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Systematic Review

Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data

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ABSTRACT

Background and purpose: While the combination of stereotactic radiosurgery (SRS) and immune checkpoint inhibitors (ICI) is becoming more widely used in the treatment of brain metastases (BM), there is a paucity of prospective data to validate both the safety and efficacy, as well as the optimal timing of these two therapies relative to one another.

Methods: A PICOS/PRISMA/MOOSE selection protocol was used to identify 17 studies across 15 institutions in 3 countries. Inclusion criteria were patients: diagnosed with BM; treated with SRS/ICI, either concurrently or non-concurrently; with at least one of the primary or secondary outcome measures reported. Weighted random effects meta-analyses using the DerSimonian and Laird method were performed. The primary outcome was 1-year overall survival (OS). Secondary outcomes were 1-year local control (LC), 1-year regional brain control (RBC), and radionecrosis incidence.

Results: A total of 534 patients with 1,570 BM were included. The 1-year OS was 64.6% and 51.6% for concurrent and non-concurrent therapy, respectively ($p < 0.001$). Local control at 1-year was 89.2% and 67.8% for concurrent and non-concurrent therapy, respectively ($p = 0.09$). The RBC at 1-year was 38.1% and 12.3% for concurrent and ICI administration prior to SRS, respectively ($p = 0.049$). The overall incidence of radionecrosis for all studies was 5.3%.

Conclusions: Concurrent administration of SRS/ICI may be associated with improved safety and efficacy versus sequential therapy. These findings, however, are hypothesis-generating and require further validation by ongoing and planned prospective trials.

Brain metastases (BM) are the most common intracranial tumor seen in adults and may be seen up to 10 times more frequently than primary brain tumors [1]. Up to 30% of adults with cancer and more than 200,000 patients are affected by brain metastases annually in the United States [2], primarily from cancers of the lung, kidney, breast, or melanoma [1–4]. Brain metastases are associated with a poor prognosis and often carry a median overall survival (OS) of 4–5 months [5–7].

The utility of systemic therapies in the management of brain metastases has long been limited due to the view of the brain "immunologically privileged". Interestingly, recent studies have demonstrated the presence of microglia and other immune cells within the brain that have been shown to respond to systemic cytokines [8–10]. In parallel to these discoveries, by 2011 the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agent ipilimumab was approved for use in metastatic melanoma [11,12], which was followed by the programmed cell death protein 1 (PD-1) inhibitors pembrolizumab and nivolumab in 2014 [13–15].

Stereotactic radiosurgery (SRS), defined as the precise delivery of a single-dose of ablative radiation to a tumor, is the preferred treatment option in select patients with BM [1], and multiple randomized control trials have assessed the efficacy and safety SRS in this setting [16,17]. Moreover, early evidence suggesting synergy between SRS and immune system modulation has been observed, presumably because SRS causes tumor associated antigen release, which may produce an abscopal response [18–24].

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With the approval of these immune checkpoint inhibitors (ICIs) in the treatment of metastatic cancer, there has been heightened enthusiasm in exploring the synergy of SRS and immunotherapy in the treatment of BM [18,25]. However, there are concerns regarding increased toxicity resulting from host autoimmune responses when combined with radiation, for example, myocarditis after treatment of intra-thoracic tumors [26,27].

Presently, the National Comprehensive Cancer Network (NCCN) recommends the use of SRS as local therapy for management of brain metastases [1]. Multiple retrospective studies, usually from single institutions, have been published exploring the safety and efficacy between SRS and ICI in the treatment of brain metastases with multiple prospective trials currently underway or planned. As these trials mature, clinicians are left to make clinical decisions based on limited data. Therefore, we sought to pool published data on this topic and determine the safety and efficacy of SRS and ICI in terms of OS, local control (LC), regional brain control (RBC), and incidence of radionecrosis, as well as the optimal timing sequence of these two therapies relative to one another.

Methods

The methodology detailing evidence acquisition and data extraction is detailed in Supplementary Text 1.

Outcome measures

The primary outcome measure was 1-year OS from SRS. Secondary outcome measures were 1-year LC, 1-year RBC, and incidence of radionecrosis. Definitions of LC and RBC were dependent on each institution, but generally included radiographic and/or clinical changes that resulted in consideration of additional local therapies; all instances of radionecrosis were included. The primary and secondary endpoints (with the exception of radionecrosis incidence) were also assessed based on the temporal relationship of ICI and SRS administration. Institutional definitions of "concurrent," "non-concurrent," "ICI before SRS," and "ICI during SRS" were used. Due to a paucity of data involving toxicities other than radionecrosis, an in-depth statistical analysis was not possible. Treatment-related toxicities were summarized and coded using the Common Terminology criteria for Adverse Events (CTCAE) Version 4.03 [34].

