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Date:
2025

Citation:
Mittal, A., Green, A., Fitzgerald, X., Spain, L., Phillips, C., Wirth, A., Haghighi, N., Plumridge, N., Li, M. & Sia, J. (2025). Impact of stereotactic radiosurgery timing relative to immune checkpoint blockade administration on brain metastasis disease and radionecrosis outcomes. Neuro-Oncology Advances, 7 (1), https://doi.org/10.1093/noajnl/vdaf130.

Neuro-Oncology Advances
7(1), vdaf130, 2025 | https://doi.org/10.1093/noajnl/vdaf130 | Advance Access date 18 June 2025

# Impact of stereotactic radiosurgery timing relative to immune checkpoint blockade administration on brain metastasis disease and radionecrosis outcomes

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**Abstract**

**Background**. Whether stereotactic radiosurgery (SRS) and immune checkpoint blockade (ICB) for brain metastases (BrM) have a time window for synergistic efficacy and toxicity is unclear. We examined this question in a large, contemporary cohort of patients who received concurrent SRS and ICB.

**Methods**. Patients who received SRS for intact BrM within 1 month before to 6 months after an ICB cycle at a single center from 2018 to 2023 were included if they had no prior whole-brain radiotherapy or SRS to the same BrM. Intracranial progression-free survival (icPFS), local control (LC), distant brain control (DBC), overall survival (OS), and radionecrosis were analyzed by Kaplan–Meier and log-rank methods. Cox regression was used for uni/multivariable analysis (UVA/MVA).

**Results**. A total of 419 BrM, 170 treatment episodes, and 134 patients were analyzed. In total, 43% and 40% of patients had melanoma and non-small cell lung cancer. A shorter SRS-ICB interval significantly correlated with improved icPFS, LC, and OS, but not DBC. This was true when analyzed as either a categorical or continuous factor. On MVA, SRS-ICB interval outperformed all factors including histology, ICB type, and de novo BrM status in predicting icPFS ($P = .030$), LC ($P = .042$), and OS ($P = .033$). In the absence of corticosteroids, pre-SRS lymphocyte counts correlated with improved LC ($P = .02$). Radionecrosis was not associated with SRS-ICB interval, but with BrM size and number of ICB cycles received prior to SRS.

**Conclusion**. Delivering SRS closer to ICB cycles was associated with improved icPFS, LC, and OS without affecting radionecrosis rates. This may present a therapeutic opportunity to improve BrM outcomes.

## Key Points

- Shorter intervals between stereotactic radiosurgery (SRS) and immune checkpoint blockade correlated with better brain metastases (BrM) local control (LC) and OS.
- Pre-SRS lymphocyte count correlated with LC in patients, not on corticosteroids.
- SRS timing did not affect radionecrosis risk, which was more closely linked to BrM size.

The management of brain metastases (BrM), a significant oncological burden affecting nearly a third of all patients with solid cancers, has seen significant flux in recent years.[1] Stereotactic radiosurgery (SRS), a highly precise form of ablative radiation therapy (RT) that targets individual BrM while sparing surrounding brain tissue, has largely supplanted whole-brain RT and is now widely adopted as standard-of-care for limited-volume BrM.[1] More recently, the increasing

## Importance of the Study

This study highlights the potential importance of stereotactic radiosurgery (SRS) timing relative to immune checkpoint blockade (ICB) administration for brain metastases (BrM) by performing a comprehensive analysis of the largest cohort of patients receiving concurrent SRS and ICB in the literature. By focusing on a defined timeframe for SRS and ICB administration, we found a significant improvement in BrM control and patient survival, without an increased risk of radionecrosis, when SRS was delivered closer to ICB dosing. This timing effect was robust across various analyses and outperformed other factors such as histology and ICB type. This study raises a possible optimal time window between SRS and ICB for therapeutic synergy, supporting the need for further investigation in prospective trials. Overall, these findings have a high translational potential as a strategy to improve outcomes for patients with BrM receiving these therapies concurrently.

use of immune checkpoint blockade (ICB) for metastatic cancer has also revealed the exciting possibility of reprogramming the BrM immune microenvironment to durably control BrM, albeit currently in a limited subset of patients with melanoma and non-small cell lung cancer (NSCLC).[2,3]

In this context, the effect of combining SRS and ICB is unclear. Multiple retrospective studies have suggested their concurrent administration is associated with improved survival and, intriguingly, improved control of not only SRS-treated BrM but also of those elsewhere in the brain, compared to when SRS and ICB are given temporally apart.[4–6] This clinical observation is consistent with pre-clinical and translational data suggesting RT can evoke and support anti-tumor T cell responses which are further amplified by ICB, resulting in improved tumor eradication, both within and beyond the irradiated field (the latter commonly called the radiation abscopal effect).[7,8] While most of this work has been in the extracranial setting, similar observations of immune responses are emerging for SRS in BrM.[9,10] In contrast, data on the toxicity risk of radionecrosis with combined SRS and ICB are conflicting.[11–13]

