Stereotactic radiosurgery for melanoma brain metastases: Concurrent immune checkpoint inhibitor therapy associated with superior clinicoradiological response outcomes

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Abstract

Introduction/purpose: This study assessed long-term clinical and radiological outcomes following treatment with combination stereotactic radiosurgery (SRS) and immunotherapy (IT) for melanoma brain metastases (BM).

Methods: A retrospective review was performed in a contemporary cohort of patients with melanoma BM at a single tertiary institution receiving Gamma Knife® SRS for melanoma BM. Multivariate Cox proportional-hazards modelling was performed with a \( P < 0.05 \) for significance.

Results: 101 patients (435 melanoma BM) were treated with SRS between January-2015 and June-2019. 68.3% of patients received IT within 4 weeks of SRS (concurrent) and 31.7% received SRS alone or non-concurrently with IT. Overall, BM local control rate was 87.1% after SRS. Median progression free survival was 8.7 months. Median follow-up was 29.2 months. On multivariate analysis (MVA), patients receiving concurrent SRS-IT maintained a higher chance of achieving a complete (CR) or partial response (PR) \( [HR 2.6 \ (95\% \ CI: \ 1.2 - 5.5, \ P = 0.012)] \) and a reduced likelihood of progression of disease (PD) \( [HR 0.52 \ (95\% \ CI: \ 0.16 - 0.60, \ P = 0.048)] \). Any increase in BM volume on the initial MRI 3 months after SRS predicted a lower likelihood of achieving long-term CR or PR on MVA accounting for concurrent IT, BRAF status and dexamethasone use \( [HR 0.048 \ (95\% \ CI: \ 0.007 - 0.345, \ P = 0.0026)] \). Stratified volumetric change demonstrated a sequential relationship with outcomes on Kaplan-Meier analysis.

Conclusion: Concurrent SRS-IT has favourable clinical and radiological outcomes with respect to CR, PR and a reduced likelihood of PD. Changes in BM volume on the initial MRI 3 months after SRS were predictive of long-term outcomes for treatment response.

Key words: brain metastases; Gamma-Knife; immunotherapy; melanoma; radiosurgery.

Introduction

Improvements in drug therapies have fundamentally changed the management of advanced melanoma over the past decade. Immunotherapy (IT) and targeted therapies have demonstrable intracranial efficacy for melanoma brain metastases (BM), with response rates ranging from 20% for single agent IT, 46% with combination IT and 58% for combination BRAF/MEK inhibitors.1-3 The durability of intracranial response for combination IT with ipilimumab and nivolumab is particularly impressive, with 5-year intracranial PFS rates of 46%, and 5-year OS rates of 51% in asymptomatic melanoma brain metastasis patients not requiring steroids.4
Historically, prospective randomised trials enrolling patients with BM from primaries of mixed histologies have established surgery and stereotactic radiosurgery (SRS) as the standard of care for up to 3 BM,5 the latter with control rates of 75–95%.5–7 The number of patients with melanoma BM in these studies was small and the optimal sequencing of treatment modalities for this disease in the context of new drugs with intracranial activity is evolving and currently debated.8–15 Retrospective series and preliminary non-randomised prospective studies suggest superior survival outcomes when SRS is combined with IT (SRS-IT) in the management of melanoma BM.6,7,11–16 However, the impact of SRS-IT on local control is less well reported and multivariate analyses accounting for the range other relevant clinicopathologic factors has been lacking. Interpreting radiological response following SRS and the differentiation between BM progression and treatment-related changes (including pseudoprogression and pseudoresponse) is challenging,17 particularly in the setting of concurrent IT.18–20 A number of metrics have been proposed to describe BM response and control after SRS, and heterogeneity in the criteria used complicates disease quantification, interpretation and implications for ongoing management.18 Pathological confirmation is considered the gold standard, but this is not appropriate or feasible in most patients. Existing assessment tools such as RECIST 1.0, RECIST 1.1, Macdonald, WHO and Response Assessment in Neuro-Oncology (RANO)-HGG have distinct limitations in their ability to address BM response.19–24 Based on consensus opinion, newer response assessment tools encompassing both radiological and clinical response assessment parameters have been developed. The RANO-BM working group have proposed normative criteria for use in BM trials and provide guidance on the number of target lesions to consider, corticosteroid use and pseudoprogression after SRS or IT.19,25 To date, very few studies have used RANO-BM criteria. Given the increasing importance of incorporating both radiological and clinical parameters in response assessment, this data is important for trial planning and design. Thus, for patients with BM, clinical versus radiological responses to therapy and subsequent outcomes are not always concordant. The ability to prospectively interpret radiological changes after therapy (as opposed to only retrospectively or using a trend in serial scans), especially in the setting of concurrent SRS-IT, could improve management through individualising surveillance imaging frequency or facilitating earlier changes to therapy, if appropriate. This is particularly relevant in melanoma BM cohorts where a relatively longer survival is expected in patients who initially respond to therapy. This study aimed to report outcomes according to RANO-BM criteria in a contemporary cohort of patients with melanoma BM, following treatment with SRS and IT and/or targeted therapy. An additional aim was to assess for associations between clinical, treatment and early radiological factors with long-term outcomes in these patients.

