of administration of these two treatment modalities, SRS fractionation scheme and per-fraction/total dosages, the choice of appropriate ICIs, therapeutic impact, and side effects, among others. Furthermore, despite most studies indicating improved local control and overall survival with acceptable toxicity rates, such studies were retrospective cohort analyses with a small population where primary histology was mostly for MM, and IPI was the most used ICI. These constraints make it challenging to comprehend the published results and their true impact on brain metastasis originating from other tumor primaries (19). Tables 1, 2, and 3 provide an overview of the studies, which were primarily retrospective series of brain metastasis from MM (20–46), non-small cell lung cancer NSCLC (47–52), and RCC, among others (53–59).

To assess the impact of IPI on survival outcomes, Knisely et al. retrospectively analyzed the data of 77 MM patients who underwent SRS (20). Patients who received IPI and SRS had a median overall survival of 21.3 months, compared to 4.9 months for patients who only received SRS. The 2-year survival rate was also higher for patients who received the combination therapy (19.7% vs. 47.2%). According to the authors, the addition of IPI to SRS was the unique factor that significantly lowered the risk of death ($P = 0.03$). The outcomes of 33 MM patients who underwent SRS with or without IPI were compared in a different

TABLE 1 **Clinical trials of combination stereotactic radiosurgery and immune checkpoint inhibitors in malignant melanoma patients with brain metastasis**

Reference	Year	Patients (n)	Design	ICI	Primary	LC (%)	Median OS (Mo.)	1-yr OS (%)
Knisely et al. (20)	2012	16	SRS + ICI	IPI	MM	NR	21.3	47.2 (2-y)
		11	ICI + SRS			NR	19,8	NR
		50	SRS alone			NR	4.9	19.7
Silk et al. (21)	2013	16	SRS alone	IPI	MM	NR	4.0	NR
		17	SRS + ICI			NR	19,9	NR
Kaidar-Person et al. (22)	2017	58	SRS + ICI	NIVO or IPI	MM	52	15.0	NR
			SRS alone			86	5.5	NR
Diao et al. (23)	2018	23	Concurrent	IPI	MM	58	11.8	50
		28	Non-concurrent			70	18.7	63
		40	SRS alone			45	7.8	28
Trommer et al. (24)	2018	26	SRS alone		MM	80	NR	NR
			SRS + ICI	PEMBRO		86	NR	NR
Mathew et al. (25)	2013	25	SRS + ICI	IPI	MM	65	5.9	56 (6-mo)
		33	SRS alone			63		46
Kiess et al. (26)	2015	19	SRS + ICI	IPI	MM	87	NR	56
		15	Concurrent			100	19.5	65
		12	ICI + SRS			89	NR	40
Tazi et al. (27)	2015	10	SRS + ICI	IPI	MM	NR	29.3	90

Table continued on following page

TABLE 1 **Clinical trials of combination stereotactic radiosurgery and immune checkpoint inhibitors in malignant melanoma patients with brain metastasis (*Continued*)**

Reference	Year	Patients (n)	Design	ICI	Primary	LC (%)	Median OS (Mo.)	1-yr OS (%)
Schoenfeld et al. (28)	2015	5	SRS + ICI	IPI	MM	NR	26.0	NR
		4	Concurrent			NR	14.4	54
		7	ICI + SRS			NR	6.0	NR
Qian et al. (29)	2016	22	Non-concurrent	IPI or NIVO or	MM	NR	9.0	NR
		33	Concurrent	PEMBRO		NR	19.1	62.5
Ahmed et al. (30)	2016	26	SRS + ICI	IPI	MM	82	12.0	55
Choong et al. (31)	2017	108	SRS + ICI		MM	78	14.2	NR
Patel et al. (32)	2017	20	ICI+ SRS	IPI	MM	71.4	8.0	37.1
Cohen-Inbar et al. (33)	2017	32	SRS + ICI	IPI	MM	54.4	13.8	59.2
		14	ICI + SRS			16.5	6.4	33.3
Skrepnik et al. (34)	2017	25	SRS + ICI or Concurrent	IPI	MM	94.8	35.8	83
Yusuf et al. (35)	2017	6	Non-concurrent	IPI or PEMBRO	MM	NR	7.1	NR
		12	Concurrent			87.6	11.9	45
Williams et al. (36)	2017	11	Concurrent	IPI	MM	NR	NR	60
Anderson et al. (37)	2017	11	Concurrent	PEMBRO	MM	NR	NR	NR
Rahman et al. (38)	2018	39	Non-concurrent	IPI or NIVO or	MM	NR	11.6	NR
		35	Concurrent	PEMBRO		NR	17.8	NR
Nardin et al. (39)	2018	25	SRS + ICI	PEMBRO	MM	80	15.3	49

Table continued on following page

TABLE 1 **Clinical trials of combination stereotactic radiosurgery and immune checkpoint inhibitors in malignant melanoma patients with brain metastasis (*Continued*)**