Importantly, the interpretation of current retrospective data is limited by the considerable heterogeneity of study parameters.[4] Firstly, definitions of "concurrent" and "non-concurrent" administration of SRS and ICB vary widely and may not reflect the time windows of RT-induced T cell responses and ICB-mediated T cell reinvigoration. The inclusion of patients who received SRS at a substantial period prior to ICB also introduces survivor bias, whereby patients must survive long enough to receive subsequent ICB therapy. Many of these studies employed ICB strategies that are now outdated and considered sub-optimal, such as the use of ipilimumab (anti-CTLA-4) monotherapy without combined PD-1 blockade, or ICB agents as last-line therapy where the modulated tumor immune microenvironment is less favorable for response. Therefore, it remains uncertain, particularly in the modern landscape of BrM management, if SRS and ICB can beneficially interact.

To examine this question more deeply, we interrogated a large, contemporary cohort of patients with BrM who received "concurrent" SRS and ICB within a period when synergistic biological activities of both modalities likely overlap. Our hypothesis was that an anti-tumor interplay between SRS and ICB, if present, would be time-dependent, thus influencing clinical outcomes based on the timing of SRS relative to ICB administration.

## Materials and Methods

### Patients

Patients receiving SRS for BrM at the Peter MacCallum Cancer Centre (PMCC) between August 2018 and November 2023 were screened. Eligible patients received SRS between 1 month prior to (before the first ICB cycle) and 6 months following administration of an ICB cycle. The former limit was to minimize survivor bias while allowing overlap of SRS-induced effects and ICB and the latter limit (approximately 5–6 half-lives of common ICB agents) was to capture residual ICB activity potentially interacting with SRS.[5,6,14] Patients with previous whole-brain RT, repeat SRS to the same BrM, and post-operative cavity SRS were excluded.

Information on patients, tumors, treatment details, and clinical outcomes were extracted from electronic medical records. The interval between SRS and ICB was the number of days between the start of SRS (if fractionated) and the dosing of the nearest ICB cycle (whether before or after SRS). Use of corticosteroids at the time of SRS was noted and doses were converted to the equivalent of oral dexamethasone. Pre-SRS extracranial disease (ECD) status was based on radiology reporting of the most recent scan preceding SRS. Where there was ambiguity, structural scans were interpreted according to RECIST version 1.1 criteria.[15] Performance status was graded using the Eastern Cooperative Oncology Group (ECOG) system. Where patients received more than one type of ICB regimen over time, the regimen nearest to the SRS treatment episode was recorded. Generally, patients received 3 monthly magnetic resonance imaging (MRI) of the brain for surveillance following SRS. The conduct of the study including waiver of informed consent was approved by the PMCC Human Research Ethics Committee was obtained for this study.

### Endpoints

Intracranial progression-free survival (icPFS) was defined as the time from SRS completion to the first event of local failure (a progressive disease in the SRS-treated BrM, defined as a 20% increase in the longest lesion diameter), distant brain failure (progressive disease at intracranial sites that did not receive SRS, as determined by the

RANO-BM criteria[16]), or death from any cause. Local control (LC) was the time from SRS completion to local failure, defined as a 20% increase in the longest lesion diameter on an MRI of the brain. Distant brain control (DBC) was defined as the time from SRS completion to distant brain failure, and overall survival (OS) was the time from SRS completion to death from any cause. Radionecrosis was either diagnosed histologically, if resected, or radiologically based on MRI appearances and temporal characteristics in a multi-disciplinary setting. In brief, radiological features suggestive of radionecrosis vs local failure include: thin vs nodular T1 enhancing rim, crossing vs respecting anatomical boundaries, presence vs absence of central diffusion restriction and/or magnetic susceptibility, non-elevated vs elevated perfusion characteristics, and changing *vs* concentric enlargement of lesion shape over time.[17,18] Where an observation period of lesion stability or regression was required, the date of radionecrosis diagnosis was made retrospectively.

### Treatment and Follow-Up

All patients underwent MRI for SRS planning and follow-up. SRS was delivered either using a Varian TruBeam™ linear accelerator (LINAC) with ExacTrac image guidance, or the Elekta Gamma Knife™ Icon. A 1 mm and 0 mm PTV expansion was applied for LINAC and GammaKnife-based SRS respectively. SRS dose-fractionation was prescribed at the discretion of the treating radiation oncologist based on BrM size, whereby BrM larger than 20 mm diameter usually received fractionated SRS. In general, LINAC-based SRS was delivered within 1 week of the SRS-planning MRI, and Gamma Knife-based SRS within 1 day. Follow-up imaging was normally performed every 3 months for at least 2 years. No specific effort was made to coordinate timing between SRS and ICB in our center. Thus, SRS and ICB treatment dates were booked for the earliest availabilities.