**Methods**

A retrospective review was performed of patients receiving Gamma Knife® SRS for melanoma BM between October 2015 and June 2019 at a single institution. Medical records were reviewed to extract clinicopathologic data including details about systemic therapy. Explanatory systemic therapy data was further stratified to assess single- versus double-agent IT and timing relative to SRS; IT prior to SRS only (≥4 weeks) (pre SRS-IT), concurrent with SRS and ongoing after (commencing within ±4 weeks of SRS) (concurrent SRS-IT) or if only after SRS (commencing ≥4 weeks post-SRS) (post-SRS-IT).26–29 Targeted therapy for BRAF/MEK was defined as concurrent when administered within ±3 days of SRS (concurrent SRS-BRAF).29 All patients were discussed in a multidisciplinary meeting (MDM) comprising neurosurgeons, radiation oncologists and a neuroradiologist before SRS and in consultation with the treating medical oncologist. SRS was delivered on the Gamma Knife Perfexion™ and ICON™ models (Elekta™, Stockholm, Sweden) using frame or thermoplastic mask immobilisation. On the day of SRS, a 3 T planning magnetic resonance imaging (MRI) brain was acquired for target delineation with 3-dimensional (3D) T1 weighted post-Gadolinium sequences and 1.5 mm axial reconstruction. BMs were treated without a margin and dosing was according to an institutional adaption of the Radiotherapy Oncology Group 95-08 protocol.30 Steroid administration at the time of SRS was individualised but not routinely commenced in patients without symptoms. After SRS, all patients underwent telephone review within 48 h and then clinical review with repeat surveillance MRI, consistent with ‘Standardised Brain Tumor Imaging Protocol’ (BTIP) guidelines,31 every 2–3 months for at least 2 years if they remained well enough to do so. Individual BM were segmented on MRI at baseline and at each imaging interval after SRS to report their volume (cc) and diameter (cm) using Leksell GammaPlan® treatment planning software (Version 10, Elekta™, Stockholm, Sweden) and AGFA Impax (Version 6, Agfa-Gevaert N.V.™, Mortsel, Belgium). Response assessment was commensurate with RANO-BM specified guidelines taking clinical and radiological criteria to stratify target lesions into complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) in terms of best response by time of last follow-up.19 For lesions smaller than 10 mm, a minimum change of 3 mm in the longest diameter was required to represent meaningful change from baseline. Volumetric changes in target lesions after SRS were analysed as binary categorical, continuous (per percentage volume increase) and stratified.
(following the RANO-BM criteria of ≥20% increase in size, <30% decrease to <20% increase and ≥ 30% decrease in size compared to baseline) variables. Cubic spline interpolation was used to impute missing data across time intervals and standardised to 3-monthly intervals for the purposes of analysis. For clinically important outcomes, overall control rate was defined as the combination of CR, PR and SD and treatment response was defined as the combination of CR and PR only. Progression of disease was defined per RANO-BM criteria for target lesions.

Data was also collected on neurological symptoms and toxicity outcomes after SRS graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.32 Radionecrosis (RN) was defined radiologically by MDM consensus, or when histological confirmation was obtained. Symptomatic RN was defined as clinical signs or symptoms attributable to and commensurate with radiological evidence of RN. MRI perfusion and permeability or PET-based imaging was performed in select cases.

