Integration of stereotactic radiosurgery or whole brain radiation therapy with immunotherapy for treatment of brain metastases

Zhou Su¹², Lin Zhou¹, Jianxin Xue¹, You Lu¹

¹Department of Thoracic Oncology, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China; ²Department of Oncology, Sichuan Mianyang 404 Hospital, Mianyang 621000, China

Correspondence to: Jianxin Xue. Department of Thoracic Oncology, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China. Email: radjianxin163.com; You Lu. Department of Thoracic Oncology, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China. Email: radyoulu@hotmail.com.

Abstract

The prognosis of brain metastases (BM) is traditionally poor. BM are mainly treated by local radiotherapy, including stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT). Recently, immunotherapy (i.e., immune checkpoint inhibitors, ICI) has demonstrated a survival advantage in multiple malignancies commonly associated with BM. Individually, radiotherapy and ICI both treat BM efficiently; hence, their combination seems logical. In this review, we summarize the existing preclinical and clinical evidence that supports the applicability of radiotherapy as a sensitizer of ICI for BM. Further, we discuss the optimal timing at which radiotherapy and ICI should be administered and review the safety of the combination therapy. Data from a few clinical studies suggest that combining SRS or WBRT with ICI simultaneously rather than consecutively potentially enhances brain abscopal-like responses and survival. However, there is a lack of conclusion about the definition of “simultaneous”; the cumulative toxic effect of the combined therapies also requires further study. Thus, ongoing and planned prospective trials are needed to further explore and validate the effect, safety, and optimal timing of the combination of immunotherapy with radiotherapy for patients with BM.

Keywords: Immunotherapy; radiotherapy; immune checkpoint inhibitors; brain metastases; review

Submitted Jun 05, 2020. Accepted for publication Aug 19, 2020.

doi: 10.21147/j.issn.1000-9604.2020.04.03

View this article at: https://doi.org/10.21147/j.issn.1000-9604.2020.04.03

Introduction

As a medical challenge affecting approximately 1 in 5 adult patients with systemic tumors, brain metastases (BM) have their highest incidence in breast cancer, melanoma, and lung cancer (1-3). To date, BM are typically treated by the combination of radiotherapy (RT), chemotherapy, and surgical resection (4). The outcomes and prognosis in patients have remained poor despite contemporary progress in BM treatment (5).

Immunotherapy has been very useful in many cancer types. Findings of clinical studies, such as the EORTC 18071 (6), KEYNOTE-001 (7), and CheckMate 057 (8), have proven that immune checkpoint inhibitors (ICIs) based on programmed cell death protein 1 (PD-1) (such as pembrolizumab or nivolumab) or ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can improve patient survival. However, the above clinical trials have routinely excluded patients with active or untreated BM. In most instances, BM management requires supportive approaches, such as corticosteroids, to relieve intracranial pressure (9). Therefore, evidence regarding the use of ICIs in treating patients with BM is limited, and many questions remain unresolved. In some clinical studies, findings have suggested that ICIs are effective in enhancing the OS of patients with BM (10,11). However, the results have not been confirmed by a large prospective phase III clinical study.
Immunotherapy is known to provide lasting results for the responders. However, only about one-third of patients are responsive. Therefore, strategies to increase the response rate are being investigated (5). RT is an effective therapy for BM. The immune system’s interaction with irradiation has been characterized (12-14). Enhanced susceptibility of BM to immunotherapy following their increased immunogenicity caused by RT has been increasingly demonstrated by consecutive studies (15,16). These findings have attracted much attention, and many preclinical and clinical studies are underway.

In this review, we summarize the existing clinical and preclinical research findings supporting RT as an immunotherapy sensitizer for BM. Further, we discussed the optimal scheduling of immunotherapy and RT administration with respect to each therapy, and appraised the safety of combination therapy. The scope of current review is mainly focused on combination of immunotherapy and RT for BM in solid tumor including melanoma, renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC).

**Evidence of immunotherapy for patients with BM**

ICIs have gained revolutionary progress in anti-cancer therapy (17). Ipilimumab is the first ICI to be granted Food and Drug Administration (FDA) approval in 2011. Not long after, nivolumab and pembrolizumab were also approved (18).

As an organ once considered to be shielded from broad bodily immune surveillance, the brain was believed to be immune-privileged (18-21). A lack of lymphatic vessels directing antigen presenting cells (APC) to lymph nodes combined with the presence of the blood-cerebrospinal fluid barrier (BCB) or blood-brain-barrier (BBB) (4) may have contributed to this view. However, independent groups have published evidence showing that the brain and indeed the central nervous system (CNS) are accessible to the rest of the immune system, thus contradicting prevailing opinion on the brain’s immune privilege. The CNS was demonstrated to have a resident lymphatic system in 2015, which sequesters CNS antigens from the cerebrospinal fluid (22). Additionally, in brain tumors, increased permeability of BBB, associated with the expression of vascular endothelial growth factor (VEGF), and clinically deformed microvessels were observed. Activated circulating CD4+ T cells have been shown to cross the BBB, inducing local T cell activation (23). Furthermore, the CNS has the capacity to play important immunological roles, such as cytotoxicity through abundant resident microglial cells that are responsible for mediating innate immune functions within the CNS (22). These findings demonstrate that ICIs, which are the immune targets for tumor cell escape, can activate T-cells trafficking across BBB to play a role in BM, as shown in several preclinical studies (24,25).

Multiple case series and retrospective studies have investigated patients prescribed ICIs for BM (26). Among them, the largest study was conducted by Iorgulescu et al. They conducted analysis on data, from the National Cancer Database, of 220,439 patients diagnosed with melanoma from 2010 to 2015, and found that in comparison to OS of 5.2 months for patients not treated with ICIs, immunotherapy lengthened OS to 12.4 months (10). In contrast, the number of prospective clinical trials in this field is small. CheckMate-017 (NCT01642004), CheckMate-057 (NCT01673867), Keynote-189 (NCT02578680), and OAK (NCT02008227) were the original reports on large prospective ICI trials investigating immunotherapy for BM that included patients with asymptomatic BM (27,28).