### Statistical Analysis

Statistical comparison between groups was performed using the *t* and chi-square tests for continuous and categorical variables, respectively. Median follow-up time was assessed by the reverse Kaplan–Meier method. icPFS, LC, DBC, ECD control, OS, and radionecrosis rates were estimated using the Kaplan–Meier method, calculated from the date of SRS completion and analyzed per-lesion (for LC and radionecrosis), per-treatment episode (for DBC and ECD control; defined by the use of a new SRS-planning MRI) and per-patient (for icPFS and OS). Time-to-event comparison between groups was performed using the log-rank method. Cox proportional hazard regression analysis was used to examine associations between potential prognostic factors with icPFS, LC, DBC, OS, and radionecrosis. The proportional hazards assumption was first confirmed with Schoenfeld residual testing. Because histology is a critical factor to adjust for, it was included in multivariable Cox regression analysis, together with any other factors that were statistically significant in univariable analysis. Timing of SRS relative to ICB administration was categorized into 0–7, 8–30, and 30 + days for plotting in survival curves (7 days being when the ICB antibody plasma concentrations appear to drop most sharply,[19] and 30 days being the most used cutoff in literature[4]) but preferentially analyzed as a continuous variable in Cox regression analysis. To test for possible correlation between BrM local failure events by the patient, a shared frailty model was tested using the *frailtyEM* package in R,[20] where BrM from the same patient was considered a cluster with a gamma frailty distribution. Statistical significance was set at a threshold of $P < .05$.

## Results

### Patient and BrM Tumor Characteristics

134 consecutive patients, 170 treatment episodes, and 419 BrM met the study eligibility criteria. Baseline patient and BrM tumor characteristics are outlined in Table 1. The median patient age was 64 years and 85% were ECOG 0-1. The most common histology types were melanoma and NSCLC (43% and 40%, respectively). A small subset (7.5%) of patients grouped as having "other" histology comprised patients with small cell lung cancer, transitional cell carcinoma, colorectal carcinoma, salivary ductal carcinoma, head and neck squamous cell carcinoma, and carcinoma of unknown primary. A total of 30% of BrM were diagnosed de novo (ie at the time of initial cancer diagnosis and thus naïve to treatments). The median BrM diameter was 7 mm (range 1–42 mm, interquartile range [IQR] 4–13 mm) and 75% of BrM received 20 Gy in 1 fraction. 78% of patients had received ICB prior to SRS. The median time between SRS and the nearest ICB cycle was 13 days (range 0–179 days, IQR 7.0–26.5 days). The most common ICB regimens were combined ipilimumab/nivolumab (33.9%) and pembrolizumab (31.3%). Other than durvalumab regimens, which were used almost exclusively for NSCLC, all other ICB regimens were used for multiple cancer types (Supplementary Table S1). Due to known differences in activity between anti-PD(L)-1 monotherapy and dual anti-PD-1/anti-CTLA-4 therapy against BrM,[21] ICB regimens were categorized as such for analyses below.

Supplementary Tables S2–S4 describe patient, SRS treatment and BrM tumor characteristics by time interval between SRS and nearest ICB administration. Patient characteristics were balanced between subgroups (Supplementary Table S2). The number of BrM for SRS and the time between planning MRI and SRS delivery per treatment episode were comparable between subgroups (Supplementary Table S3). There were more de novo BrM and BrM receiving combination ipilimumab/nivolumab in the 0–7 days subgroup, but other characteristics, including BrM size, were not significantly different (Supplementary Table S4). These factors were adjusted in the multivariable analysis below.

The median follow-up time was 24.6 months. The 1-year LC, DBC, and OS rates for the entire cohort were 70.1%, 38.7%, and 50.8%. The 2-year rates were 62.1%, 21.5%, and 28.5%, respectively. The 2-year OS rates for the de novo melanoma and NSCLC subgroups were comparable to the literature at 44.4% and 27.4%, respectively.[2,3]