The methodology detailing the statistical analysis is presented in Supplementary Text 2.

Results

Study characteristics

The meta-analysis included 534 patients (n) from 17 studies published from 2013 to 2018, involving 1570 brain metastases (Fig. 1) [30–34,37–49]. The patients were treated from 2005 to 2016. Studies were conducted in the United States [30–38,37–41, 44,46–49], Australia [43], and France [45]. Patient demographics, treatment characteristics, 1-year OS, 1-year LC, 1-year RBC, and radionecrosis data were recorded (Table 1). Center for evidence-based medicine levels of evidence were assigned next to each individual study [28]. Available toxicity data and available data reporting the use of steroids are summarized in Supplementary Table 4. The results of a search on clinicaltrials.gov are presented in Supplementary Table 5.

The majority of the studies consisted of patients with melanoma brain metastases [30–34,37–40,42–49]; however, two included non-small cell lung cancer (NSCLC) metastases [33,41], and one included renal cell carcinoma metastases [33]. A total of 17/535 (3%) of patients included received WBRT [31,40,55–57,49]. The median follow-up time was 9.1 months (range: 6.0–22.7 months). The median age was 61.7 years (range: 54.5–68.5 years). Median OS was 12 months from radiosurgery. The most commonly used ICI were anti-CTLA-4 agents (ipilimumab), which were utilized in 14 of the studies [30–33,37,39,40,43–49]. Anti-PD-1 agents (pembrolizumab, nivolumab) were administered in 9 of the studies [33,38,40–43,45,48,49]. The most commonly used SRS dose was 20 Gy (range: 18–24 Gy). In the included studies, SRS was administered via Gamma Knife (R) in 6 studies, Cyberknife (R) in 3 studies, and via linear accelerator in 8 studies. Additional information regarding timing of ICI and SRS, as well as radiation treatment, such as median dose, gross tumor volume, and median number of lesions were recorded (Table 2).

1-Year overall survival

There were 488 patients across 16 studies whose 1-year OS rates were evaluated [30–35,38–40,45–49]; the 1-year OS for these patients was 56.7% (Fig. 2A). There were 300 patients across 8 studies who either received ICI concurrently or non-concurrently with SRS (Fig. 2B) [33,37,39,40,44,45,47,48]; a comparison between groups revealed a statistically significant difference in 1-year OS (64.6% versus 51.6%; $p = 0.00027$), favoring the concurrent group. Similarly, there were 218 patients across 7 studies who received ICI before SRS, ICI concurrent with SRS, or ICI after SRS (Fig. 2C) [33,39,40,44,45,47,48]; a comparison between the three groups revealed a statistically significant difference in 1-year OS (40.7% [ICI before SRS] versus 56% [ICI after SRS] versus 65% [ICI concurrent with SRS]; $p = 0.00045$). When comparing concurrent therapy to ICI before SRS or ICI after SRS, there was a statistically significant difference favoring concurrent therapy ($p = 0.00055$ [Supplementary Fig. 2] and $p = 0.0027$ [Supplementary Fig. 3], respectively).

1-Year local control

There were 919 brain metastases across 10 studies whose 1-year LC rates were evaluated [30,32,33,38,39,41,44,46,48,49].

Local control rates at 1-year ranged from 40% to 92% in the included studies (Fig. 3). The overall summary estimate for 1-year LC was 81.2% (95% CI: 66.8%–90.2%). Stratification of subgroups by timing revealed an overall summary estimate of 89.2% (95% CI: 79.9%–94.5%) for studies administering ICI concurrent with SRS [39,44,48]; studies with non-concurrent administration of ICI and SRS [33,39,44] revealed an overall summary estimate of 67.8% (95% CI: 40.2%–86.8% (Supplementary Fig. 4)). A statistically significant difference between the timing of ICI relative to SRS for 1-year LC was not observed ($p = 0.09$).

1-Year regional brain control

There were 241 patients across 9 studies whose 1-year RBC rates were evaluated [30,32,38,39,41,44,46,48,49]. Five out of these 241 (2%) patients received prior WBRT [44,49].

Regional brain control rates at 1-year ranged from 0% to 72.7% in the included studies (Supplementary Fig. 5). The overall summary estimate for 1-year RBC was 36.8% (95% CI: 22.7%–53.5%). When stratifying by the different ICI and SRS timing combinations, 1-year RBC for studies reporting ICI administration after SRS [39,44] demonstrated an overall summary estimate of 29.4% (95% CI: 18.2%–43.7%), ICI administration before SRS [39,44] demonstrated an overall summary estimate of 12.3% (95% CI: 4.0%–31.9%), and concurrent administration demonstrated an overall summary estimate of 38.1% (95% CI: 20.1%–60.1%) for of ICI and SRS (Supplementary Fig. 6) [39,48]. A statistically significant difference between RBC at 1-year for concurrent versus ICI administration before SRS was observed ($p = 0.049$).