Reference	Year	Patients (n)	Design	ICI	Primary	LC (%)	Median OS (Mo.)	1-yr OS (%)
Robin et al. (40)	2018	38	SRS + ICI	NIVO or IPI	MM			
Minniti et al. (41)	2019	45	SRS + ICI	NIVO	MM	85	22.0	78
		35	SRS + ICI	IPI		70	14.7	68
Murphy et al. (42)	2019	26	SRS + ICI	IPI or NIVO or PEMBRO	MM	NR	26.1	NR
Galli et al. (43)	2019	18	SRS + ICI	IPI or NIVO or	MM	NR	7.0	NR
		18	WBRT + ICI	PEMBRO		NR	5.0	NR
Carron et al. (44)	2020	50	SRS + ICI	NIVO or PEMBRO	MM	94	16.62	NR
Rhun et al. (45)	2020	32	SRS + ICI	IPI or NIVO or	MM	NR	11	NR
		20	SRS + ST	PEMBRO			13	
		10	ICI alone				5	
Hassel et al. (46)	2022	19	SRS/WBRT + ICI	IPI or IPI +	MM	NR	15	NR
		31	ICI + SRS/WBRT	NIVO			11	

ATEZO: Atezolizumab; ICI: Immune checkpoint inhibitor; IPI: Ipilimumab; LC: Local control; MM: Malignant melanoma; Mo: Month; NIVO: Nivolumab; NR: Not reported; OS: overall survival; PEMBRO: Pembrolizumab; SRS: Stereotactic radiosurgery; WBRT: Whole-brain radiotherapy; yr: Year

TABLE 2 **Clinical trials of combination stereotactic radiosurgery and immune checkpoint inhibitors in NSCLC patients with brain metastasis**

Reference	Year	Patients (n)	Design	ICI	Primary	LC (%)	Median OS (Mo.)	1-yr OS (%)
Ahmed et al. (47)	2017	17	SRS + ICI	IPI	NSCLC	NR	5.6	51
Schapira et al. (48)	2018	29	Non-concurrent	NIVO or PEMBRO or	NSCLC	77	17.6	58
		8	Concurrent	ATEZO		100		87.3
Shepard et al. (49)	2019	17	SRS + ICI	NIVO or PEMBRO or	NSCLC	84.9	NR	55
		34	ICI alone	ATEZO		76.3	15.9	NR
Singh.C et al. (50)	2020	39	SRS + ICI	NIVO or PEMBRO or	NSCLC	NR	10.0	NR
		46	SRS + CT	NIVO/IPI or ATEZO			11.6	
Enright et al. (51)	2020	44	SRS alone	NIVO or PEMBRO or	NSCLC	86	13.9	64
		33	SRS + ICI	ATEZO		97		68
Lee et al. (52)	2021	27	Non-concurrent	NIVO or PEMBRO	NSCLC	NR	42.1	NR
		24	Concurrent				22.5	
		26	ICI alone				10.0	

ATEZO: Atezolizumab; ICI: Immune checkpoint inhibitor; IPI: Ipilimumab; LC: Local control; Mo: Month; NIVO: Nivolumab; NR: Not reported; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PEMBRO: Pembrolizumab; SRS: Stereotactic radiosurgery; yr: Year

TABLE 3 **Clinical trials of combination stereotactic radiosurgery and immune checkpoint inhibitors in MM, NSCLC, RCC and other patients with brain metastasis**

Reference	Year	Patients (n)	Design	ICI	Primary	LC (%)	Median OS (Mo)	1-yr OS(%)
Chen et al. (53)	2018	51 28 181	Non-concurrent Concurrent SRS alone	IPI or NIVO or PEMBRO	NSCLC, MM, RCC	79 88 82	14.5 24.7 12.9	58 77.9
Koenig, et al. (54)	2019	97	Non-concurrent Concurrent	IPI or NIVO or PEMBRO	NSCLC, MM, RCC, other	97 96	9.4	NR
Lanier et al. (55)	2019	170 101	SRS alone SRS + ICI	NIVO or PEMBRO or NIVO/IPI or IPI	NSCLC, MM, other	96 91	6.1 15.9	
Kowalski et al. (56)	2020	179	SRS alone SRS + ICI	IPI or NIVO or PEMBRO or ATEZO or DURVA	NSCLC, MM, RCC	89.5 98.0	NR	58 56
Travis et al. (57)	2020	74	SRS + ICI	IPI or NIVO or PEMBRO or DURVA	NSCLC, MM, RCC	90.3	NR	NR
Qian et al. (58)	2020	110	Non-concurrent Concurrent	IPI or PEMBRO and/or NIVO	NSCLC, MM	NR	14.2	NR
Trommer et al. (59)	2022	6 (WBRT) + 24 (SRS) 22 (WBRT) + 41 (SRS)	Non-concurrent Concurrent	NIVO or PEMBRO	NSCLC, MM, other	69.2 95.3	6.8 17.6	NR