**Table 1.** Baseline Patient and BrM Tumor Characteristics

| Patient characteristics (*n* = 134) | |
|---|---|
| Age, years (median [IQR]) | 63.8 [54.9, 72.6] |
| Sex (%) | |
| Male | 89 (66.4) |
| Female | 45 (33.6) |
| ECOG (%) | |
| 0–1 | 114 (85.1) |
| 2–3 | 20 (14.9) |
| Histology (%) | |
| Breast | 3 (2.2) |
| Melanoma | 58 (43.3) |
| NSCLC | 54 (40.3) |
| Renal cell | 9 (6.7) |
| Other | 10 (7.5) |
| ECD status (%) | |
| CR/PR/SD | 38 (28.4) |
| PD | 96 (71.6) |
| BrM characteristics (*n* = 419) | |
| Histology (%) | |
| Breast | 19 (4.5) |
| Melanoma | 176 (42.0) |
| NSCLC | 168 (40.1) |
| Renal cell | 30 (7.2) |
| Other | 26 (6.2) |
| De novo diagnosis (%) | |
| Yes | 124 (29.6) |
| No | 295 (70.4) |
| BrM size (mm), median [IQR] | 7 [4, 13] |
| SRS type (%) | |
| LINAC | 305 (72.8) |
| Gamma Knife | 114 (27.2) |
| SRS dose (%) | |
| 14–18 Gy/1 fraction | 14 (3.3) |
| 20 Gy/1 fraction | 314 (74.9) |
| 21–27 Gy/3 fractions | 75 (17.9) |
| 25–30 Gy/5 fractions | 14 (3.3) |
| 37.5 Gy/15 fractions | 2 (0.5) |
| SRS-ICB sequencing | |
| SRS before ICB start | 94 (22.4) |
| SRS after ICB start | 325 (77.6) |
| Time between SRS and nearest ICB cycle (days), median, [IQR] | 13.0 [7.0, 26.5] |
| ICB regimen | |
| Atezolizumab | 53 (12.6) |
| Durvalumab | 10 (2.4) |
| Ipilimumab/nivolumab | 142 (33.9) |
| Nivolumab | 80 (19.1) |
| Pembrolizumab | 131 (31.3) |
| Pembrolizumab/durvalumab | 3 (0.7) |
| Number of ICB cycles prior to SRS, median [IQR] | 3 [1, 8] |

**Abbreviations:** IQR: interquartile range; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

## Timing of SRS Relative to Administration of Nearest ICB Cycle

We observed that a shorter interval between delivery of SRS and administration of the nearest ICB cycle significantly correlated with improved icPFS (1-year icPFS for 0–7 vs 8–30 vs 30 + days: 36.8% vs 23.8% vs 25.0%, *P* = .022), LC (1-year LC: 88.7% vs 56.7% *vs* 67.4%, *P* < .0001) and OS (1-year OS: 67.5% vs 47.0% vs 33.3%, *P* = .041), but not DBC or ECD control (Figure 1a–d).

In univariable analysis, a closer interval between SRS and ICB (both as categorical and continuous variables), better ECOG performance status, and lower dexamethasone-equivalent corticosteroid dose at the time of SRS were associated with improved icPFS (Table 2). When these factors were accounted together and adjusted for histology in a multivariable model, SRS timing remained significantly associated with icPFS (HR 1.01, *P* = .030) alongside ECOG performance status (HR 1.76, *P* = .031) (Table 2). For LC, the SRS-ICB interval also emerged as the only significant predictive factor on multivariable analysis (HR 1.01, *P* = .042), outperforming the receipt of dual anti-PD-1/anti-CTLA-4 therapy (compared to anti-PD[L]-1 monotherapy), de novo BrM status, and other factors (Supplementary Table S5). Timing of SRS also correlated with OS on univariable analysis, again both as categorical and continuous variables, together with ECOG performance status and dexamethasone-equivalent dose at the time of SRS (Table 3). In multivariable analysis, timing of SRS maintained statistical significance (HR 1.01, *P* = .033) alongside dexamethasone dose (HR 1.06, *P* = .039) (Table 3). Interestingly, whether SRS was given pre- or post-ICB initiation (before or after the first ICB cycle) did not influence overall LC or OS (Supplementary Table S5 and Table 3), even if the analysis was restricted to the same 30-day timeframe pre- or post-ICB initiation (*P* = .755 and *P* = .841 for LC and OS). Whether SRS was given before or after the nearest ICB cycle (as opposed to pre- or post-ICB initiation) also did not matter (0–7 days: *P* = .396 and *P* = .237 for LC and OS; 8–30 days: *P* = .343 and *P* = .815, respectively).

Given the striking impact of SRS timing on LC, we performed an exploratory analysis of its influence in major subsets of interest. Notably, the impact of SRS timing on LC was seen in melanoma and NSCLC BrM (*n* = 176 and 168, respectively), but not those of other histology (*n* = 75), and appeared to be most strongly driven by melanoma BrM receiving SRS with combined ipilimumab/nivolumab (Supplementary Table S6). We found no suggestion that the LC of individual BrM in each treatment episode was interrelated rather than independent, as the number of treatment episodes yielding discordant LC and local failure events between individual BrM was the same compared to those yielding concordant events. Nevertheless, to confirm our observed trends, we further analyzed the impact of SRS timing on LC of all BrM in each treatment episode (rather than per lesion) and accordingly found it to be the only significant predictive factor in univariable analysis (HR 1.01, *P* = .04). We also tested the addition of a patient-specific random effect to account for possible correlation of local failure events within the same patient and found the impact of SRS timing on LC to remain strong (HR 1.03, *P* < .001, in a multivariable model of the same covariates as in Table 2). Altogether, these findings suggest that SRS may work more effectively in controlling BrM when given closer to the administration of an ICB cycle, with a possible related effect on survival.