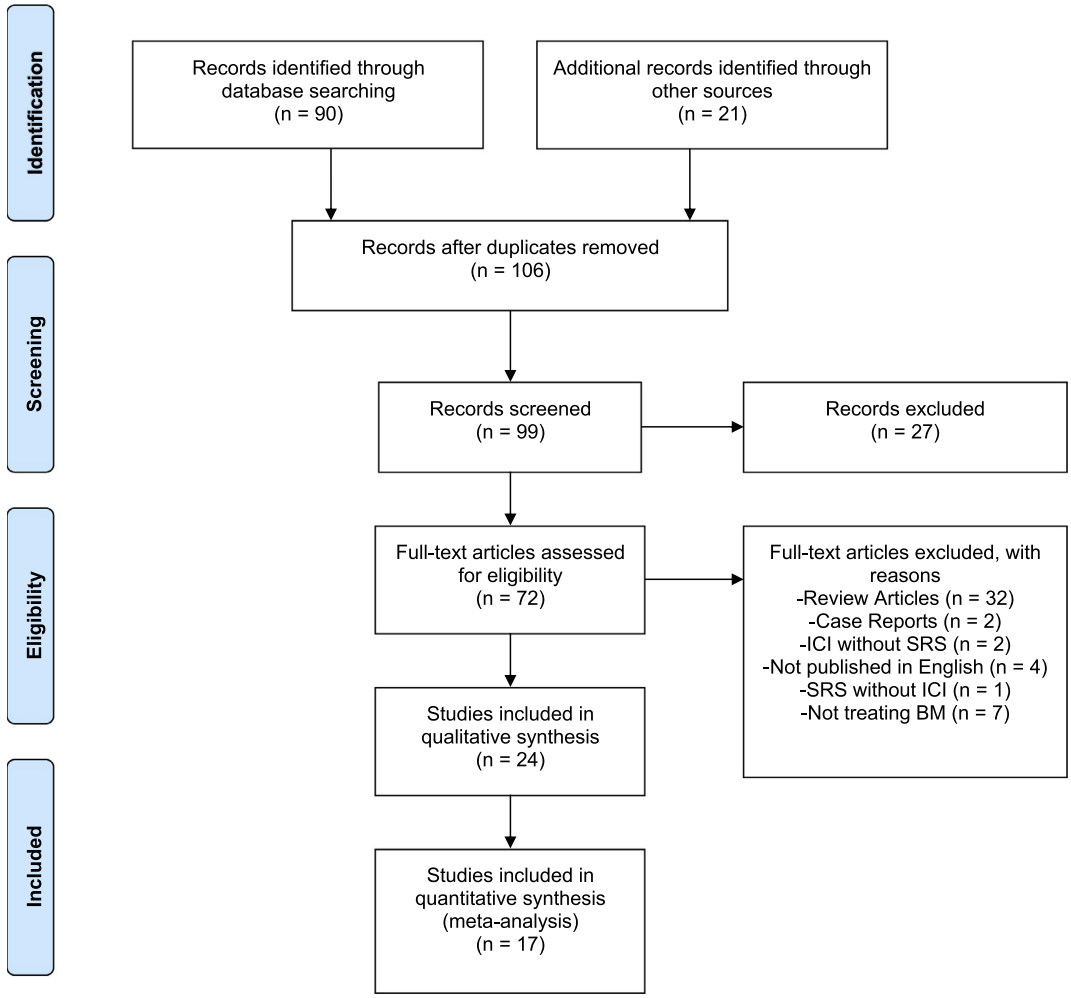

Fig. 1. PRISMA Flow Diagram. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting the stages of literature selection. Initially, 106 articles were found to warrant further investigation. Ultimately, 17 articles met inclusion criteria and were incorporated into the quantitative analysis.

Radionecrosis

There were 335 lesions across 5 studies whose incidences of radionecrosis were evaluated [42,44,59–61]. Rates of radionecrosis ranged from 0 to 20.7% in the included studies (Fig. 4). The overall summary estimate for radionecrosis incidence was 5.3% (95% CI: 0.3%–15.7%). All studies reporting incidence of radionecrosis involved the use of ipilimumab [44,46,48]. Radionecrosis could not be analyzed with respect to the temporal relationship between ICI and SRS administration due to limited data. Only 2 studies [44,48] provided radionecrosis rates relative to ICI and SRS administration.

Timing of therapy

Of the 17 studies included, individual study definitions of timing of ICI relative to SRS administration were used. In 5 of these studies, the time elapsed between ICI and SRS administration was reported [39,40,44,46,48]. In each of these studies, concurrent therapy was defined as ICI and SRS being administered within one month of one another. Non-concurrent therapy was defined as either >4 weeks before SRS (ICI before SRS) or >4 weeks after SRS (ICI after SRS).