ATEZO: Atezolizumab; DURVA: Durvalumab; ICI: Immune checkpoint inhibitor; IPI: Ipilimumab; LC: Local control; MM: Malignant melanoma; Mo: Month; NIVO: Nivolumab; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PEMBRO: Pembrolizumab; RCC: Renal cell carcinoma; SRS: Stereotactic radiosurgery; yr: Year

comparative retrospective report by Silk et al. (21). The findings demonstrated that the addition of IPI to SRS was linked to significantly longer median overall survival durations (4.0 versus 19.9 months). Kiess et al. (26) examined the efficacy and safety of single-fraction SRS in 46 MM patients with brain metastasis who had previously received IPI. A total of 113 brain metastases were managed with a median dose of 21 Gy and 4 cycles of IPI. SRS was administered to patients before, during, or after IPI. The order of SRS and IPI was found to be significantly related to overall survival outcomes ($P = 0.035$). SRS administration during or before IPI resulted in significantly better 1-year overall survival (65% vs. 56% vs. 40%, $P = 0.008$) and regional recurrence rates than SRS administration after IPI (69% vs. 64% vs. 92%, $P = 0.003$). Notably, the authors reported that SRS administration during IPI produced numerically superior but not statistically significant 1-year local control rates (100% vs. 87% vs. 89%; $P = 0.21$) compared to SRS administration before or after IPI. Qian et al. conducted a study to determine the effect of the type and timing of ICIs on the response of MM brain metastasis to SRS treatment (29). The results of 75 MM patients with 566 brain metastases who received SRS and ICIs were examined. The authors considered SRS and ICIs to be concurrent if SRS was administered within 4 weeks of ICIs. Concurrent treatment with significantly reduced brain metastasis volumes at 1.5 (–63.1% vs. –43.2%, $P < 0.0001$), 3 (–83.0% vs. 52.8%, $P < 0.0001$), and 6 months (–94.9% vs. 66.2%, $P < 0.0001$) when compared to non-concurrent treatment. The authors also noted that anti-PD-1 agents resulted in a greater median volume reduction than their anti-CTLA-4 counterparts. The prospective non-randomized phase 2 study, ELEKTRA, is a considerable investigation into the effects of combination therapies such as pre-ICIs-RT or pre-RT-ICIs on antitumor and peripheral T cell responses in MM patients with brain metastasis (46). Patients with brain metastasis received RT (WBRT or SRS depending on the number of brain metastasis) in two different sequences in combination with NIVOIPI (RT before or after ICIs). The comparison groups included patients who received either only chemotherapy (without brain metastasis) or combination chemotherapy (without IPI) and radiotherapy. The investigators of this study discovered that IPI-NIVO combination therapy resulted in a significant increase in activated CD4 and CD8 T cells in the RT-ICIs group. They also noted inhibition of the immunosuppressive effect and a decline in Treg activity in this group. Additionally, this group showed more evidence of the abscopal effect of radiotherapy. The final comment was that sequencing ICIs treatment after RT may improve immunological responses and clinical outcomes in patients with brain metastasis from MM, and RT before ICIs treatment also showed a better response rate and progression-free survival than the RT after ICIs regimens.

The SRS and ICIs combination protocols have also been tested at other tumor sites. Schapira et al. (48) conducted one such study, reviewing the medical records of NSCLC patients with brain metastasis who had previously been treated with PD-1 pathway inhibitors and SRS. A total of 37 patients received PD-1 pathway inhibitors (83.8% NIVO, 10.8% atezolizumab (ATEZO), and 5.4% PEMBRO) for 85 lesions, mostly with a single fraction dose of 18 Gy SRS. Concurrent SRS and PD-1 pathway inhibitors improved 1-year overall survival (87.3% vs. 70.0% vs. 0%; $P = 0.008$) and distant brain failure (DBF) rate (38.5% vs. 65.8% vs. 100%, $P = 0.042$) compared to SRS before or after PD-1 pathway inhibitor strategies.

Similarly, the 1-year local control rate in SRS concurrent with or after PD-1 pathway inhibitor treatment was significantly higher than the 72.3% observed in SRS prior to PD-1 pathway inhibitor treatment. Chen et al. examined the outcomes of 260 patients who received SRS for 623 brain metastases of NSCLC, MM, and RCC (53). One hundred eighty-one patients were treated with SRS alone, while 79 received SRS and ICIs (35% received concurrent SRS and ICIs). The SRS with concurrent ICIs group outperformed the SRS with non-concurrent ICIs, and SRS alone groups in terms of median OS [24.7 vs. 14.5 (P = 0.006) vs. 12.9 (P = 0.002) months]. The survival benefit provided by SRS and concurrent ICIs was without an increase in neurologic toxicity rates.

Although IPI is the most used ICI in combination with SRS, especially in brain metastasis originating from MMs, results of studies comparing the efficacy of IPI to other ICIs are scarce. Robin et al. (40) compared the outcomes of anti-CTLA4 alone (N = 25) versus anti-PD-1 alone or anti-PD-1 plus CTLA-4 combination (N = 13) delivered within 8 weeks before or after SRS in 38 patients with brain metastasis of MM. The authors reported that the anti-PD-1 alone or anti-PD-1 plus CTLA-4 combination groups surpassed the anti-CTLA4 alone group in terms of out-of-field brain progression (P = 0.049), extracranial progression (P = 0.015), and progression-free survival (P = 0.043). As a result, these findings provided preliminary evidence that ICIs other than IPI may have higher viability with SRS for brain metastases, either alone or in combination, than IPI plus SRS, which will be addressed in future trials.