Continuous variable characteristics were assessed using the Shapiro–Wilk test for deviations from normality and then divided categorically into equivalent quartiles for categorical analysis if appropriate. Univariate and multivariate logistic regression analyses were performed using the Wald χ² test with respective odds ratios reported. Kaplan–Meier curves were generated for time to progression of disease and cumulative incidence function plots were generated for time to best response after SRS excluding patients who ultimately progressed locally at time of last follow-up. The log-rank test was used to test for differences between groups. Patients were censored at time of last follow-up or death. Hazard ratios (HR) with their respective 95% confidence intervals (CI) were determined with Cox proportionate hazards modelling. A statistical significance of P <0.25 was utilised in univariate analyses to signify inclusion in the final multivariate Cox proportionate model and P <0.05 was used in the multivariate analysis (MVA). Additionally, a Cox frailty model was performed to account for clustering or vectorization of events within individual patients. The frailty model incorporated cluster-specific random effects to test for deviations from the baseline hazard function and account for treatment response and progression of disease events at both a lesion and patient level. All statistical analysis was performed on SAS (Statistical Analytical Sciences Studio Release 3.7, SAS Institute INC, Cary, NC. USA).

Results

101 patients with a total of 435 melanoma BM were treated with Gamma Knife SRS during the study period. 51.5% of patients were BRAF-mutant and 65.4% of these patients had progressed on BRAF/MEK inhibitors and/or switched to IT at the time of SRS. 34.4% of BRAF-mutant patients received concurrent BRAF inhibitors and 68.3% of all patients received concurrent IT with SRS. 24.8% of all patients received dexamethasone and 20.8% of all patients were neurologically symptomatic at the time of SRS. 60% of patients had stable extracranial disease at time of SRS; 17.8% were active and 21.8% were untreated. Additional baseline characteristics are presented in Table 1. Median follow-up was 29.2 months (interquartile range, IQR 19.7–39.8) and median overall survival (OS) was 15.5 months after SRS (IQR 7.1–27.4). 40.6% of patients had died at the time of median follow-up.

The overall crude local control rate after SRS at last follow-up was 87.1% (371/425 BM). According to RANO-BM criteria, 50.5% of patients achieved SD as the best response after SRS (214/425), 30.8% PR (131/425) and 5.9% CR (23/425). The median interval to best response of PR or CR after SRS was 5 months (IQR 1.1–8.9). 12.9% demonstrated local PD after SRS at a median time to progression of 8.7 months (IQR 3.4–14.1). 27.2% of patients developed new BM during the follow-up period. 18.8% of patients had any grade 3 or higher neurological symptoms after SRS during the follow-up period. 5.0% of patients developed grade 3 or higher symptomatic RN at a median timepoint of 10.5 months after SRS (IQR 4.9–11.9).

Predicting target lesion best response CR or PR after SRS according to RANO-BM

Univariate cox proportional-hazards regression analysis demonstrated that patients receiving concurrent SRS-IT, patients not receiving dexamethasone at time of SRS and patients who did not have any volumetric increase on the first MRI after SRS compared to baseline (as opposed to sufficient change to meet the RANO-BM criteria for PD) had a greater likelihood of achieving a subsequent CR or PR as the best response at a later timepoint. 6-month and 12-month treatment response was 40% versus 21.2% and 49% versus 22.3% in the concurrent SRS-IT versus the non-concurrent groups respectively. Assessing pre SRS-IT, concurrent SRS-IT and post-SRS-IT, 6-month and 12-month treatment response was 23.8% versus 40% versus 15.4% and 42.9% versus 49% versus 18.6% respectively. Univariate outcomes for best RANO-BM treatment response are presented in Table 2. Multivariate cox regression analysis demonstrated that patients receiving concurrent SRS-IT maintained a higher chance of achieving a CR or PR when adjusted for BRAF status, symptoms or dexamethasone at time of SRS, ECOG performance status and MRI volumetric characteristics on the initial MRI at 3 months after SRS (HR 2.6, 95% CI: 1.2–5.5, P = 0.012). On MVA, patients demonstrating any increase in volume on initial post-SRS imaging were significantly less likely to ultimately achieve CR or PR as their best response (HR 0.048, 95% CI: 0.007–0.35, P = 0.0026).
Predicting target lesion PD after SRS according to RANO-BM

Univariate cox proportional-hazards regression analysis demonstrated that patients receiving concurrent SRS-IT had a significantly lower chance of local progression. 6-month and 12-month local control was 91% versus 74% and 86% versus 68% in the concurrent SRS-IT versus the non-concurrent groups respectively. Assessing pre-SRS-IT, concurrent SRS-IT and post-SRS-IT, 6-month and 12-month local control was 76.2% versus 91% versus 71.3% and 76.2% versus 86% versus 62.9% respectively. Kaplan–Meier curves are presented in Figure 1. Lesions which demonstrated any increase in volume on the first 3-month surveillance MRI after SRS were more likely to demonstrate clinical and radiological local progression later (HR 7.6, 95% CI: 4.5–12.9, \( P < 0.0001 \)). Univariate outcomes for RANO-BM local progression of disease are presented in Table 3. On multivariate survival analysis, the benefit of concurrent IT with SRS remained significant when adjusting for relative volumetric change on initial MRI after SRS and age.