Discussion

The NCCN currently recommends SRS as a treatment option for patients with limited BM with the option of systemic ICI use as clinically indicated, although there is limited data supporting the safety of this combination [1]. Our results revealed several key findings about SRS and ICI for BM. Combination SRS and ICI does not appear to be associated with untoward rates of radionecrosis (Fig. 4). However, since only 5 studies provided radionecrosis rates and there was an inability to perform a statistical analysis based on the temporal relationship of ICI and SRS administration, prospective trials are sorely needed to ascertain the safety of this treatment combination. Interestingly, radionecrosis is markedly more pronounced in patients receiving anti-CTLA-4 therapy (Fig. 4).

The 1-year LC rates are favorable, approximately 81% among a diverse group of tumors (Fig. 3; Table 1); furthermore, there is improvement in 1-year LC when administering SRS and ICI concurrently versus non-concurrently with LC rates of 89.2% and 67.8% (Supplementary Fig. 4), respectively ($p = 0.09$). The multi-institutional trial N0574 compared patients who received SRS with those who received combined SRS and WBRT [17]. The SRS arm

Table 1
Patient and study characteristics.

Study	CEBM Level of Evidence	Arm	*n*	No. of lesions	Median Age (years)	Median FU (mos.)	BrM Histology	DS-GPA	ICI	1-Year OS (%)	1-Year LC (%)	1-Year RBC (%)	RN Lesions (n)	Median OS (mos.)	Definitions
Mathew et al., 2013 [30]	2b	Total	25	75	62	6	MBM	NR	CTLA-4	32.6	40.0	16.0	NR	8.3	*LC*: 25% increase in lesion size and MacDonald Criteria [60]; *RBC*: appearance of new brain metastases
Silk et al., 2013 [37]	2b	Total	17	NR	56.6	NR	MBM	0–1: 25%; 2: 39.3%; 3: 25%; 4: 10.7%	CTLA-4	82.3	NR	NR	NR	19.9	NA
Ahmed et al., 2016 [38]	2b	Total	26	73	54.5	15.1	MBM	1–2: 27%; 3–4 (19%)	PD-1	74.7	82.0	45.9	NR	12.0	*LC*: RECIST criteria [58]; *RBC*: new BrM or leptomeningeal enhancement outside SRS field
Kiess et al., 2015 [39]	2b	ICI after SRS	19	47	57	22	MBM	3	CTLA-4	56.0	87.0	36.0	NR	18.0	*LC*: lesion recurrence within SRS field; *RR*: lesion recurrence outside SRS field
		Concurrent	15	37						65.0	100.0	31.0	NR	19.5	
		ICI before SRS	12	29						50.0	89.0	8.0	NR	11.5	
Schoenfeld et al., 2015 [31]	2b	ICI after SRS	5	13	57	NR	MBM	NR	CTLA-4	NR	NR	NR	NR	26	NA
		Concurrent	4	10						NR	NR	NR	NR	NR	
		ICI before SRS	7	18						NR	NR	NR	NR	6	
Qian et al., 2015 [40]	2b	Non-concurrent	22	253	61.4	15.5	MBM	3	CTLA-4 or PD-1	44.4	NR	NR	NR	NR	NA
		Concurrent	33	313	61.1			2		62.5	NR	NR	NR	NR	
Ahmed et al., 2017 [41]	2b	Total	17	49	60	8.7	NSCLC	0–1.5: 59%; 2–3: 41%	PD-1	40.0	96.0	0.0	NR	5.6	*LC*: iRANO criteria [59]; *RBC*: new brain metastases or leptomeningeal enhancement outside SRS field
Anderson et al., 2017 [42]	2b	Total	11[a]	23	67	9.2	MBM	3	PD-1	NR	NR	NR	0	NR	NA
Choong et al., 2017 [43]	2b	Total	39[a]	NR	64.3	8.6	MBM	NR	CTLA-4 or PD-1	54.9	NR	NR	5	11.1	NA
Cohen-Inbar et al., 2017 [44]	2b	ICI after or during SRS	32[a]	160	62	7.9	MBM	0–1: 2.5%; 2: 53%; 3: 18.8%; 4: 15.6%	CTLA-4	59.0	54.4	25.8	31	13.8	*LC/RBC*: progression on MRI
		ICI before SRS	14[a]	72	62.7			0–1:14.3%; 2: 64.3%; 3: 0%; 4: 21.4%		33.0	16.5	26.8	7	6.4	
Gaudy-Marqueste et al., 2017 [45]	2b	ICI after SRS	43	NR	NR	NR	MBM	NR	CTLA-4 or PD-1	52.4	NR	NR	NR	NR	NA
Patel et al., 2017 [32]	2b	Total	20	50	56.5	7.3	MBM	1: 10%; 2: 35%; 3: 30%; 4: 25%	CTLA-4	37.1	71.4	12.7	NR	8.0	*LC*: progression on MRI; *regional brain control*: new enhancing lesion(s) outside of SRS field
Skrepnik et al., 2017 [46]	2b	Total	25	58	68.5	22.7	MBM	NR	CTLA-4	83.0	94.8	72.0	12	36	*LC/RBC*: RECIST 1.1 [58]
Williams et al., 2017 [47]	1b	Total	11	22	57	10.5	MBM	NR	CTLA-4	60.0	NR	NR	0	Not reached	*LC*: RECIST 1.1 [58] and irRC [61]
Yusuf et al., 2017 [48]	2b	Concurrent	12	41	65	7	MBM	NR	CTLA-4 or PD-1	45.0	87.6	46.4	2	11.9	*LC*: RECIST 1.1 [58], growth on MRI, lesion requiring additional SRS; *RBC*: new brain metastases after SRS on imaging
		Non-concurrent	6	18	59					21.5	NR	0.0	0	7.1	
Acharya et al., 2017 [49]	2b	Total	18[a]	48	61	8.9	MBM	1: 6%; 2: 28%; 3: 39%; 4: 0%	CTLA-4 and/or PD-1	58.5	85.0	60.0	NR	28.9	*LC*: increase in brain metastases size, allowing for radionecrosis and PP on pathology and imaging