Margolin et al. undertook a phase II trial, which was among the earliest published trials focused on investigating BM treatment with immunotherapy (29). In that trial, ipilimumab’s effects on BM and melanoma patients were investigated (NCT00623766). Patients with both asymptomatic and symptomatic BM were included in the study. The symptomatic and asymptomatic group disease control rates were 5% (1/11) and 18% (9/51), respectively.

NCT02085070 is a phase II study to evaluate the efficacy of pembrolizumab in BM of both NSCLC and melanoma (30). Interim study data analysis revealed that 22% (4 out of 18) and 33% (6 out of 18) of melanoma and NSCLC patients, respectively, achieved a BM response (30). The final results and long-term follow-up for the full melanoma cohort in this study were reported in 2019 (31). Overall, 26% of patients had a BM response, and the respective median OS and progression-free survival durations were 17 and 2 months, respectively. Two-year survival was similar to that in patients treated with anti-PD-1 agents, but without BM, suggesting that melanoma BMs could be treated using pembrolizumab with acceptable toxicity and durable responses. A recently published study from the Yale Cancer Center has revealed that pembrolizumab was effective in BM from NSCLC with PD-L1 expression at...
least 1%, indicating that PD-L1 expression is an important factor for ICI treatment (32).

A combination of two ICIs for BM has also been reported in some phase I/II clinical trials. CheckMate-204 (NCT02320058) is a phase II study, which combined nivolumab and ipilimumab to treat melanoma patients with non-irradiated BM (33). The results showed that the combined treatment had clinically meaningful intracranial efficacy, with a clinical benefit rate of 57%, concordant with extracranial activity. A similar result was found in a phase II study in Australia (NCT02374242) (34). This study, combining ipilimumab and nivolumab, is one of the patient cohorts with asymptomatic untreated BM, that achieved 46% of brain response rate.

The trials mentioned above were all early clinical studies with small sample sizes. Therefore, confirmation of these initial findings will require comprehensive studies with more patients. On the other hand, treatment with ICIs combined with other therapies has been attempted for BM. RT [stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT)], has attracted much attention for possible combination with immunotherapy to increase intracranial responses. This combination approach has been examined in multiple studies (35,36).

**Role of SRS and WBRT in BM**

Standard RT for nonresectable BM patients is currently SRS, as clinical practice progressed from historical use of WBRT as gold standard. By convention, only patients with good performance status (PS) or few BM are given SRS, while those with bad prognosis, poor PS or numerous BM are assigned WBRT (37).

Most commonly, WBRT is given in 10 fractions during a 2-week period, to doses totaling 30 Gy (38). WBRT has been shown to increase OS to 3–7 months, up from 1 month in the absence of therapy with 64%–83% of patients reporting symptom improvements following single-agent treatment with WBRT (39,40). However, neurocognition and quality of life can be harmed by WBRT. As shown in a randomized controlled trial (C000000412), WBRT can reduce neurocognitive capacity in as many as 49% of cases (41). Brown et al. also generated concordant results from their phase III trial (NCCTG N0574) (42).

Highly efficient selectivity in targeting large doses to tumor tissues while avoiding normal surrounding brain cells makes SRS an advantageous RT method (43). SRS, usually provided in a single session, is commonly used to treat tiny intracranial lesions in a discreet, productive and reliable manner. Nevertheless, it may be challenging to achieve an optimal tumor control equilibrium for broad lesions or those in near proximity to vital tissues, thus minimizing disruption to normal tissues by utilizing single-fraction SRS. Treatment of a lesion in 2–5 fractions of SRS (known as “hypofractionated SRS”) may have the opportunity to treat a lesion with a total radiation dose that provides sufficient tumor control and appropriate toxicity as well (44). WBRT doses ≥30 Gy are invariably associated with improved intracranial tumor control and survival in BM patients (45). The Japan Clinical Oncology Group carried out a randomized phase III trial and their results suggested that the efficacy of SRS is noninferior to that of WBRT, for the treatment of patients with 1–4 BM (46). Moreover, SRS has fewer neurocognitive side effects compared with WBRT; thus, SRS has been increasingly used for treating BM (47). The study conducted by Chang et al. (NCT00548756) assessed 58 patients who were assigned to either SRS + WBRT or SRS alone to treat 1–3 recently discovered BM (48). While 20% of patients who received SRS suffered cognitive decline after 4 months, but the proportion was 64% in patients treated with WBRT + SRS. The OS after one year in the SRS group was 63% compared to 21% for combination therapy (48). Brown et al. randomized 213 patients to be given either WBRT + SRS or SRS alone to treat 1–3 BM in a multi-center phase III trial published (NCT00377156) (49). Three months following treatment, the results from this study showed less decline in cognition with SRS alone than when combined with WBRT; despite this, a survival advantage could not be proven, and local control was similar in both groups. From the study results, prescribing SRS alone may therefore be an optimal therapeutic regimen for patients designated to receive radiosurgery while having 1–3 BM (49).

**Potential mechanisms of synergy between RT and ICIs**

Over the past 10–15 years, multiple studies have shown the association between tumor control using RT and the immune system (3,50). Moreover, irradiation at one location leading to metastatic cancer regression at a separate, remote site, which is referred to as an “abscopal effect”, is further proof of the contribution of RT to tumor control (18,51).