### Impact of Pre-SRS Lymphocyte Count

As an interaction between SRS and ICB will likely be immune-mediated, pre-SRS lymphocyte counts were examined to determine if they impacted clinical outcomes. 141 of 170 treatment episodes (for 366 BrM) in the overall cohort had contemporaneous blood tests within 30 days prior to SRS available.

The correlation of lymphocyte counts with LC trended towards but did not reach statistical significance in univariable analysis for the overall cohort ($P = .085$). Because corticosteroids can dampen immune responses and ICB efficacy,[22] we attempted to clarify this signal by focusing on patients who were not on corticosteroids at the time of SRS (45 patients, 88 treatment episodes, and 208 BrM). Interestingly, lymphocyte counts emerged in this subset as predictive for LC and remained significantly so when other factors were accounted for in the multivariable analysis (HR 0.47, $P = .02$) (Supplementary Table S7). We did not detect an interaction between lymphocyte counts and the timing of SRS. Lymphocyte counts were not significantly correlated with DBC ($P = .10$) or OS ($P = .14$) in the univariable analysis of this subset of patients not on corticosteroids.

### Radionecrosis

We next examined if giving SRS closer to ICB administration was associated with an increased risk of radionecrosis, alongside improved LC. Overall, the 1- and 2-year all-grade radionecrosis rates for our cohort were 8.3% and 12.0%. In contrast to LC and OS, radionecrosis rates were not affected by the timing of SRS relative to ICB administration (Table 4, Supplementary Figure S1). Rather, the risk of radionecrosis was correlated with BrM size (HR 1.06, $P = .004$) and the cumulative number of ICB cycles received prior to SRS (HR 1.04, $P = .005$) (Table 4). When both factors were analyzed in a multivariable model, BrM size showed a stronger correlation to the risk of radionecrosis than the cumulative number of ICB cycles received prior to SRS (HR 1.05, $P = .04$ vs HR 1.02, $P = .07$) (Table 4).

## Discussion

In this study, rather than comparing to non-concurrent SRS and ICB therapy, we focused exclusively on BrM patients who received both modalities within a timeframe for RT-induced T cell responses and ICB-mediated T cell reinvigoration to likely coincide. Thus, this work uniquely represents an examination of the largest concurrent SRS and ICB cohort in the literature. Even within this stricter time window, we found a significant improvement in control of SRS-treated BrM and survival, without a corresponding increase in the risk of radionecrosis, when SRS was given closer to the administration of an ICB cycle. This correlation held up when timing was analyzed as both continuous and categorical variables, outperforming all other factors including histology, ICB regimen type, and de novo BrM status. Furthermore, BrM size and time from planning MRI to SRS were comparable between subgroups, arguing against the possibility that a longer interval from ICB to SRS reflected a delay in decision for SRS or in SRS planning and treatment. In the subset of patients whose immune responses were not dampened by corticosteroid use, lymphocyte counts at the time of SRS were significantly correlated with improved LC. Remarkably, a significant association between a shorter SRS-ICB interval and improved OS was also observed, which was not explained by differences in either DBC or ECD control. Collectively, these findings suggest a time-sensitive interaction between SRS delivery and ICB dosing that have implications for tumor control and survival.

The observation of a timing effect even within a single half-life of the ICB agent is interesting. While biological half-lives of most ICB agents are measured in weeks, their plasma concentration, and thus by inference intratumoural BrM concentration, drops most sharply within the first week following dosing.[19] However, ICB agents have varying dose- and exposure-response relationships, and their duration of effect depends more primarily on T cell stimulation, which is difficult to measure, than antibody circulating half-lives.[19,23–25] It is therefore complex to speculate on the pharmacokinetics of ICB within BrM tumors and their differential effects on any interaction with SRS. On the SRS side of the equation, pre-clinical and human data in the extracranial setting suggest tumor-directed T-cell responses occur 1–2 weeks post-irradiation, following immediate radiation-induced cell death.[26–28] Noting that the brain has a distinctly regulated immunosurveillance program that was long assumed silent,[21] recent studies on BrM treated with pre-operative SRS followed by planned resection have suggested SRS can also evoke adaptive immune responses in BrM,[9,10] though much remains to be learned. Thus, an overlapping time window of a week for optimal clinical synergy between SRS and ICB, in either sequence, is biologically conceivable.