While the current evidence, for the most part, supports the improved local control and overall survival rates with the concurrent administration of ICIs and SRS, this sequence is associated with higher rates of perilesional brain edema and radionecrosis (RN). According to Cohen-Inbar et al. (33), overall, the post-SRS perilesional edema was 26.3%, 27.9%, 21.8%, and 24.1% of lesions at 3, 6, 9, and 12 months. The authors noticed that the incidence of perilesional edema was significantly higher in the concurrent than the sequential treatment group at 3 months (31.3% versus 15.3%; P = 0.011) and 12 months (30.2% versus 0%; P = 0.048). However, the overall intralesional hemorrhage and 12 months RN rates were not different between the two groups, though both were higher in the concurrent treatment arm.

Because the SRS and ICIs studies are small retrospective observational cohort series involving various SRS schemes and ICIs, meta-analyses may be more effective for statistically evaluating the true value of this approach more powerfully. In the first meta-analysis, Lu et al. (60) compared the survival outcomes of brain metastasis patients receiving concurrent ICIs with SRS against the non-concurrent ICIs administered before or after SRS. A total of 8 retrospective observational cohort studies incorporating 408 patients were included. Concurrent ICIs with SRS conferred a significant 1-year overall survival benefit (P = 0.011) over the non-concurrent protocols. A subsequent meta-analysis published by Lehrer et al. included a total of 534 patients with 1,570 brain metastases who participated in 17 studies (61). The one-year overall survival rate was 13% higher in the concurrent SRS and ICIs group than in the non-concurrent treatment group (51.6% versus 64.6%); Q < 0.001). The local control rates at 1-year also trended to favor the SRS and ICIs group over its non-concurrent treatment counterpart (89.2% versus 67.8%; P = 0.09). Further this

meta-analysis provided the most reliable toxicity data on the RN incidence following various ICIs combined with SRS. The overall RN incidence was fortunately only 5.3%, suggesting a distinctive RN risk with different ICIs. The authors called attention to that the RN risk was more pronounced in patients treated with IPI than the PEMBRO or NIVO.

He et al. (62) evaluated more than 1,500 patients receiving ICIs and intracranial RT (SRS or WBRT) from 26 retrospective studies. Compared with intracranial RT alone, they found that combination therapy significantly improved overall survival in patients with brain metastases ($P < 0.001$). There was a significant difference in RN risk compared to RT alone ($P = 0.55$), whereas local brain failure (LBF) and DBF were not significantly improved with RT in combination with ICIs (12 months LBF: $P = 0.48$, DBF: $P = 0.90$). According to the authors, ICIs plus RT improved overall survival in patients with brain metastasis while having no discernible increase in treatment-related toxicity rates. Similarly, Gagliardi et al. found that there was a significant increase in overall survival and lesion response rates without an increase in RN frequency with the combination of SRS and immunotherapy (63). The researchers concluded that combining SRS and immunotherapy is safe and effective in achieving noticeable improvements in relevant clinical and radiological outcomes in patients with melanoma and NSCLC brain metastasis.

In another study, Badrigilan et al. examined 16 retrospective studies with a combined total of 1356 brain metastasis patients for their meta-analysis (64). They discovered that when compared to non-concurrent treatment, concomitant treatment resulted in a significantly longer overall survival ($P = 0.008$), 12 months of LBF ($P = 0.04$), and a similar DBF ($P = 0.547$). According to the authors, concurrent treatment had a significantly higher overall survival than ICIs before SRS ($P = 0.0003$). Finally, Chu et al. investigated the efficacy of immunotherapy by reviewing a total of 3160 NSCLC patients with brain metastasis from 46 studies (65). This meta-analysis is significant and noteworthy as it represents the first attempt to compare the effectiveness of immunotherapy, including ICIs, chemotherapy, RT, and ICIs combined with chemotherapy or RT. The authors found that patients treated with immunotherapy had a longer progression-free survival (Hazard ratio (HR):0.48,95% confidence interval (CI): 0.41–0.56) and overall survival (HR:0.64, 95%CI: 0.60–0.69) than patients who did not receive immunotherapy. Also in this study, it was shown that concurrent ICIs combined RT reduced the DBF rate (Odds ratio (OR) = 0.15, 95% CI: 0.03–0.73) compared to post-ICIs RT. Additionally, it was stated that single or dual ICIs in combination with RT were effective treatments for NSCLC patients with brain metastasis. Concurrent administration of SRS and ICIs led to better outcomes for patients in terms of response and survival than non-concurrent or non-SRS regimens.

Although the aforementioned studies offer crucial knowledge regarding the efficacy and side effects of combining SRS and ICIs, the outcomes of prospective studies will provide a much more trustworthy roadmap for clinicians in the field (Table 4).