The following various candidate mechanisms have been postulated to explain RT effects on the immune system...
(Figure 1). Firstly, tumor-associated antigens (TAAs), which are released upon RT-mediated tumor cell death (52-55), could activate APCs and then prime cytotoxic T cells to kill cells in remote locations (56,57). RT has also been shown to stimulate tumor cell major histocompatibility complex (MHC) I expression (58). Secondly, RT is a potent inducer of immunogenic cell death (ICD) as it stimulates all three arms of ICD (52). ICD is typified by the migration of calreticulin (CRT) to the cell surface, release of adenosine triphosphate (ATP) and secretion of high motility group box 1 (HMGB1) protein out of the cell (53). The induction of ICD is linked to the exposure of damage-associated molecular patterns (DAMP), which induces the recruitment and affects the functions of immune cells (4). Moreover, DNA damage caused by RT can increase mutational burden (59), which may be transcribed into new antigens detected by the immune system (60). The stimulator of interferon genes (STING) is activated by DNA leaking into the cytosol following DNA damage induced by RT, which incidentally also leads to adaptive and innate immune response activation (61). Finally, RT has been reported to change the tumor environment and induce cancer cell secretion of proinflammatory chemotactic factors (such as interferons,
tumor necrosis factor α, and interleukin 1) with strong immunostimulatory effects (62,63). These factors facilitate dendritic cell maturation, increase T-cell infiltration (64-67), and even increase tumor cell PD-L1 expression (68), thus enhancing anti-PD-L1 antibody effects on tumors (69).

Under physiological conditions the presence of BCB and BBB blocks the entry of various immune cells along with macromolecule exchange across the brain parenchyma (70). Furthermore, brain tumor microenvironments are characterized by a small proportion of CD8+ effector T cells and abundant myeloid cells (4). Due to these facts, brain tumors show higher systemic tolerance than tumors at extracranial sites (71). Importantly, systemic tolerance was shown to potentially be reversed by RT. RT can stimulate immune cell migration into brain tumors (72) to generate tumor-specific cytotoxic T lymphocytes (73-75). Like the effect of RT on extracranial tumors, RT impacts cytokine secretion which attracts various immune cells, such as macrophages and dendritic cells for brain tumors. Furthermore, RT can modify important effector functions, including cytotoxicity, antigen presentation and phagocytosis, thus altering immune cell activation states which contributes to the triggering of immune responses stimulated by RT (4). Since competent T cells are crucial for effective immunotherapy, the role of RT in activating immune cells gives an opinion that immunotherapy can be sensitized by RT, thereby enabling it to treat BM.

This opinion has been backed by evidence from many preclinical trials. Smilowitz et al. developed an intracerebral B16 mouse model and observed that mice treated with RT alone had a shorter median survival period than those treated with immunotherapy combined with RT (76). Xia et al. investigated the impact of integrating RT with anti-PD-1 therapy on mouse models against metastatic osteosarcoma in the brain. They proposed that combining anti-PD-1 immunotherapy with RT could boost remote as well as local control through induction of abscopal responses, with the benefit of combination therapy being greater than anti-PD-1 alone (77). A similar finding was observed in the study conducted by Pfannenstiel et al. (78).

Clinical evidence of combined RT and immunotherapy to treat BM

Numerous clinical trials have explored approaches to incorporate immunotherapy with SRS or WBRT to improve BM response. Table 1 presents 28 studies conducted in the context of BM on the combination of RT and ICI. Of these, 26 reports involved melanoma patients (35,36,79-101), 4 enrolled NSCLC patients (89,102-104), and 1 enrolled RCC patient (89). Nearly all the 28 studies were retrospective, except for one prospective study (35).

Ipilimumab was the most commonly used ICI in these trials and SRS was the most frequently used approach of RT. A total of 23 out of 28 studies have assessed a mixture of ipilimumab with SRS. Initial retrospective evidence included data emerging from a study published in 2015 by Kiess et al. This study evaluated the results of 46 patients treated with SRS and ipilimumab for BM. The report indicated that simultaneous therapy with SRS and ipilimumab correlated with better locoregionally regulation and longer survival (1-year OS 40%−65%; 1-year regional recurrence 64%−92%), and the combination appeared to be well tolerated (91). Cohen-Inbar et al. performed a related study that involved 46 patients treated with SRS and ipilimumab. The findings suggest enhanced response when prescribing ipilimumab at the same time as SRS (93). Ninety-nine metastatic melanoma patients treated with ipilimumab who were then prescribed SRS for emergent BM were retrospectively reviewed by An et al. In the patient cohort that received SRS for new BM within 5.5 months of ipilimumab treatment (83), increased intracranial regulation was confirmed. The rapid growth of BM is often accompanied by peritumoral edema (105). Diao et al. conducted a retrospective study that included 72 patients with BM and found that the application of SRS and ipilimumab strengthened tumor responses and reduced the amount of edema (11). However, not all studies had good outcomes. The retrospective study undertaken by Mathew et al. (81) and Patel et al. (95) found that it was possible to use ipilimumab and SRS safely, but this joint therapeutic approach was inconsistent with better performance.