Until we have randomized data for the addition of SRS to ICB for BrM, it is worth contextualizing these findings in the current knowledge base of this space. A similarly large retrospective study involving 150 patients focusing on SRS and anti-PD(L)-1 therapy for BrM also demonstrated a graduated timing effect between SRS and ICB, whereby patients receiving SRS within 1 biological half-life of the ICB agent (either before or after) had an earlier, more durable, and greater magnitude of BrM size reduction, compared to patients receiving "non-immediate" but "concurrent" SRS and ICB within 5 biological half-lives of the ICB agent.[5] In contrast, patients receiving "non-concurrent" ICB had the poorest intracranial response. OS was also correlated with BrM response in this study. A possible bias in these comparisons is that BrM which developed after the initiation of ICB therapy could reflect a more treatment-resistant biology. Accounting for this, a study of 99 patients restricted investigation to melanoma BrM that developed after at least 2 doses of ipilimumab and found SRS given within 5.5 months from the last ICB

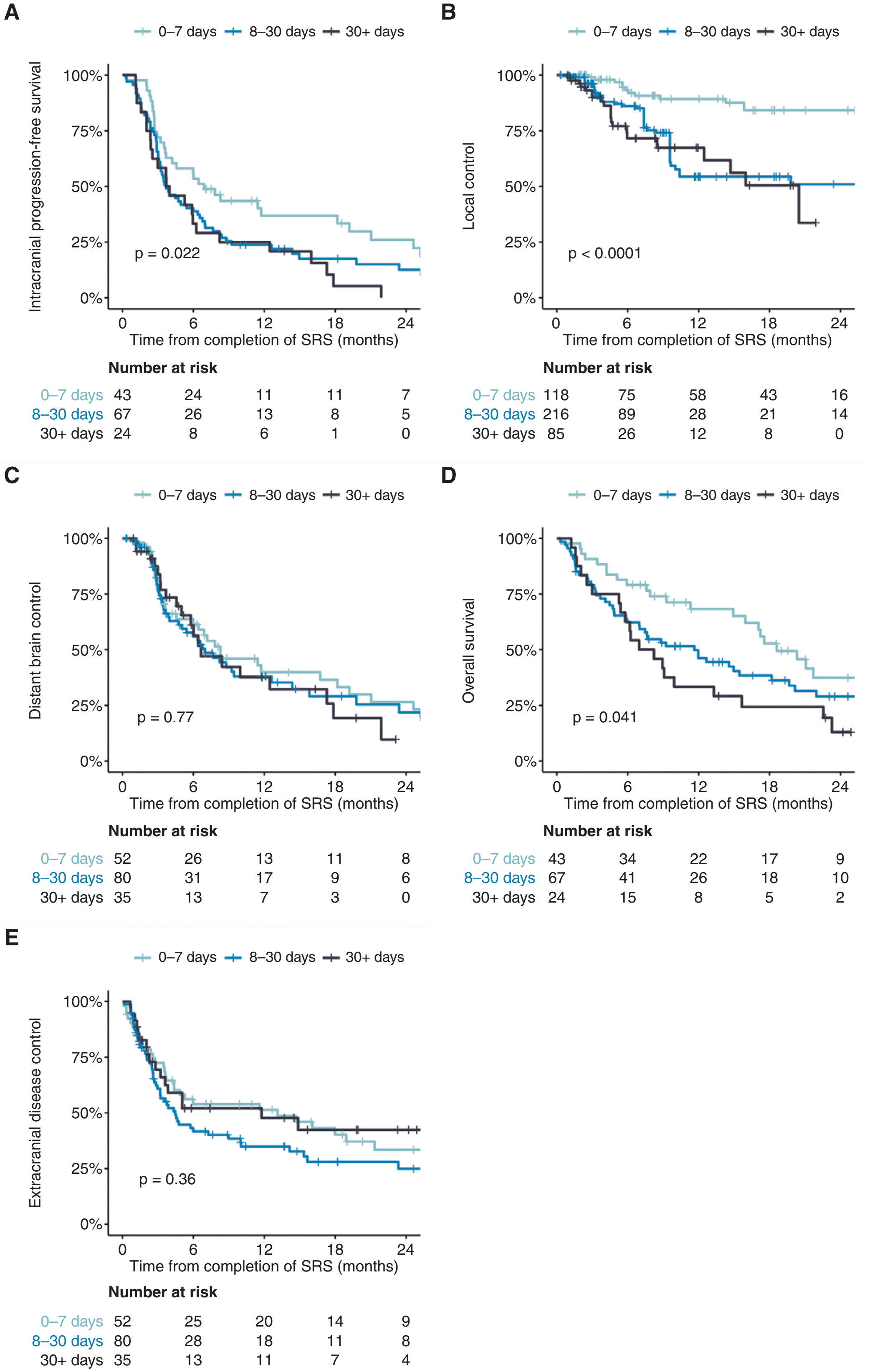

**Figure 1.** (A) icPFS, (B) LC, (C) DBC, (D) OS, and (E) ECD control over time.

**Table 2.** Univariable and Multivariable Analysis of icPFS

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Variable | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age (per year increase) | 1.01 (0.99–1.02) | .422 | | |
| Sex | | | | |
| Male | Reference | | | |
| Female | 1.12 (0.76–1.66) | .557 | | |
| ECOG | | | | |
| 0–1 | Reference | | Reference | |
| 2–3 | 2.01 (1.24–3.27) | **.005** | 1.76 (1.05–2.94) | **.031** |
| Dexamethasone dose (per mg/day increase) | 1.06 (1.02–1.11) | **.005** | 1.04 (1.00–1.09) | .062 |
| Histology | | | | |
| Breast | Reference | | | |
| Melanoma | 0.80 (0.25–2.56) | .702 | 0.96 (0.29–3.16) | .959 |
| NSCLC | 0.94 (0.29–3.03) | .917 | 0.95 (0.29–3.10) | .927 |
| RCC | 0.73 (0.19–2.83) | .647 | 0.90 (0.23–3.55) | .885 |
| Other | 1.76 (0.47–6.52) | .399 | 2.05 (0.54, 7.86) | .295 |
| ICB regimen type | | | | |
| Anti-PD(L)-1 monotherapy | Reference | | | |
| Dual anti-PD-1/anti-CTLA-4 therapy | 0.86 (0.58–1.26) | .425 | | |
| ECD status | | | | |
| CR/PR/SD | Reference | | | |
| PD | 1.32 (0.88–1.98) | .183 | | |
| Number of BrMs | 1.01 (0.99–1.03) | .166 | | |
| Time between SRS and nearest ICB cycle (categorical) | | | | |
| 0–7 days | Reference | | | |
| 8–30 days | 1.63 (1.07–2.50) | **.024** | | |
| 30 + days | 1.99 (1.16–3.43) | **.013** | | |
| Time between SRS and nearest ICB cycle (continuous, per day increase) | 1.01 (1.00–1.01) | **.010** | 1.01 (1.00–1.01) | **.030** |
| SRS-ICB sequencing | | | | |
| SRS before ICB start | Reference | | | |
| SRS after ICB start | 0.87 (0.56–1.38) | .563 | | |
| Number of ICB cycles prior to SRS | 0.99 (0.98–1.00) | .409 | | |

*P* values < 0.05 are bolded.