TABLE 4 **Completed or ongoing clinical trials whose results are awaited**

Study	Phase	Primer Tumor	ICI Target/Drug	Arms
NCT01703507	1	MM	CTLA-4/ IPI	WBRT vs. SRS
NCT01950195	1	MM	CTLA-4/ IPI	NR
NCT02107755	2	MM	CTLA-4/ IPI	NR
NCT02696993	1/2	NSCLC	CTLA-4/ IPI and PD-1/NIVO	WBRT vs. SRS
NCT02716948	1	MM	PD-1/ NIVO	NR
NCT02858869	1	NSCLC, MM	PD-1/PEMBRO	(30 Gy in 5 F) vs. (27 Gy in 3 F) vs. (18–21 Gy in 1 F)
NCT02886585	2	MM	PD-1/PEMBRO	NR
NCT02978404	2	NSCLC, RCC	PD-1/NIVO	NR
NCT03340129	2	MM	CTLA-4/ IPI and PD-1/NIVO	(16–22 Gy in 1 F) or (24–30 Gy in 3–5 F)
NCT03807765	1	Breast	PD-1/NIVO	NR
NCT04427228 (MIGRAINE)	2	NSCLC, MM, other	NR	(27 Gy in 3 F) vs. (18–20 Gy in 1 F)
NCT04650490 (STICK-IM)	2	NSCLC	NR	NR

CTLA-4:Cytotoxic T-lymphocyte-associated antigen 4; F: Fraction; Gy: Gray; IPI: Ipilimumab; MM: Malignant melanoma; NIVO: Nivolumab; NR: Not reported; NSCLC: Non-small-cell lung cancer; PD-1: programmed cell death protein 1 ; PEMBRO: Pembrolizumab; RCC: Renal cell carcinoma

CONCLUSION

The local and systemic immune responses induced by SRS can be strengthened when combined with ICIs. Such a plan might improve the effectiveness of both therapeutic modalities, which might benefit outcomes in patients with brain metastasis. Both preclinical and clinical studies substantiate this assertion. The mechanisms by which the SRS schedule and ICIs agents collaborate to provide antitumor effects, on the other hand, may overlap and increase the toxicity profiles of both modalities. Although the majority of the evidence comes from single-institutional retrospective cohort studies, the results show that the SRS and ICIs combination is more effective than either modality alone, at the cost of modest increases in severe toxicity rates. Finally, there is no doubt that ongoing research on the optimal dosage, fractionation, and timing of SRS with various ICIs and dosages will provide unique insights for maximizing benefits while minimizing toxicity risk.

Conflict of Interest: The author declares no potential of interest with respect to the research, authorship, and/or publication of this chapter.

Copyright and Permission Statement: The authors confirm that the materials included in this chapter do not violate copyright laws. Where relevant, appropriate permissions have been obtained from the original copyright holder(s), and all original sources have been appropriately acknowledged or referenced. Where relevant, informed consent has been obtained from patients or their caregivers as per applicable national or institutional policies.

REFERENCES

1. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. Neuro Oncol. 2015;17(Suppl 4):1–62. https://doi.org/10.1093/neuonc/nov189
2. Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, Butowski N, et al. NCCN practice guidelines in oncology-Central nervous system cancers, version 1.2017. J. Natl. Compr. Canc. Netw. 2017;15: 9–20. https://doi.org/10.6004/jnccn.2017.0166
3. Nayak L, Lee EQ, Wen PY. Epidemiology of Brain Metastases. Curr Oncol Rep 2012;14:48–54. https://doi.org/10.1007/s11912-011-0203-y
4. Soffietti R, Abacioglu U, Baumert B, Neuro SC. Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the European Association of Neuro-Oncology (EANO). Neuro-Oncology. 2017;19:162–174. https://doi.org/10.1093/neuonc/now241
5. Billing PS, Miller DL, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Surgical treatment of primary lung cancer with synchronous brain metastases. J Thorac Cardiovasc Surg. 2001;122(3):548–553. https://doi.org/10.1067/mtc.2001.116201
6. Rusthoven CG,Camidge DR, Robin TP, Brown PD. Radiosurgery for small-cell brain metastases: challenging the last bastion of preferential whole-brain radiotherapy delivery. J Clin Oncol. 2020; 38:3587–359. https://doi.org/10.1200/JCO.20.01823
7. Ashrafizadeh M, Farhood B, Eleojo Musa A, Taeb S, Rezaeyan A, Najafi M. Abscopal effect in radio immunotherapy. Int. Immunopharmacol. 2020;85:106663. https://doi.org/10.1016/j.intimp.2020.106663
8. Brown PD, Jaeckle K, Ballman KV. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA. 2016 Jul 26;316(4):401–409. https://doi.org/10.1001/jama.2016.9839
9. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu. Rev. Immunol. 2005;23: 515–548. https://doi.org/10.1146/annurev.immunol.23.021704.115611
10. Zou W, Chen L. Inhibitory B7 family molecules in the tumour microenvironment. Nature Rev. Immunol.2008;8:467–477. https://doi.org/10.1038/nri2326
11. Chow MT, Moller A, Smyth MJ. Inflammation and immune surveillance in cancer. Semin Cancer Biol. 2012;22:23–32. https://doi.org/10.1016/j.semcancer.2011.12.004
12. Zeng J, Harris TJ, Lim M, Drake CG, Tran PT. Immune modulation and stereotactic radiation: improving local and abscopal responses. Biomed Res Int. 2013;2013:658126. https://doi.org/10.1155/2013/658126
13. Tang C, Wang X, Soh H, Seyedin S, Cortez MA, Krishnan S, et al. Combining radiation and immunotherapy:a new systemic therapy for solid tumors? Cancer Immunol Res. 2014;2(9):831–838. https://doi.org/10.1158/2326-6066.CIR-14-0069
14. Salama AK, Postow MA, Salama JK. Irradiation and immunotherapy: From concept to the clinic. Cancer. 2016;122:16591671. https://doi.org/10.1002/cncr.29889
15. Shahabi V, Postow MA, Tuck D, Wolchok JD. Immune priming of the tumor microenvironment by radiotherapy: rationale for combination with immunotherapy to improve anticancer efficacy. Am J Clin Oncol. 2015;38:90–97. https://doi.org/10.1097/COC.0b013e3182868ec8

16. Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. Int J Radiat Oncol Biol Phys. 2012;83(4):1306–1310. https://doi.org/10.1016/j.ijrobp.2011.09.049
17. Eljalby M, Pannullo SC, Schwartz TH, Parashar B, Wernicke GA. Optimal timing and sequence of ımmunotherapy when combined with stereotactic radiosurgery in the treatment of brain metastases. World Neurosurgery. 2019;127:397–404. https://doi.org/10.1016/j.wneu.2019.04.093
18. Young KH, Baird JR, Savage T, Cottam B, Friedman D, Bambina S, et al. Optimizing timing of ımmunotherapyımproves control of tumors by hypofractionated radiation therapy. PLoS One. 2016;11(6):e0157164. https://doi.org/10.1371/journal.pone.0157164
19. Trapani S, Manicone M, Sikokis A, D'Abbiero N, Salaroli F, Ceccon G,et al. Effectiveness and safety of "real" concurrent stereotactic radiotherapy and immunotherapy in metastatic solid tumors: a systematic review. Crit. Rev. Oncol. Hematol. 2019;142:9–15. https://doi.org/10.1016/j.critrevonc.2019.07.006
20. Knisely JP, Yu JB, Flanigan J. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. J Neurosurg. 2012;117(2):227–233. https://doi.org/10.3171/2012.5.JNS111929
21. Silk AW, Bassetti MF, West BT, Tsien CI, Lao CD. Ipilimumab and radiation therapy for melanoma brain metastases. Cancer Med. 2013;2:899–906. https://doi.org/10.1002/cam4.140
22. Kaidar-Person O, Zagar TM, Deal A, Moschos SJ, Ewend MG, Sasaki-Adamset D, al. The incidence of radiation necrosis following stereotactic radiotherapy for melanoma brain metastases: The potential impact of immunotherapy. Anticancer Drugs 2017, 28, 669–675. https://doi.org/10.1097/CAD.0000000000000497
23. Diao K, Bian SX, Routman DM, Yu C, Ye JC, Wagleet NA al. Stereotactic radiosurgery and ipilimumab for patients with melanoma brain metastases: clinical outcomes and toxicity. J. Neurooncol. 2018;139(2):421–429. https://doi.org/10.1007/s11060-018-2880-y
24. Trommer-Nestler M, Marnitz S, Kocher M, Rueß D, Schlaak M, Theurich S, et al. Robotic stereotactic radiosurgery in melanoma patients with brain metastases under simultaneous anti-PD-1 treatment. Int. J. Mol. Sci. 2018; 19: 2653. https://doi.org/10.3390/ijms19092653
25. Mathew M, Tam M, Ott PA, Pavlick AC, Rush SC, Donahue BR, et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. Melanoma Res. 2013;23(3):191–195. https://doi.org/10.1097/CMR.0b013e32835f3d90
26. Kiess AP, Wolchok JD, Barker CA, Postow MA, Tabar V, Huse JT et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys. 2015;92(2):68–75. https://doi.org/10.1016/j.ijrobp.2015.01.004
27. Tazi K, Hathaway A, Chiuzan C, Shirai K. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. Cancer Med. 2015;4(1):1–6. https://doi.org/10.1002/cam4.315
28. Schoenfeld JD, Mahadevan A, Floyd SR, Dyer MA, Catalano PJ, Alexander BM, et al. Ipilimumab and cranial radiation in metastatic melanoma patients: a case series and review. J Immunother Cancer. 2015;3:50. https://doi.org/10.1186/s40425-015-0095-8
29. Qian JM, Yu JB, Kluger HM, Chiang VL. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. Cancer. 2016;122:3051–3058. https://doi.org/10.1002/cncr.30138
30. Ahmed KA, Stallworth DG, Kim Y, Johnstone PAS, Harrison LB, Caudell JJ, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. Ann Oncol. 2016;27:434–441. https://doi.org/10.1093/annonc/mdv622
31. Choong ES, Lo S, Drummond M, Fogarty GB, Menzies AM, Guminski A, et al. Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies. Eur. J Cancer. 2017;75:169–178. https://doi.org/10.1016/j.ejca.2017.01.007
32. Patel KR, Shoukat S, Oliver DE, Chowdhary M, Rizzo M, Lawson DH, et al. Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. Am J Clin Oncol. 2017;40:444–450. https://doi.org/10.1097/COC.0000000000000199
33. Cohen-Inbar O, Shih HH, Xu Z, Schlesinger D, Sheehan JP. The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab. J Neurosurg. 2017;127:1007–1014. https://doi.org/10.3171/2016.9.JNS161585