In a randomized clinical trial for metastatic melanoma, pembrolizumab therapy led to reduced toxicity and better OS relative to ipilimumab, resulting in broad prescription of anti-PD-1 agents for metastatic melanoma (NCT01866319) (106). However, proof of efficacy of using a mixture of RT and anti-PD-1 agents for treating BM is less convincing than that of an ipilimumab and RT combination. Anderson et al. reported 21 patients undergoing concomitant pembrolizumab and RT for BM. The findings showed that combined SRS with pembrolizumab appeared effective and safe in substantially reducing BM size (82). Acharya et al. demonstrated that SRS with ICI (i.e., anti-PD-1 agent or ipilimumab) is
| Authors             | Tumor type  | N  | Study design | ICI target | Type of RT | Arms                      | Median survival (months) | Intracranial control |
|---------------------|-------------|----|--------------|------------|------------|---------------------------|--------------------------|----------------------|
| Williams et al. (35)| Melanoma    | 16 | Prospective  | CTLA-4     | SRS/WBRT   | RT (WBRT) + ICI RT (SRS) + ICI RT→ICI | 10.6                     | 40% at 6 months 18% at 6 months |
| Skrepnik et al. (36)| Melanoma    | 25 | Retrospective| CTLA-4     | SRS        | RT=ICI RT=ICI (±30 days) RT≠ICI | 35.8                     | 94.8%                |
| Murphy et al. (79)  | Melanoma    | 26 | Retrospective| CTLA-4/PD-1| SRS        | RT+ICI RT+ICI RT | 26.1 | NR |
| Acharya et al. (80) | Melanoma    | 56 | Retrospective| CTLA-4 and/or PD-1 | SRS | RT+ICI RT | 58% OS at 1 year 31% OS at 1 year 56% OS at 6 months 45% OS at 6 months | 85% at 1 year 66% at 1 year 63% at 6 months 65% at 6 months | SRS=ICI 32% SRS≠ICI 22% |
| Mathew et al. (81)  | Melanoma    | 58 | Retrospective| CTLA-4     | SRS        | RT=ICI RT | 26.1 | NR |
| Anderson et al. (82)| Melanoma    | 21 | Retrospective| PD-1       | SRS/WBRT   | NR NR | NR |
| An et al. (83)      | Melanoma    | 99 | Retrospective| CTLA-4     | SRS        | ICI→RT (early SRS) ICI→RT (late SRS) RT=ICI RT≠ICI | 13.4 11.5 19.1 9.0 | 51% at 1 year 25% at 1 year |
| Qian et al. (84)    | Melanoma    | 75 | Retrospective| CTLA-4/PD-1| SRS        | RT=ICI RT≠ICI | 19.1 | NR |
| Liniker et al. (85) | Melanoma    | 53 | Retrospective| PD-1       | Extracranial RT and / or SRS, WBRT | NR NR | NR |
| Ahmed et al. (86)   | Melanoma    | 55 | Retrospective| CTLA-4/PD-1| SRS        | RT+ICI RT+ICI RT+ICI (anti-PD-1) RT+ICI (anti-CTLA-4) | 48% OS at 12 months 41% OS at 12 months | NR |
| Gerber et al. (87)  | Melanoma    | 13 | Retrospective| CTLA-4     | WBRT       | RT=ICI RT=ICI (±30 days) RT≠ICI RT≠ICI (±2 weeks) RT | 4 18.3 12.9 14.5 24.7 7.1 | 56% by irRC criteria |
| Silk et al. (88)    | Melanoma    | 70 | Retrospective| CTLA-4     | SRS /WBRT  | RT + ICI RT + ICI RT | 13.4 11.5 19.1 9.0 | NR |
| Chen et al. (89)    | NSCLC, Melanoma, RCC | 260 | Retrospective| CTLA-4/PD-1| SRS | RT=ICI RT=ICI (±4 weeks) RT≠ICI RT≠ICI (±2 weeks) RT | 7.4 | NR |
| Yusuf et al. (90)   | Melanoma    | 51 | Retrospective| CTLA-4/PD-1| SRS        | RT=ICI RT≠ICI | 7.4 | NR |
| Kiess et al. (91)   | Melanoma    | 46 | Retrospective| CTLA-4     | SRS        | RT=ICI | 56% OS at 1 year | 100% at 1 year |
| Authors          | Tumor type | N  | Study design | ICI target | Type of RT | Arms                      | Median survival (months) | Intracranial control |
|------------------|------------|----|--------------|------------|------------|---------------------------|--------------------------|----------------------|
| Choong et al. (92) | Melanoma   | 39 | Retrospective | CTLA-4 /PD-1 | SRS        | RT→ICI | 65% OS at 1 year          | 87% at 1 year           |
|                  |            |    |              |            |            | ICI→RT | 50% OS at 1 year          | 89% at 1 year           |
|                  |            |    |              |            |            |              |                          |                      |
| Cohen-Inbar et al. (93) | Melanoma | 46 | Retrospective | CTLA-4     | SRS        | RT→ICI, RT=ICI | 59% OS at 1 year | 54.4% at 1 year |
|                  |            |    |              |            |            | ICI→RT | 33% OS at 1 year          | 16.5% at 1 year          |
|                  |            |    |              |            |            |              |                          |                      |
| Amaral et al. (94) | Melanoma   | 290| Retrospective | CTLA-4 and PD-1 | SRS/WBRT | NR    | 24.0 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Patel et al. (95)  | Melanoma   | 54 | Retrospective | CTLA-4     | SRS        | RT + ICI (≥4 months) | 38.5% OS at 1 year | 71.4% at 1 year |
|                  |            |    |              |            |            | ICI→RT | 37.1% OS at 1 year          | 92.3% at 1 year          |
|                  |            |    |              |            |            |              |                          |                      |
| Rahman et al. (96) | Melanoma   | 74 | Retrospective | CTLA-4/PD-1 | SRS        | RT=ICI (±30 days) | 13.9 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Schmidberg et al. (97) | Melanoma | 41 | Retrospective | CTLA-4     | SRS/WBRT | RT→ICI | 11.0 |                      |
|                  |            |    |              |            |            | ICI→RT | 3.0 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Diao et al. (98)  | Melanoma   | 72 | Retrospective | CTLA-4     | SRS        | RT=ICI | 16.9 |                      |
|                  |            |    |              |            |            | ICI→RT | 6.1 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Fang et al. (99)  | Melanoma   | 137| Retrospective | CTLA-4/PD-1 | SRS        | NR    | 16.9 |                      |
|                  |            |    |              |            |            | RT=ICI | 15.0 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Kaidar-Person et al. (100) | Melanoma | 58 | Retrospective | CTLA-4/PD-1 | SRS        | RT→ICI | 5.5 |                      |
|                  |            |    |              |            |            | RT=ICI | 12.0 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Martins et al. (101) | Melanoma | 84 | Retrospective | CTLA-4/PD-1 | SRS        | NR    | 10.0 |                      |
|                  |            |    |              |            |            | RT+ICI | 6.1 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Singh et al. (102) | NSCLC      | 39 | Retrospective | PD-1       | SRS        | RT→ICI | 15.9 |                      |
|                  |            |    |              |            |            | RT+ICI | 6.1 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Hubbeling et al. (103) | NSCLC | 50 | Retrospective | PD-1       | SRS        | RT→ICI | 15.9 |                      |
|                  |            |    |              |            |            | RT+ICI | 6.1 |                      |
|                  |            |    |              |            |            |              |                          |                      |
| Lanier et al. (104) | NSCLC/Melanoma | 271 | Retrospective | CTLA-4 and/or PD-1 | SRS | RT+ICI | 15.9 |                      |