dose resulted in higher LC and DBC compared to patients who received SRS later.[6] A higher pre-SRS lymphocyte level was associated with better intracranial control in patients receiving early SRS, but not late SRS. An opposite study focused instead on newly diagnosed, ICB-naïve melanoma BrM and found improved DBC and OS when SRS and ICB were given 1–11 days apart, compared to 12–29 days apart.[29] Similarly, neither a de novo BrM status nor the number of ICB cycles received prior to SRS in our current study impacted the effect of SRS timing on LC. Lastly, large multi-center retrospective studies have suggested improved OS with the upfront addition of SRS to ICB, compared to ICB alone.[30–32] Taken together, our results herein further highlight the intriguingly consistent observation in the literature thus far of a timing effect between SRS and ICB on intracranial BrM control and survival, despite the limitations of retrospective studies and heterogeneity of study parameters.[4] A randomized Phase 2 trial of combined ipilimumab and nivolumab, with and without SRS, for patients with melanoma BrM is ongoing and will clarify this observation.[33]

A potential tumor control benefit should be tempered with concern about increased toxicity. Reports on radionecrosis rates after combined SRS and ICB are conflicting, though increasing studies have not corroborated an elevated risk.[5] The radionecrosis rate for our cohort (12% at 2 years) is within the range reported for SRS alone (6%–20%),[34] thus not providing a gross signal for increased toxicity. More specifically, we did not find the delivery of SRS closer to the administration of ICB to impact on risk of radionecrosis. Noteworthily, a Phase I/II trial of SRS (for up to 10 BrM) delivered within 7 days of combined

**Table 3.** Univariable and Multivariable Analysis of OS

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| Variable | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age (per year increase) | 1.01 (0.99–1.03) | .224 | | |
| Sex | | | | |
| Male | Reference | | | |
| Female | 1.11 (0.72–1.73) | .627 | | |
| ECOG | | | | |
| 0–1 | Reference | | Reference | |
| 2–3 | 2.15 (1.25–3.71) | **.006** | 1.72 (0.96–3.08) | .067 |
| Dexamethasone dose (per mg/day increase) | 1.08 (1.03–1.13) | **.001** | 1.06 (1.00–1.11) | **.039** |
| Histology | | | | |
| Breast | Reference | | | |
| Melanoma | 1.08 (0.26–4.55) | .919 | 1.29 (0.30–5.52) | .729 |
| NSCLC | 1.63 (0.39–6.87) | .504 | 1.66 (0.39–7.09) | .497 |
| RCC | 0.97 (0.19–4.87) | .966 | 1.29 (0.25–6.60) | .759 |
| Other | 4.07 (0.84–19.67) | .081 | 4.58 (0.92, 22.87) | .064 |
| ICB regimen type | | | | |
| Anti-PD(L)-1 monotherapy | Reference | | | |
| Dual anti-PD-1/anti-CTLA-4 therapy | 0.73 (0.47–1.15) | .173 | | |
| ECD status | | | | |
| CR/PR/SD | Reference | | | |
| PD | 1.38 (1.00–1.04) | .176 | | |
| Number of BrMs | 1.02 (1.00–1.04) | .053 | | |
| Time between SRS and nearest ICB cycle (categorical) | | | | |
| 0–7 days | Reference | | | |
| 8–30 days | 1.57 (0.95–2.62) | .081 | | |
| 30 + days | 2.14 (1.17–3.94) | **.014** | | |
| Time between SRS and nearest ICB cycle (continuous, per day increase) | 1.01 (1.00–1.01) | **.020** | 1.01 (1.00–1.01) | **.033** |
| SRS-ICB sequencing | | | | |
| SRS before ICB start | Reference | | | |
| SRS after ICB start | 0.94 (0.56–1.58) | .810 | | |
| Number of ICB cycles prior to SRS | 0.98 (0.96–1.00) | .100 | | |