(*continued on next page*)

Table 1 (*continued*)

Study	CEBM Level of Evidence	Arm	*n*	No. of lesions	Median Age (years)	Median FU (mos.)	BrM Histology	DS-GPA	ICI	1-Year OS (%)	1-Year LC (%)	1-Year RBC (%)	RN Lesions (n)	Median OS (mos.)	Definitions
Chen et al., 2018 [33]	2b	ICI after SRS	30	60	NR	9.2	MBM, NSCLC, RCC	NR	CTLA-4 and/or PD-1	63.6	NR	NR	NR	NR	*LC*: pathologic confirmation or radiographic progression of previously treated brain metastases
		Concurrent	28	56	NR					77.9	88.0	NR	NR	NR	
		ICI before SRS	23	66	NR					50.7	NR	NR	NR	NR	

Abbreviations: brain metastases; BrM: brain metastases; CEBM: Centre for Evidence-Based Medicine; CTLA-4: cytotoxic t-lymphocyte-associated protein 4; FU: follow-up; Gy: gray; ICI: immune checkpoint inhibitor; iRANO: immune response assessment in neuro-oncology; irRC: immune-related response criteria; LC: local control; LR: local recurrence; MBM: melanoma brain metastases; *n*: number of patients; NA: not applicable; No.: number; NR: not reported; NSCLC: non-small cell lung cancer; OS: overall survival; PD-1: programmed cell death protein 1; PP: pseudoprogression; RBC: regional brain control; RCC: renal cell carcinoma; RN: radionecrosis; RR: regional recurrence; SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy.

[a] Includes patients who received WBRT prior to SRS.

reported a 1-year LC rate of 72.8%, while similar to our findings for non-concurrent therapy, concurrent therapy may result in improved rates of 1-year LC. While our LC analysis did not reach statistical significance, the large differences between these groups and a *p*-value of 0.09 may indicate a trend toward significance that may be seen as more data becomes available, although this is viewed as hypothesis generating.

Overall rates of 1-year OS are also favorable at 56.7%, and there appears to be synergy between ICI and SRS with concurrent versus non-concurrent therapy (Fig. 2). This is similar to the findings of Yusuf et al., where patients received ipilimumab or pembrolizumab and were treated to a median SRS dose of 18 Gy either concurrently or non-concurrently [48]. Overall survival at 1-year was 21.5% and 45% in the non-concurrent and concurrent groups, respectively.

While it had long been believed that the brain is "immunologically privileged," recent discoveries, such as the ability of activated T-cells to cross the blood–brain barrier (BBB) and the presence of lymphatic vessels in the central nervous system have demonstrated that the brain has the potential to communicate with the immune system [50–52]. Additionally, studies have demonstrated that SRS increases the degree and duration of BBB permeability when compared to conventional RT [53–55]. The administration of ablative doses of RT has been shown to increase CD8+ T-cell activity against primary and distant metastases [19], enhance tumor antigen presentation and tumor-specific T-cell activation [20], and decrease the fraction of FOXP3+ regulatory T-cells, all of which enhance anti-tumor immunity [56]. Several tumors are capable of activating immune-checkpoint pathways, evading the host's immune system [57]. Multiple studies combining SRS with ICI have demonstrated marked reductions in primary tumor volume as well as abscopal effects [57]. Both local toxicities, such as radionecrosis and intracranial hemorrhage; and systemic toxicities, such as nausea, vomiting, and hepatitis, are possible (Supplementary Table 4).