RT, radiotherapy; ICI, immune checkpoint inhibitor; BM, brain metastases; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; irRC, immune-related response criteria. ICI→RT indicates ICI was administered prior to RT; RT=ICI indicates that ICI was administered concurrently with RT; RT→ICI indicates that ICI was administered after RT; RT≠ICI indicates that RT was not administered concurrently with SRS; RT+ICI indicates ICI was administered with RT but the relative timing of each treatment was not provided. NR indicates that the results were not reported.

associated with reduced local and distant brain tumor resistance relative to SRS alone in BM patients (80). Nonetheless, no further work has been conducted on which form of ICI has a better treatment result when paired with SRS for BM. Choong et al. (92) retrospectively analyzed 108 melanoma patients with BM who were treated with
SRS and systemic treatment (including inhibitors of BRAF or agents targeting PD-1 and/or CTLA4). For patients treated with SRS and anti-PD-1 agent, the mean OS was far higher than for those who received SRS and an anti-CTLA4 agent (27.4 months vs. 7.5 months). A study by Martins et al. revealed a similar finding (101). Nonetheless, there were some drawbacks to the study results. Therefore, in the future, head-to-head analysis of anti-PD-1 agents plus RT vs. ipilimumab plus RT for BM will be required.

Most of the reports discussed in this study used SRS to treat BM instead of WBRT. Some reports, however, were already concentrating on integrating WBRT and ICIs. Gerber et al., for example, performed a retrospective analysis of 13 BM patients treated with WBRT within 30 days of ipilimumab administration; their findings revealed that ipilimumab and WBRT combination provided encouraging efficacy (87).

The Thomas Jefferson University (35) performed the first prospective phase I analysis pairing RT with ipilimumab (NCT01703507). In that investigation, 16 patients were enrolled to receive WBRT plus ipilimumab or SRS plus ipilimumab. SRS was applied to patients with postoperative cavity (all less than 4 cm) or fewer than 5 BM, while WBRT was used to treat patients with any postoperative cavity/lesion larger than 4 cm in diameter or ≥5 BM. From this report, concomitant WBRT or SRS with ipilimumab was safe and well tolerated. For the 16 patients who were admitted, 14 of them showed progressive disease with some also dying during follow-up. In the end, due to slow accrual, the WBRT arm was closed prematurely, and the effectiveness was not as anticipated. As it was a phase I study, the primary endpoint was safety rather than effectiveness. Lack of appropriate patients to assess effectiveness may have led to the unexpected results.

The above listed studies were all retrospective studies except for NCT01703507; hence, the validity of these data is limited. Many prospective trials are scheduled or currently being conducted to confirm the use of ICIs in conjunction with RT in BM therapy. Details on these trials are summed up in Table 2. After evaluating these trials, we find that they are all phase 1 and 2 trials, suggesting that the combination of ICIs and RT remains at an exploratory level.

**Establishing the best performing sequence and schedule of integrated RT and immunotherapy for BM treatment**

From the data shown in Table 1, the combination of ICIs and RT can be performed in three different ways: patients receive RT during ICIs (concurrent RT and ICIs), patients receive RT before ICIs, and patients receive RT after ICIs. However, the optimal timing of ICIs when combined with RT remains controversial.

Kiess et al. (91) observed that patients with BM who received SRS before or during ipilimumab treatment had fewer regional recurring tumors and greater OS than those who received SRS after ipilimumab. “SRS during ipilimumab” means <1 month (4 weeks) following the final ipilimumab dose or between doses of ipilimumab. “SRS after ipilimumab” refers to patients who received SRS following the last dose of ipilimumab. Different effects were observed in a later retrospective analysis at the University of Virginia (93). A group of 32 patients undergoing SRS either before or during ipilimumab treatments (including patients treated with SRS up to a month following the final dose of ipilimumab) showed a significantly longer local recurrence-free duration compared to 14 patients receiving ipilimumab prior to SRS. This research reinforced previous findings that SRS might be more suitably received during the initiation of ICIs (concurrent treatment).

Chen et al. (89) retrospectively reported the results of melanoma, RCC and metastatic NSCLC patients with BM who had been treated with SRS. They observed that combined use of SRS and ICI correlated to better OS compared to non-concomitant ICI and SRS. In this study, patients were classified as having combined ICI and SRS if they were administered a dose of ICI within two weeks before or after SRS. In comparison to conceptualization of concurrent ICIs and SRS conducted by Chen et al., in Qian’s study, SRS treatment and immunotherapy of any particular lesion were deemed concurrent if SRS was performed inside four weeks of immunotherapy cessation or initiation; all other patients were classified as non-concurrent (84). In fact, OS was significantly shorter in the non-concurrent treatment group at just 8 months compared to 19.1 months for the concurrent therapy cohort (84). Many trials, including those done by Diao et al. (98), Anderson et al. (82) and Yusuf et al. (88), have also used “4 weeks or 1 month” as the threshold value to describe “concurrent therapy”. In these trials, patients treated with combined ICIs and SRS experienced better results than those diagnosed with non-concurrent therapy (79,82,90,98). In the study carried out by An et al., they suggested that “5.5 months” could also be used to describe “concurrent therapy” as a threshold value (83). In Acharya’s
study, concurrent therapy was described as the administration of SRS within 3 months of ICIs or targeted therapy (80). In addition, Skrepnik et al. in their retrospective study detected a group of 25 ICI-treated (pembrolizumab and ipilimumab) BM patients and SRS; the optimum period for ICI administration was stated to be 15−30 d after SRS treatment. However, their analysis did not include evidence to justify parallel use of SRS and ICIs (107).