*P* values < 0.05 are bolded.

ipilimumab/nivolumab for patients with NSCLC recently reported meeting its safety endpoint.[35] In our study, we showed radionecrosis to be correlated with a different set of risk factors, namely BrM size (as has been reported widely[34]) and the cumulative number of ICB cycles received prior to SRS, though the latter was borderline in statistical significance in multivariable analysis ($P = .07$). Even so, the cumulative number of ICB cycles received prior to SRS, which may alter the tumor and brain microenvironment makeup, is rarely examined and we suggest may account for the inconsistent reports of increased radionecrosis risk with SRS and ICB. The impact of this factor should be considered in future studies for validation.

The main weakness of the current study is its retrospective nature, which is inherently prone to known and unknown biases. As much as possible, we have attempted to account for potential confounders such as histology, BrM size, ICB regimen type, and the de novo status of BrM, as well as a survivor bias. Moreover, our focus within a large cohort of patients receiving concurrent SRS and ICB (rather than comparing with non-concurrent therapy, which reflects a clinically and biologically distinct population), together with a rationally defined timeframe between SRS and ICB for inclusion, strengthen the interpretation of this study. Ancillary findings that align with well-established observations such as the correlation of ICB regimen type with LC and dexamethasone dose with OS[21,22] also suggest a reliable dataset. Lastly, it is worth noting that our patient cohort, all of whom received concurrent SRS and ICB, is not comparable to the broader population receiving SRS for BrM with respect to either patient or BrM characteristics.

**Table 4.** Univariable and Multivariable Analysis of Radionecrosis

| Variable | Univariable HR (95% CI) | *P* | Multivariable HR (95% CI) | *P* |
|---|---|---|---|---|
| SRS-ICB sequencing | | | | |
| SRS before ICB start | Reference | | | |
| SRS after ICB start | 0.90 (0.26–3.10) | .866 | | |
| Time between SRS and nearest ICB cycle (categorical) | | | | |
| 0–7 days | Reference | | | |
| 8–30 days | 0.94 (0.34–2.61) | .913 | | |
| 30 + days | 1.36 (0.43–4.30) | .605 | | |
| Time between SRS and nearest ICB cycle (continuous, per day increase) | 1.00 (0.99–1.01) | .719 | | |
| ICB regimen type | | | | |
| Anti-PD(L)-1 monotherapy | Reference | | | |
| Dual anti-PD-1/anti-CTLA-4 therapy | 0.59 (0.23–1.53) | .277 | | |
| Dexamethasone dose (per mg/day increase) | 1.04 (0.91–1.20) | .546 | | |
| BrM size (per mm increase) | 1.06 (1.02–1.11) | **.004** | 1.05 (1.00–1.10) | **.043** |
| Number of ICB cycles prior to SRS | 1.04 (1.01–1.06) | **.005** | 1.02 (1.00–1.05) | .071 |

*P* values < 0.05 are bolded.

Although within this contemporary "concurrent" cohort we could not find an impact of SRS timing on DBC, we argue there is now sufficiently compelling data to suggest a potential true link between improved LC, and perhaps even OS, with the proximity of SRS and ICB administration. Future prospective and randomized studies should investigate this highly translatable potential to improve outcomes for a large proportion of patients affected by BrM.

## Supplementary material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

## Keywords

brain metastases | immunotherapy | neuro-oncology | stereotactic radiosurgery

## Funding

J.S. receives a Peter Mac Foundation Discovery Partner Fellowship.

## Conflict of interest statement

The authors declare no competing interests.

## Author contributions

Conceptualization, J.S.; Methodology, J.S.; Investigation, A.M., A.G., and X.F.; Writing—Original Draft, A.M., and J.S.; Writing—Review & Editing, A.G., X.F., L.S., C.P., A.W., N.H., N.P., M.L., and J.S.; Resources, C.P., A.W., N.H., N.P., M.L. and J.S.; Supervision, J.S.

## Ethics approval

Ethics approval (waiver of consent) for this study was granted by the Peter MacCallum Cancer Centre Human Research Ethics Committee.

## Data availability

Individual patient data is available from the corresponding author on reasonable request.

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