34. Skrepnik T, Sundararajan S, Cui H, Stea B. Improved time to disease progression in the brain in patients with melanoma brain metastases treated with concurrent delivery of radiosurgery and ipilimumab. Oncoimmunology. 2017;6(3):e1283461. https://doi.org/10.1080/2162402X.2017.1283461
35. Yusuf MB, Amsbaugh MJ, Burton E, Chesney J, Woo S. Peri-SRS administration of immune checkpoint therapy for melanoma metastatic to the brain: investigating efficacy and the effects of relative treatment timing on lesion response. World Neurosurg. 2017;100:632–640. https://doi.org/10.1016/j.wneu.2017.01.101
36. Williams NL, Wuthrick EJ, Kim H, Palmer JD, Garg S, Eldredge-Hindy H, et al. Phase 1 study of ipilimumab combined with whole brain radiation therapy or radiosurgery for melanoma patients with brain metastases. Int. J. Radiat. Oncol. Biol. Phys.2017;99:22–30. https://doi.org/10.1016/j.ijrobp.2017.05.028
37. Anderson ES, Postow MA, Wolchok JD, Young RJ, Ballangrud A, Chan TA, et al. Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment. J Immunother Cancer. 2017;5:76. https://doi.org/10.1186/s40425-017-0282-x
38. Rahman R, Cortes A, Niemierko A, Oh KS, Flaherty KT, Lawrence DP, et al The impact of timing of immunotherapy with cranial irradiation in melanoma patients with brain metastases: intracranial progression, survival and toxicity. J Neurooncol. 2018;138(2):299–306. https://doi.org/10.1007/s11060-018-2795-7
39. Nardin C, Mateus C, Texier M, Lanoy E, Hibat-Allah S, Ammari S. Tolerance and outcomes of stereotactic radiosurgery combined with anti-programed cell death-1 (pembrolizumab) for melanoma brain metastases. Melanoma Res. 2018;28:111–119. https://doi.org/10.1097/CMR.0000000000000413
40. Robin TP, Breeze RE, Smith DE, Rusthoven CG, Lewis KD, Gonzalez R, et al. Immune checkpoint inhibitors and radiosurgery for newly diagnosed melanoma brain metastases. J. Neurooncol. 2018;140:55–62. https://doi.org/10.1007/s11060-018-2930-5
41. Minniti G, Anzellini D, Reverberi C, Cappellini GCA, Marchetti L, Bianciardi F, et al. Stereotactic radiosurgery combined with nivolumab or Ipilimumab for patients with melanoma brain metastases: evaluation of brain control and toxicity. J. Immunotherapy Cancer. 2019;7:102. https://doi.org/10.1186/s40425-019-0588-y
42. Murphy B, Walker J, Bassale S, Monaco D, Jaboin J, Ciporen J, et al. Concurrent radiosurgery and immune checkpoint inhibition: improving regional intracranial control for patients with metastatic melanoma. Am J Clin Oncol. 2019;42(3):253–257. https://doi.org/10.1097/COC.0000000000000509
43. Galli G, Cavalieri S, Di Guardo L, Cimminiello C, Nichetti F, Corti F, et al. Combination of ımmunotherapy and brain radiotherapy in metastatic melanoma: A retrospective analysis. Oncol Res Treat. 2019;42:182–188. https://doi.org/10.1159/000497211
44. Carron R, Gaudy-Marqueste C, Amatore F, Padovani L, Malissen N, Balossier A, et al. Stereotactic radiosurgery combined with anti-PD1 for the management of melanoma brain metastases: A retrospective study of safety and efficacy. Eur. J. Cancer. 2020;135:52–61. https://doi.org/10.1016/j.ejca.2020.04.028
45. Le Rhun E, Wolpert F, Fialek M, Devos P, Andratschke N, Reyns N, et al. Response assessment and outcome of combining immunotherapy and radiosurgery for brain metastasis from malignant melanoma. ESMO Open. 2020;5(4):e000763. https://doi.org/10.1136/esmoopen-2020-000763
46. Hassel JC, SchankTE, Smetak H, Mühlbauer J, Salzmann M, Machiraju D, et al. Evaluation of radio-immunotherapy sequence on immunological responses and clinical outcomes in patients with melanoma brain metastases (ELEKTRA). Oncoimmunology. 2022;11(1):2066609. https://doi.org/10.1080/2162402X.2022.2066609
47. Ahmed KA, Kim S, Arrington J, Naghavi AO, Dilling TJ, Ben C. Creelan BC, et al. Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases. J Neurooncol. 2017;133:331–338. https://doi.org/10.1007/s11060-017-2437-5
48. Schapira E, Hubbeling H, Yeap BY, Mehan WA Jr., Shaw AT, Oh K, et al. Improved overall survival and locoregional disease control with concurrent PD-1 pathway ınhibitors and stereotactic radiosurgery for lung cancer patients with brain metastases. Int J Radiat Oncol Biol Phys. 2018;101(3):624–629. https://doi.org/10.1016/j.ijrobp.2018.02.175