Various postulations may theoretically clarify the difference between these trial findings. Firstly, the optimum timing will depend on the half-life of ICIs. Ipilimumab has a half-life of 14.9 d (108), and pembrolizumab and nivolumab have a half-life of 25 d and 25.2 d, respectively. Patel et al. (95) observed no better results when ipilimumab was given to BM patients within 4 months of SRS compared to those who received SRS alone. They further analyzed the evidence and found that patients who received ipilimumab and SRS within 14 d could derive an OS advantage due to ipilimumab’s half-life. Consequently, ICI’s half-life may give us a hint to select the best timing of combined therapy.

The levels of some biomarkers may change during the RT course, which would give us information on when to combine ICIs and RT. Radiation-induced mannose-6-phosphate receptor expression, a receptor essential to

| Trial number | Phase | Tumor type | Country | Status | N (planned) | Arm(s) | Primary outcomes |
|--------------|-------|------------|---------|--------|-------------|--------|------------------|
| NCT01449279 | I     | Melanoma   | USA     | Active, not recruiting | 20 | Ipilimumab + palliative radiation Pembrolizumab + SRS (30 Gy/5f) | Safety |
| NCT02858869 | I     | Melanoma/NSCLC | USA | Recruiting | 30 | Pembrolizumab + SRS (27 Gy/3f) Pembrolizumab + SRS (18−21 Gy/1f) | Safety |
| NCT02716948 | I     | Melanoma   | USA     | Recruiting | 90 | Nivolumab + SRS Nivolumab + SRS Nivolumab + WBRT Nivolumab + ipilimumab + SRS Nivolumab + ipilimumab + WBRT | Safety |
| NCT02696993 | I/II  | NSCLC      | USA     | Recruiting | 88 | Ipilimumab + SRS Nivolumab + ipilimumab + SRS Nivolumab + ipilimumab + WBRT | Recommended phase 2 dose; 4-month intracranial Progression-free survival Overall survival rate |
| NCT02107755 | II    | Melanoma   | USA     | Active, not recruiting | NR | Ipilimumab + SRS | Progression-free survival |
| NCT02097732 | II    | Melanoma   | USA     | Active, not recruiting | 40 | (a) SRS → ipilimumab (b) Ipilimumab → SRS (a) Previously untreated BM (b) Progressive BM (c) Neoplastic meningitis (d) 1−4 BM from melanoma | Local control rate |
| NCT02886585 | II    | Any solid tumor | USA | Recruiting | 102 | Nivolumab + SRS | Objective response rate; Overall survival rate; Extracranial overall Response rate |
| NCT02978404 | II    | NSCLC/RCC  | Canada  | Recruiting | 60 | Nivolumab + SRS | Intracranial progression-free survival |
| NCT03340129 | II    | Melanoma   | Australia | Recruiting | 218 | Nivolumab + ipilimumab Nivolumab + ipilimumab + SRS | Neurological specific cause of death |

RT, radiotherapy; BM, brain metastases; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy. Clinical trials were search on the database https://clinicaltrials.gov/. Clinical trials which are active or recruiting BM patients treated with immunotherapy and RT irrespective of the tumor types were included in Table 2.
radiation-enhanced ipilimumab effectiveness, was shown to peak within 3 d of irradiation and normalize over 7–14 d (109), indicating that ipilimumab administration can be more efficient during that process. Research by Dovedi et al. documented anergy in tumor-reactive T-cells 7 d following the previous fractionated RT dose and reduced expression of PD-L1 in mouse models (110), suggesting that PD-1 inhibitor therapy would be best suited to that direction. Such findings also illustrate the need for studies investigating inherent pathways and optimum scheduling of ICI and RT administration based on tumor cell molecular expression.

In conclusion, patients treated with concurrent ICIs and RT might have better outcomes than those treated with non-concurrent treatment. Nevertheless, the concept of “concurrent” remains ambiguous, with some reports stating “concurrent” to be provision of ICIs as early as 2 weeks before or after SRS, and some extending this time to 4 weeks or 1 month, or as long as 5.5 months. Most studies typically used 4 weeks/1 month as the threshold value. Indeed, studies supporting the simultaneous use of ICIs and RT showed a better synergistic effect, but the cumulative toxic effect of the two kinds of therapy also merits attention.

Safety of combined immunotherapy and RT

One specific issue is the potential increased and unforeseen toxicity when mixing RT and immunotherapy. By their own definition, immunotherapies stimulate the immune response, which induces inflammatory side effects sometimes referred to as immune-related adverse events (irAEs) (111). irAEs most commonly affect organs such as liver, skin, endocrine glands, and CNS (112,113). In patients treated with CTLA-4 inhibitory therapy, hypophysitis and colitis are typical irAEs, while thyroiditis and pneumonitis are more generally seen in patients undergoing treatment with PD-1 inhibitors (114-116). Clinical trials evaluating the efficacy and safety of ipilimumab or anti-PD-1 antibodies as monotherapy recorded irAEs of any grade in 13%–65% of patients, with third to fourth grade irAEs registered in 1%–27% of patients (17,117-122). Among them, neurological AE caused by ICIs occur in about 1% of patients and numerous autoimmune neurological side effects have been recorded, including encephalomyelitis, demyelinating polyneuropathy, encephalitis and hypophysitis (18).