Table 1. Summary of patient, lesion and treatment characteristics

| Patient and lesion characteristics (continuous) | Median (range/IQR) |
|-----------------------------------------------|-------------------|
| Age (years)                                   | 63 years (range 20–90, IQR 48–73) |
| Follow-up (months)                            | 29.2 months (IQR 19.7–39.8) |
| Median overall survival from 1st course of SRS (months) | 15.5 months (range 0.6–50.2, IQR 7.1–27.4) |
| Number of lesions cumulatively treated per SRS session (n) | 3 (range 1–23, IQR 1–6) |
| Median cumulative GTV (cc)                    | 2.3 cc (range 0.03–34, IQR 1.1–5.1) |
| Median dose per lesion (Gy) for single fraction regimens | 20 Gy (range 8–22) |
| Median courses of SRS (n)                     | 1 (range 1–8) |
| Median dose delivered intracranially for multi-fraction SRS | 24 Gy/3 fractions |
| Median individual brain metastasis volume (cc) | 0.24 cc (IQR 0.06–1.02) |
| Median individual brain metastasis diameter (cm) | 0.77 cm (IQR 0.48–1.25) |
| Median LDH                                    | 221 U/L (IQR 184–274) |

| Patient and treatment characteristics (categorical) | n (patients) | % |
|-----------------------------------------------------|--------------|---|
| Gender                                               |              |   |
| Male                                                 | 66           | 65.4% |
| Female                                               | 35           | 34.6% |
| BRAF status                                          |              |   |
| Mutant                                               | 52           | 51.5% |
| Wild type                                            | 49           | 48.5% |
| Immunotherapy sequence                               |              |   |
| >4 weeks prior to SRS                                 | 4            | 4% |
| Commenced within 4 weeks of SRS and ongoing          | 69           | 68.3% |
| Commenced >4 weeks post-SRS and ongoing              | 14           | 13.8% |
| No immunotherapy received                            | 14           | 13.9% |
| Single versus double-agent immunotherapy at time of SRS |              |   |
| Single                                               | 47           | 46.5% |
| Double                                               | 23           | 22.8% |
| Non-immunotherapy or non-concurrent                  | 31           | 30.7% |
| Developed new BM in follow-up period                 |              |   |
| Yes                                                  | 28           | 27.8% |
| No                                                   | 73           | 72.2% |
| Symptomatic at time of SRS                           |              |   |
| Yes                                                  | 21           | 20.8% |
| No                                                   | 80           | 79.2% |
| Dexamethasone use at time of SRS                     |              |   |
| Yes                                                  | 26           | 24.8% |
| No                                                   | 75           | 75.2% |
| Extracranial disease status at time of SRS           |              |   |
| Stable                                               | 61           | 60.4% |
| Active                                               | 18           | 17.8% |
| Untreated                                            | 22           | 21.8% |
| ECOG Performance status                              |              |   |
| 0                                                    | 41           | 40.6% |
| 1                                                    | 43           | 42.6% |
| 2                                                    | 4            | 3.9% |
| 3                                                    | 13           | 12.9% |
| Systemic therapy type                                |              |   |
| Single agent CTLA-4 antagonist                        | 4            | 3.96% of total |
| Single agent PD-1 inhibitor                          | 26           | 25.7% of total |
| Combination CTLA-4 antagonist/ PD-1 inhibitor         | 39           | 39% of total |
| Combination BRAF/MEK inhibitor                        | 18           | 17.9% of total |

BM, brain metastases; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; GTV, gross tumour volume; IQR, Interquartile range; LDH, Lactate dehydrogenase; PD-1, programmed cell death protein 1; SRS, stereotactic radiosurgery.
Modelled as both continuous (per % increase in volume) and categorical (any increase seen or not) variables, volumetric increase in lesion size on initial MRI after SRS remained significantly associated with progression when adjusting for age and IT timing status. The impact of vectorisation or clustering of outcomes at a patient level did not impact the results of progression of disease on Cox frailty analysis. Multivariate analyses are summarised in Table 4.