In 2015 Kiess et al. published a retrospective study that divided 46 patients with melanoma BM who were treated with SRS and ipilimumab into 3 groups – SRS before ipilimumab (SRS before first does of ipilimumab), SRS concurrent with ipilimumab (SRS between does of ipilimumab or <1 month after the last dose of ipilimumab), and SRS after ipilimumab (SRS >1 month after the last dose of ipilimumab) [39]. There was a survival advantage for patients receiving concurrent ICI and SRS or SRS before ICI with a 1-year OS of 65% and 56%, respectively, compared to the 40% seen in the SRS after ICI group. RBC at 1-year was 31% in the concurrent ICI and SRS group and 36% in the SRS before ICI group when compared to the SRS after ICI group 1-year RBC was 8% ($p < 0.01$). These results were among the first supporting the notion of an abscopal-like effect in response to ICI and SRS when SRS is given concurrently or prior to ICI administration, our analysis revealed similar findings as shown in Supplementary Figs. 5 and 6.

In 2017 Cohen-Inbar et al. published a similar study where patients with BM were treated with SRS and ipilimumab [44]. Patients were divided into 2 groups, SRS administration during or prior to ipilimumab and SRS administration after ipilimumab. Survival at 1-year was 59% for the former and 33% for the latter; additionally, local recurrence free duration was significantly higher in the ICI after or during SRS group than in the ICI before SRS group ($p = 0.005$). While there was a clear LC advantage in the former, this group also experienced a higher incidence of treatment-related complications. Our findings are similar in patients receiving anti-CTLA-4 therapy, as shown in Supplementary Table 4 and Fig. 4.

Multiple phase 1 and 2 clinical trials are planned or are currently underway that will further explore the synergy of SRS and ICI in the treatment of BM, as shown in Supplementary Table 5.

Table 2
Treatment characteristics.

Study	Median Dose/Fx (Gy)	BED_{10}	GTV (cm^3)	Largest Dimension (cm)	Number of Lesions (median)	SRS Platform
Mathew et al., 2013 [30]	20 (15–20)	60	0.6	≤3	3	Gamma Knife
Silk et al., 2013 [37]	NR (14–24)	NR	NR	NR	NR	NR
Ahmed et al., 2016 [38]	21 (16–24)	65.1	0.22	NR	2	Brainlab Novalis LINAC
Kiess et al., 2015 [39]	21 (15–24)	65.1	NR	0.8	2	Brainlab Novalis LINAC
Schoenfeld et al., 2015 [31]	22 (18–24)	70.4	NR	NR	NR	Cyberknife
Qian et al., 2015 [40]	20 (12–24)	60	0.11	NR	NR	Gamma Knife
Ahmed et al., 2017 [41]	24 (18–24)	81.6	0.19	NR	3	Brainlab Novalis LINAC
Anderson et al., 2017 [42]	21 (18–21)	65.1	NR	1.0	1.5	NR
Choong et al., 2017 [43]	NR	NR	NR	NR	NR	LINAC or Gamma Knife
Cohen-Inbar et al., 2017 [44]	20 (14–22)	60	NR	0.5	5	Gamma Knife
Gaudy-Marqueste et al., 2017 [45]	NR	NR	NR	NR	NR	Gamma Knife
Patel et al., 2017 [32]	NR	NR	1.1	NR	NR	LINAC
Skrepnik et al., 2017 [46]	21 (16–24)	65.1	NR	NR	NR	LINAC
Williams et al., 2017 [47]	24 (15–24)	81.6	NR	NR	2	NR
Yusuf et al., 2017 [48]	18 (13–24)	50.4	0.19	0.8	NR	LINAC or Cyberknife
Acharya et al., 2017 [49]	20 (15–24)	60	0.33	NR	4	Gamma Knife
Chen et al., 2018 [33]	20 (16–25)	60	NR	NR	NR	LINAC or Cyberknife

Abbreviations: BED: biologically effective dose; LINAC: linear accelerator; NR: not reported; SRS: stereotactic radiosurgery.