For patients with BM, the association between addition of brain RT to ICIs and the incidence of irAEs seems weak. In a phase I trial by Williams, patients with BM showed no rise in neurotoxicity compared to RT alone (14 patients with neurotoxic effects in grade 1–2). Total grade 3 toxicity was just seen in 10 patients, including anemia, panhypopituitarism, pleural effusion, lymphopenia and gastrointestinal (35). A newly published retrospective study analyzed 260 patients undergoing immunotherapy and multifaction or single SRS, no elevation in acute toxicity with successive or concurrent SRS and immunotherapy administration was observed. irAE rates among patients who received simultaneous SRS and ICI or not were not significantly different (89). The occurrence of irAEs in patients treated with extracranial RT/intracranial SRS and anti-PD-1 therapy was retrospectively evaluated by Liniker et al. (85); only four patients reported grade 3 or 4 irAE, consistent with existing historical anti-PD-1 therapy evidence (123). Based on the above results, we cannot tell whether adding ICI to RT could increase irAE risk. The safety of the combination of ICIs with WBRT/SRS has been demonstrated by many other studies, but they did not provide details regarding the irAE incidence rate (79,82,124). Further studies are required to assess this issue.

Unlike the irAEs, the risk of RT-related AEs caused by combination therapy has been investigated by more studies. From the above literature, the possible RT-related toxicity of combined ICIs and RT involves intratumoral hemorrhage, neurocognitive impairment and radiation necrosis (RN), but most of these investigations concentrated on SRS rather than WBRT (13,82,85,87). Among them, RN is the most ubiquitous side effect rising with dual treatment.

RN is the development of irreversible tissue injury in previously irradiated brain tissue that occurs more than 12 weeks after irradiation. It is the result of an inflammatory response (125) and is frequently symptomatic on clinical appearance, including focal neurological defects, impaired emotional state or hallucinations. It is a typical side effect of SRS that occurs in about 5%–25% of patients (126,127). Many variables have been proposed to influence RN levels including previous radiation, treated length and RT dosage (127,128). Previously multiple case series established a possible correlation between RN and immunotherapy after SRS (129,130). Du et al. identified 7 ipilimumab and SRS-treated patients, all of whom developed RN during follow-up (130). In a separate study involving 27 BM patients treated with ipilimumab and SRS, 41% of the patients developed RN (37). Fang et al. (99) evaluated the outcomes
of 137 BM patients receiving SRS, together with ipilimumab and/or pembrolizumab. The median follow-up was 9.8 months from SRS, and the RN rate was 27%, for an average 6-month RN period. For this sample, the RN incidence for nearly one quarter of the patients was close to that found in the other two studies (36,131).

Various studies have measured the dangers of RN after SRS either with or without ICI (132). However, the cumulative data available on the efficacy of combined intracranial RT and ICI are contradictory, with some reports suggesting a higher risk of RN with combination therapy than with SRS monotherapy, and others finding no such effect. Kaidar-Person et al. observed that 13.8% (8 out of 58) of patients with RN all came from the immunotherapy plus RT group, while 29 patients who only got RT did not have RN during follow-up (100). Martin et al. (131) examined the results of 480 newly diagnosed patients with BM secondary to melanoma, RCC, and NSCLC who were treated with or without ICIs. They observed a correlation between immunotherapy receipt and symptomatic RN in patients receiving SRS. The findings revealed that symptomatic necrosis occurred in 6.85% and 20.0%, respectively, of patients who did not compare with those undergoing immunotherapy (131). Fifty-four patients with BM received SRS either in conjunction with (n=20) or without (n=24) ipilimumab in another retrospective study performed by Patel et al (95). The SRS plus ipilimumab cohort had a one-year trend towards developing higher RN rates compared to the SRS cohort alone, at rates of 20.92% vs. 30%, respectively (95).

The studies investigating safety of combined RT and ICI in BM are summarized in Table 3. Such findings pose a big warning that combined ICI and SRS could increase the risk of RN; however, evidence from subsequent studies did not indicate the same effect. Indeed, neither Silk nor Mathew reported increased rates of RN in patients treated with the combination of RT and ipilimumab (81,88). Possible reasons for these divergent outcomes include insufficient cohort sizes of multiple studies and variations in the prescribed doses of SRS, fraction numbers and isodose lines (17). For patients with BM, prospective trials which will mitigate all influencing variables that are required to better define the risks and benefits of integrating brain-directed stereotactic radiation with immunotherapy.

**Conclusions and future direction**

The introduction of ICIs has opened a new range of alternative treatment solutions for BM patients. Although much remains unclear about the impact of immunotherapy on BM, as well as its relationship with RT, evidence from a limited number of clinical trials has indicated that the combination of ICIs and RT can improve survival and abscopal responses within the brain, which can be enhanced if administered concurrently rather than sequentially. The goal of combining the two kinds of therapy is to make the treatment more effective with minimal toxicity. For this reason, we also discuss the optimal time or time window for combination therapy in this review. But most studies that we have discussed were retrospective with small sample sizes. Thus, there were some limitations in reaching a firm conclusion. In order to further investigate and verify the efficacy and optimum timing of RT and immunotherapy combination for patients with BM, current and scheduled specific prospective studies of a broader scale or more data are required. Additionally, there is lack of studies documented on the RT and immunotherapy combination for patients with BM for other tumors besides melanoma. The RT and immunotherapy combination for patients with BM need to be explored for other tumors to broaden its therapeutic avenue. Furthermore, there are many factors affecting immunotherapy, corticosteroid is one of the important factors (133). Patients with symptomatic BM are often treated with corticosteroid to reduce symptoms (133). A recent published study showed that immunotherapy with nivolumab plus ipilimumab, particularly in combination with RT could improves OS in both asymptomatic and symptomatic melanoma BM (94). But there is lack of studies documented on the optimum timing of RT and immunotherapy separately according to the presence or absence of cranial symptoms. Further studies on this field are really needed.