**Table 2. Univariate analysis for Treatment Response (CR + PR)**

| Explanatory variable                              | Hazard ratio | 95% CI low | 95% CI high | P value |
|---------------------------------------------------|--------------|------------|-------------|---------|
| Age (continuous)                                  | 1.000        | 0.990      | 1.010       | 0.9506  |
| Gender                                            | 1.040        | 0.757      | 1.429       | 0.8106  |
| BRAF-mutant                                       | 1.351        | 0.969      | 1.882       | 0.0757* |
| 2nd line immunotherapy after BRAF/MEKi           | 0.964        | 0.548      | 1.698       | 0.9001  |
| Single versus double IT at time of SRS            | 0.957        | 0.665      | 1.378       | 0.8138  |
| 1st versus 2nd line IT at time of SRS             | 1.163        | 0.687      | 1.970       | 0.5744  |
| Concurrent IT (within 4 weeks) versus non-concurrent IT | 2.032        | 1.256      | 3.289       | 0.023** |
| BRAF/MEK inhibitor concurrently with SRS          | 1.221        | 0.775      | 1.923       | 0.3892  |
| Symptomatic at time of SRS                        | 1.327        | 0.836      | 2.108       | 0.2301* |
| Baseline volume (Continuous)                      | 0.992        | 0.905      | 1.087       | 0.8580  |
| ECOG                                              | 0.813        | 0.660      | 1.002       | 0.0526* |
| LDH level at time of SRS (continuous)             | 1.000        | 0.998      | 1.002       | 0.8138  |
| Dexamethasone use at time of SRS                  | 1.726        | 1.122      | 2.654       | 0.0088**|
| Any initial radiological increase in volume of lesion compared to baseline (categorical) | 0.063        | 0.016      | 0.255       | 0.0001**|
| % Increase in initial volume compared to baseline (continuous) | 0.979        | 0.974      | 0.985       | 0<.0001**|

CR, Complete response; IT, Immunotherapy; PR, Partial response; SRS, Stereotactic radiosurgery. *P < 0.25 (for inclusion in multivariate model) and **P < 0.05.

**Fig. 1.** Kaplan–Meier Curve for time to progression of disease from SRS based on concurrent SRS-IT versus non-concurrent SRS-IT.

**Associating stratified volumetric changes on initial post-SRS MRI with subsequent RANO-BM outcomes**

Stratifying change in lesion volume at initial 3-month MRI after SRS by ≥ 20% increase, <30% decrease to <20% increase and ≥ 30% decrease compared to baseline, there was a commensurate statistically significant association between eventual best RANO-BM outcome...
When assessing PD (Fig. 2) and treatment response (CR and PR), lesions which demonstrated a ≥30% decrease in size at initial 3-month MRI after SRS compared to baseline were more likely to ultimately achieve a CR or PR best response compared to those having a <30% decrease to <20% increase or a ≥20% increase in size (P <0.0001). Inversely when assessing CR or PR best response, lesions in the ≥20% increase category were least likely to ultimately achieve a CR or PR and were most likely to ultimately have progression compared to the ≥30% decrease in size or <30% decrease to <20% increase categories (P <0.001).

**Discussion**

This study demonstrates that the use of concurrent and continuing IT within 4 weeks of SRS for melanoma BM was associated with greater likelihood of a CR or PR, compared to patients not receiving concurrent IT on multivariate analysis when adjusted for BRAF status, symptoms at time of SRS, ECOG performance status, dexamethasone use and volumetric characteristics at initial MRI after SRS. Conversely, concurrent SRS-IT was also associated with a reduced likelihood of PD on multivariate analysis. There was no association between outcomes and 1st versus 2nd line IT use at time of SRS, single versus double-agent IT or use of concurrent BRAF/MEKi (Table 2, Table 3 and Table 4).

Prior observational studies have demonstrated concurrent SRS-IT associated with more effective local control and OS for melanoma BM (Table 5). Combining Stereotactic Radiosurgery and Immunotherapy for Brain Metastases.
patient, treatment and clinical factors that have been previously lacking in the literature. We also present for the first time, outcomes after SRS in patients with melanoma BM according to RANO-BM criteria which may be useful when comparing to cohorts at other institutions and for future trial planning.