49. Shepard MJ, Xu Z, Donahue J, Muttikkal TE, Codeiro D, Hansen L, et al. Stereotactic radiosurgery with and without checkpoint inhibition for patients with metastatic non-small cell lung cancer to the brain: a matched cohort study. J Neurosurg. 2019;132(2):1–8. https://doi.org/10.1093/neuros/nyz310_217
50. Singh C, Qian JM, Yu JB, Chiang VL. Local tumor response and survival outcomes after combined stereotactic radiosurgery and immunotherapy in non-small cell lung cancer with brain metastases. J Neurosurg. 2019;132(2):512–517. https://doi.org/10.3171/2018.10.JNS181371
51. Enright TL, Witt JS, Burr AR, Yadav P, Leal T, Baschnagel AM. Combined ımmunotherapy and stereotactic radiotherapy ımproves neurologic outcomes in patients with non-small-cell lung cancer brain metastases. Clin Lung Cancer. 2021;22(2):110–119. https://doi.org/10.1016/j.cllc.2020.10.014
52. Lee MH, Cho KR, Choi JW, Kong D-S, Seol HJ, Nam D-H, et al. Immune checkpoint inhibitors for non-small-cell lung cancer with brain metastasis: The role of gamma knife radiosurgery. J Korean Neurosurg Soc. 2021;64(2):271–281. https://doi.org/10.3340/jkns.2020.0135
53. Chen L, Douglass J, Kleinberg L, Ye X, Marciscano AE, Forde PM, et al. Concurrent Immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. Int J Radiat Oncol Biol Phys. 2018;100(4):916–925. https://doi.org/10.1016/j.ijrobp.2017.11.041
54. Koenig JL, Shi S, Sborov K, Gensheimer MF, Li G, Nagpal S, et al. Adverse radiation effect and disease control in patients undergoing stereotactic radiosurgery and ımmune checkpoint ınhibitor therapy for brain metastases. World Neurosurg. 2019;126:e1399-e1411. https://doi.org/10.1016/j.wneu.2019.03.110
55. Lanier CM, Hughes R, Ahmed T, LeCompte M, Masters AH, Petty WJ, et al. Immunotherapy is associated with improved survival and decreased neurologic death after SRS for brain metastases from lung and melanoma primaries. NeurooncolPract. 2019;6(5):402–409. https://doi.org/10.1093/nop/npz004
56. Kowalski ES, Remick JS, Sun K, Alexander GS, Khairnar R, Morse E, et al. Immune checkpoint inhibition in patients treated with stereotactic radiation for brain metastases. Radiat Oncol. 2020;15(1):245. https://doi.org/10.1186/s13014-020-01644-x
57. Travis RL, Marcrom SR, Brown MH, Patel MP, Markert JM, Riley KO, et al. Control and toxicity in melanoma versus other brain metastases in response to combined radiosurgery and pd-(l)1 immune checkpoint inhibition. Adv Radiat Oncol. 2020;6(1):100561. https://doi.org/10.1016/j.adro.2020.08.017
58. Qian JM, Martin AM, Martin K, Hammoudeh L, Catalano PJ, Hodi FS, et al. Response rate and local recurrence after concurrent immune checkpoint therapy and radiotherapy for non-small cell lung cancer and melanoma brain metastases. Cancer. 2020;126(24):5274–5282. https://doi.org/10.1002/cncr.33196
59. Trommer M, Adams A, Celik E, Fan J, Funken D, Herter JM, et al. Oncologic outcome and immune responses of radiotherapy with anti-pd-1treatment for brain metastases regarding timing and benefiting subgroups. Cancers. 2022;14(5):1240. https://doi.org/10.3390/cancers14051240
60. Lu VM, Goyal A, Rovin RA, Lee A, McDonald KL, et al. Concurrent versus non-concurrent immune checkpoint inhibition with stereotactic radiosurgery for metastatic brain disease: a systematic review and meta-analysis. J. Neurooncol. 2019;141(1):1–12. https://doi.org/10.1007/s11060-018-03020-y
61. Lehrer EJ, Peterson J, Brown PD, Sheehan JP, Quiñones-Hinojosa A, Zaorsky NG, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. Radiother Oncol. 2019;130:104–112. https://doi.org/10.1016/j.radonc.2018.08.025
62. He Q, Zhang C, Tang S, Li J, Ren Q. Intracranial radiotherapy with or without immune checkpoint inhibition for brain metastases: a systematic review and meta-analysis. Transl Cancer Res. 2020;9(10):5909–5924. https://doi.org/10.21037/tcr-20-902
63. Gagliardi F, De Domenico P, Snider S, Francesca R, Pompeoa E, Barzaghia LR, et al. Role of stereotactic radiosurgery for the treatment of brain metastasis in the era of immunotherapy: A systematic review on current evidences and predicting factors. Crit Rev Oncol Hematol. 2021;165:103431. https://doi.org/10.1016/j.critrevonc.2021.103431

64. Badrigilan S, Meola A, Chang SD, Rezaeian S, Nemati H, Almasi T, et al. Stereotactic radiosurgery with immune checkpoint inhibitors for brain metastases: a meta-analysis study. Br J Neurosurg. 2022; 1–11. https://doi.org/10.1080/02688697.2021.2022098
65. Chu X, Niu L, Xiao G, Peng H, Deng F, Liu Z, et al. The long-term and short-term efficacy of ımmunotherapy in non-small cell lung cancer patients with brain metastases: A systematic review and meta-analysis. Front Immunol. 2022;13:875488. https://doi.org/10.3389/fimmu.2022.875488