In the advanced stage, immunotherapy can successfully extend the ultimate survival of patients in various tumors. Nevertheless, only a portion of people reports objective responses from such treatments which illustrate large differences in efficacy as well as adverse drug reactions (134). Loss of function as a result of heterozygosity in intrinsic resistance mechanisms previously reported include PD-1, human leukocyte antigen (HLA), beta-2 microglobulin (B2M), phosphatase and tensin homolog (PTEN), Janus-associated kinase (JAK)1, JAK2, or transporter associated with antigen processing 1 (TAP1) genes. Different cases in which the resistance catalyst is undisclosed have been identified, demonstrating the difficulty of resistance in the sense of immunotherapy, and
further rigorous attempts to combine analysis of such unusual cases to uncover mechanistic insight are needed (135-139). Therapeutically, by analyzing the alters status of these resistance-related genes, which may also be known as

| Authors               | Study characteristics                                                                 | Explore                          | RT-related toxicities                                                                 |
|-----------------------|----------------------------------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------|
| Williams et al. (35)  | Phase I study involving 16 patients with BM from melanoma                              | WBRT vs. SRS + ipilimumab        | 21 grade 1–2 neurotoxicities; no grade 4–5 toxicity or RN                               |
| Mathew et al. (81)    | Retrospective study involving 58 patients with BM from melanoma                        | SRS ± ipilimumab                 | Intratumoral hemorrhage in 28.0% of patients receiving SRS + ipilimumab vs. 30.3% of patients receiving SRS. |
| Silk et al. (88)      | Retrospective study involving 70 patients with BM from melanoma                        | RT (WBRT/SRS) ± ipilimumab       | Intratumoral hemorrhage in 12.5% of patients receiving RT vs. 3.9% of patients receiving RT + ipilimumab; RN in 9.38% of patients receiving RT vs. none of patients receiving RT + ipilimumab |
| Chen et al. (89)      | Retrospective study involving 260 patients with BM from melanoma, NSCLC, or RCC       | SRS ± ICI                        | RN occurred in 3% of patients, this was not significantly different among patients who received SRS alone, SRS and non-concurrent ICI, and concurrent SRS and ICI. |
| Patel et al. (95)     | Retrospective study involving 54 patients with BM from melanoma                        | SRS ± ipilimumab                 | RN in 21% of patients receiving SRS vs. 30% of patients receiving SRT + ipilimumab (P=0.078); intratumoral hemorrhage in 14.7% of patients receiving SRS vs. 15.0% of patients receiving SRT + ipilimumab (P=1.00) |
| Diao et al. (98)      | Retrospective study involving 72 patients with BM from melanoma                        | SRS ± ipilimumab (concurrent: 59 lesions; nonconcurrent: 160 lesions; none: 91 lesions) | RN in 3% of patients receiving concurrent therapy and 2% in those receiving nonconcurrent therapy; TRIC in 8% of patients receiving concurrent therapy and in 6% of those receiving nonconcurrent therapy; no patients receiving SRS alone had RN or symptomatic TRIC; the overall incidence of any lesion hemorrhage was 18%; nonconcurrent ipilimumab was associated with lower risk of lesion hemorrhage compared with concurrent ipilimumab |
| Fang et al. (99)      | Retrospective study involving 137 patients with BM from melanoma                       | SRS + CT and/or ICI              | RN in 27% of patients, including in 12.5% of patients receiving ipilimumab and 7.4% of patients receiving pembrolizumab. |
| Kaidar-Person et al. (100) | Retrospective study involving 58 patients with BM from melanoma                  | SRS ± ICI                        | RN in 28% of patients receiving SRS + ICI vs. none of patients receiving SRS alone. |
| Hubbeling et al. (102) | Retrospective study involving 163 patients with BM from NSCLC                    | RT (WBRT/SRS/PBI) vs. RT + ICI   | RN occurred in only one patient (grade 4, RT cohort); the incidence of grade ≥3 AEs was 8%–13% across treatment groups, and did not differ significantly between RT + ICI and RT cohorts. |
| Skrepnik et al. (107) | Retrospective study involving 25 patients with BM from melanoma                     | SRS + ipilimumab                 | RN in 21% of patients                                                              |
| Martin et al. (131)   | Retrospective study involving 480 patients with BM from melanoma, NSCLC, or RCC    | SRS/SRT vs. SRS/SRT + ICI        | Symptomatic RN in 7% of patients receiving SRS/SRT vs. 20% in patients receiving SRS/SRT + ICI. |
| Colaco et al. (132)   | Retrospective study involving 180 patients with BM from various tumor types          | RT + ICI, CT, and/or TT          | RN in 21.7% of patients including 16.9% in patients receiving RT + CT, 25.0% in patients receiving RT + TT, and 37.5% in patients receiving RT + ICI. |

RT, radiotherapy; ICI, immune checkpoint inhibitor; BM, brain metastases; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; PBI, partial brain irradiation; RN, radiation necrosis; SRT, stereotactic radiotherapy; CT, chemotherapy; TT, target therapy; AE, adverse event; TRIC, treatment-related imaging change.
biomarkers, it would be beneficial to assess the weak responders and the chance of relapse. Thus, we could also use these biomarkers to select suitable BM patients for the treatment of RT and immunotherapy combination.

**Acknowledgements**

This work was supported by National Key Research and Development Program of China (No. 2018YFC1311400, 2018YFC1311402), and National Natural Science Foundation of China (No. 81672982, 81872478).

**Footnote**

Conflicts of Interest: The authors have no conflicts of interest to declare.

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