The median time to local progression after SRS was 8.7 months but our study also demonstrates that the initial volumetric change on MRI at 3 months after SRS was associated with ultimate clinicoradiological outcomes based on RANO-BM criteria for CR, PR and PD. On multivariate analysis, initial volumetric increase in size when modelled as categorical, continuous (per percentage volume increase) and stratified ($\geq 20\%$ increase in size, $<30\%$ decrease to $<20\%$ increase and $\geq 30\%$ decrease compared to baseline) variables were associated with final best outcomes in this cohort. Any increase in treated lesion size at 3-months after SRS was associated with an increased likelihood to demonstrate clinical and radiological PD when adjusted for age and concurrent IT use. Commensurately, any initial increase in size at 3-months after SRS predicted a decreased likelihood of having a treatment response as final best response when adjusting for BRAF status, symptoms at time of SRS, ECOG performance status, dexamethasone and IT use. Stratified volumetric change demonstrated a sequential and ordinal relationship with outcomes on Kaplan–Meier analysis.

To our knowledge, this is the first study to demonstrate an association between immediate post-SRS imaging and longer-term response assessment after SRS for melanoma BM (or any other histology). Initial treatment-related increase in BM size after SRS or IT, followed by radiological stabilisation or regression is a recognised phenomenon. A recent meta-analysis demonstrated a radiological BM enlargement rate of 8–14% following combined modality treatment compared to 4% in IT alone. The relationship between initial post-SRS changes and subsequent outcomes in this cohort was more pronounced for best treatment response (PR or CR) than disease progression. Initial increase in size on post-SRS MRI was associated with a 20-fold reduced likelihood of treatment response compared to a 3.8-fold increased risk of having ultimate progression of disease accounting for concurrent IT use. Lesions demonstrating radiological failure early post-SRS, with increases in size $>20\%$ of baseline were most strongly commensurate with ultimate long-term failure (Fig. 2). The degree of dynamic volume change on the MRI at 3-months post-SRS could potentially be used to risk-stratify interpretation of evolving radiological changes in the future or inform the interval for surveillance imaging thereafter.

Dexamethasone use at time of SRS was also associated unfavourably with treatment response on both univariate and multivariate analyses but not BM volume or the presence of symptoms. Corticosteroids are commonly used to relieve symptoms related to oedema surrounding BM but may also impede the immune responses which are targeted by IT agents and augmented by concurrent SRS-IT. SRS induces cancer cell damage and can expose tumour-specific antigens that are more visible to immune surveillance, promoting priming and activation of cytotoxic T cells.
induced modulation of the tumour microenvironment may also facilitate the recruitment and infiltration of immune cells. In the context of our analysis, a relatively less prominent reduction in BM volume long-term may be due to the anti-inflammatory effects of dexamethasone dampening the impact of IT. Endpoints for corticosteroid use in clinical trials will need to be identified and will require prospective confirmation in clinical studies according to a RANO working group developed to develop consensus guidelines for evaluating therapeutic response in the setting of corticosteroid use.44

There are several limitations to this study, primarily relating to its retrospective nature and the heterogeneity of prior therapies for melanoma. Although the RANO-BM criteria do help to standardise response assessment after SRS and specifically provide guidance lesions smaller than 10 mm, determining changes in these very small lesions might be more challenging (median individual BM volume 0.24 cc and diameter 0.77 cm). While increasing the adoption of RANO-BM criteria are important in clinical trials, there are inherent limitations in the overall applicability of this approach which does not permit the use of additional advanced imaging modalities and MRI sequences that may be used in clinical practice.

Our study suggests a synergistic association between combination SRS-IT for clinical and radiological RANO-BM based outcomes with respect to CR, PR and a reduced likelihood of PD. Initial increases in lesion size
whether BM response after initial therapy according to RANO-BM differs from brain modified RECIST (as used in the ABC-X study) would be of interest. Future studies may test alternative aspects of the synergistic relationship between concurrent SRS and IT in this setting; such as whether SRS dose can be safely reduced to lower the risk of RN without abrogating local control or whether the dose for staged-SRS approaches when treating larger BM45 could be risk-adapted based on interval MRI response.

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Consent to participate

All work pertaining to consent to participate in the study and for publication was performed in accordance with the ethical standards of the Declaration of Helsinki.

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Data availability statement

Availability of data and material: The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request

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