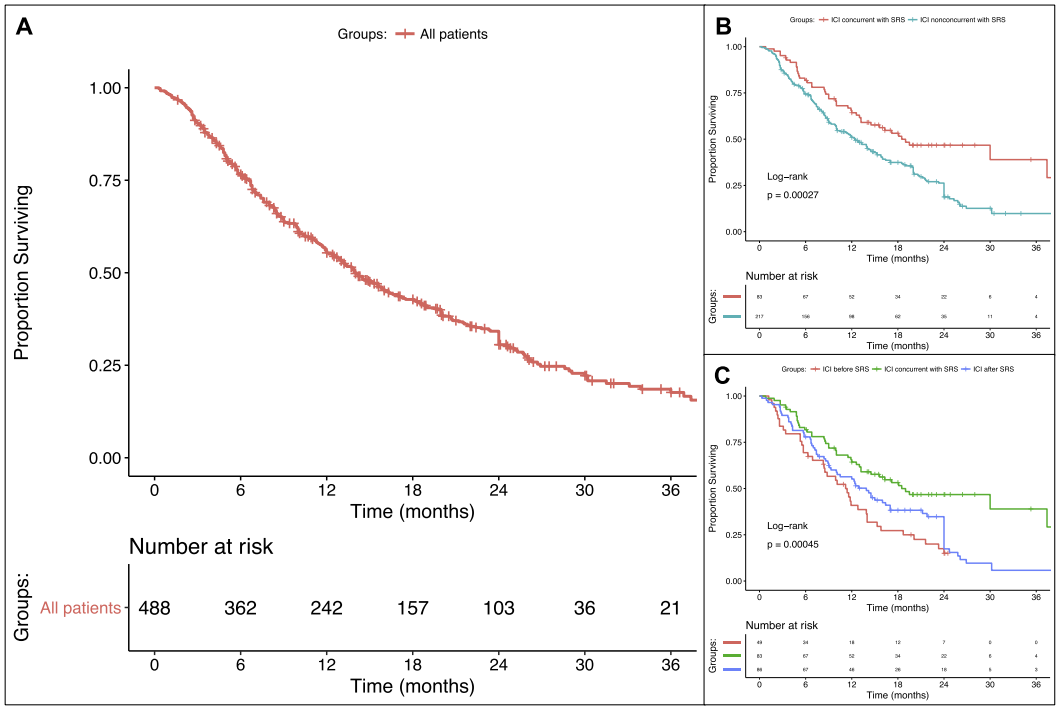

Fig. 2. 1-Year Overall Survival Kaplan-Meier Analysis. Kaplan-Meier curves for pooled analysis of survival data in each of the studies with corresponding risk tables below. Pane A represents a master survival curve including all patients with data available. Pane B compares survival data for concurrent ICI and SRS (red) with non-concurrent ICI and SRS (blue); log-rank test demonstrated a statistically significant difference favoring concurrent administration ($p = 0.00027$). Pane C compares survival data for concurrent ICI and SRS (green), ICI before SRS (red), and ICI after SRS (blue); log-rank test demonstrated a statistically significant difference favoring concurrent ICI and SRS and ICI administration after SRS compared to ICI administration before SRS ($p = 0.00045$). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

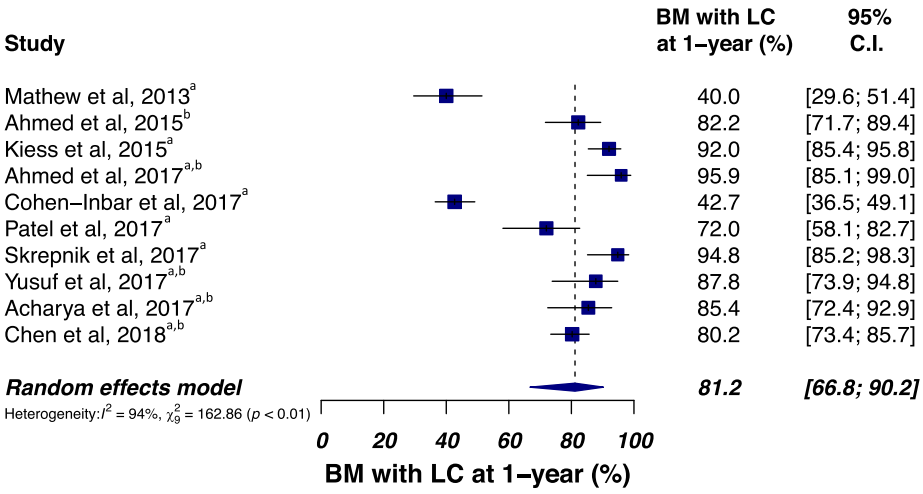

Fig. 3. 1-Year Local Control Forest Plot. Weighted random effects meta-analysis of 1-year LC. The proportion of lesions that exhibited LC at 1-year in each included study arm and their associated 95% CI with heterogeneity analysis included. Results indicate that 1-year LC is approximately 81.2%. (a = use of anti-CTLA-4 agent; b = use of anti-PD-1 agent; BM = brain metastases; LC = local control).

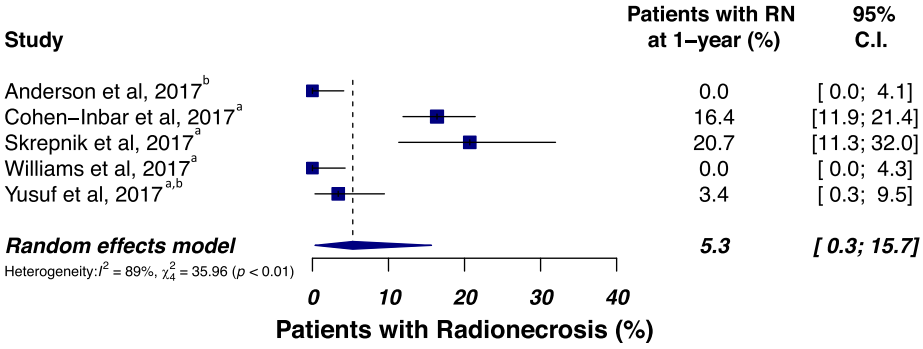

Fig. 4. Radionecrosis Incidence Forest Plot. Weighted random effects meta-analysis of incidence of radionecrosis. The proportion of lesions that exhibited radionecrosis in each included study arm and their associated 95% CI with heterogeneity analysis included. Results indicate that the overall incidence of radionecrosis is approximately 5.3%. (a = use of anti-CTLA-4 agent; b = use of anti-PD-1 agent; BM = brain metastases; RN = radionecrosis).

The Australian ABC-X study will assess the response to melanoma BM when treating with both ipilimumab and nivolumab and will then add SRS if disease progression occurs on ICI. Two recently published studies suggested that targeting the PD-1/PD-L1 axis or adding ipilimumab has a more profound impact on survival than ipilimumab monotherapy [14,59]. A similar trial assessing SRS and this ICI combination in NSCLC BM is presently recruiting [17].

Our results represent the largest meta-analysis to evaluate the impact of ICI on SRS for any tumor site. We recommend that clinicians cautiously continue to treat these patients with combination of SRS and ICI, and should strongly consider administering these therapies within one month of one another if the otherwise presumed risk of toxicity is low (i.e. low tumor volume, etc.). Additionally, many tumors are capable of inherent immunosuppression, which often manifests as decreased T-cell priming. As a result, these tumors will likely be less responsive to immune checkpoint inhibition. The half-life of these agents must also be considered when evaluating the durability of the effects seen with this treatment combination.

It is important to note that while our analysis does appear to demonstrate some benefits to this particular timing combination, there was limited data available to fully assess the risk of radionecrosis. Furthermore, the findings of our analysis are hypothesis-generating and require randomized prospective trials for further validation.

This work has several limitations. First, these studies were conducted at multiple different international institutions with differing treatment guidelines. Patients likely had differences in their comorbidities, staging, work-up, and selection criteria. Next, during the time period that these studies were conducted there have been advances in ICI therapy with changes in recommendations for mono and dual therapy. Next, data regarding radionecrosis rates were only available in 5/17 studies [42,44,46–48], which amounted to 335/1570 (21.3%) of all lesions, thus preventing an analysis with respect to ICI and SRS timing. Furthermore, an analysis of certain covariates that may have an impact on the incidence of radionecrosis, such as SRS dose, size of BM, and number of BM was not possible due to a limited number of studies reporting each of these variables. Only 1/17 studies [47] were prospective in nature; these studies tend to code variables, such as toxicity, in a more precise manner than their retrospective counterparts due to strict follow-up requirements.

Additionally, LC and RBC were defined differently at the various institutions. While the Response Evaluation Criteria in Solid Tumors 1.1 criteria [60] were the most commonly used; the Immune Response Assessment in Neuro-oncology criteria [61], MacDonald criteria [62], Immune-Related Response criteria [63], and institution specific guidelines involving imaging findings and pathologic studies were all used to define local and RBC. Institutional definitions of concurrent and non-concurrent therapy also

differed in several of the included studies. In the future, standardized criteria for the reporting of local and elsewhere tumor control, as well as uniform timing intervals between these two therapies will be critical. Furthermore, while we have patient-level survival data, but we lack other covariates; therefore, we could not further adjust for covariates, such as performance status, age, and comorbidities prior to performing the survival analysis. This is particularly true when conducting a meta-analysis that contain single arm and non-randomized two arm studies that do not adjust for patient-level covariates when comparing treatment arms. Finally, a statistical analysis of Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) was not possible, as multiple tumor histologies were included [64,65]. While overall survival is an important outcome measure, DS-GPA is more reflective of modern outcomes and treatment paradigms. Taken together, our analysis and findings are hypothesis-generating in nature and require robust prospective randomized trials to further investigate these results.

Conclusion

Concurrent administration of ICI and SRS does not appear to be associated with untoward rates of radionecrosis with a possible survival advantage observed. Additionally, enhanced RBC within the brain with excellent rates of 1-year LC may be associated with concurrent therapy. Multiple ongoing and planned prospective trials will further investigate these hypotheses.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.08.025.

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