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

Mihir D Shanker,[1,2,3] (iD) Sidyarth Garimall,[2] Nick Gatt,[4] Heath Foley,[1] Samuel Crowley,[1] Emma Le Cornu,[1] Kendall Muscat,[1] Wei Soon,[2] Victoria Atkinson,[2,4] Wen Xu,[4] Trevor Watkins,[4] Michael Huo,[1,2] Matthew C Foote[1,2] and Mark B Pinkham[1,2] (iD)

1 Gamma Knife Centre of Queensland, Princess Alexandra Hospital, Brisbane, Queensland, Australia
2 Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia
3 Princess Alexandra Hospital Research Foundation, Brisbane, Queensland, Australia
4 Princess Alexandra Hospital, Brisbane, Queensland, Australia

MD Shanker FRANZCR, MBBS, MPhil MMed, BEng (Biomedical)(Hons); **S Garimall** MBBS; **N Gatt** MBBS; **H Foley** BAppSc (MRT); **S Crowley** BAppSc (MRT); **E Le Cornu** BMedRadSc (Radiation Therapy); **K Muscat** BAppSc (MRT); **W Soon** MBBS; **V Atkinson** MBBS, FRACP; **W Xu** MBBS, FRACP; **T Watkins** MBBS, FRANZCR; **M Huo** MBBS, FRANZCR, **MC Foote** MBBS, FRANZCR, **MB Pinkham** BMBCh, FRANZCR.

Correspondence

Dr Mihir D Shanker, Department of Radiation Oncology, Gamma Knife Centre of Queensland, Princess Alexandra Hospital, 199 Ipswich Rd, Woolloongabba Qld, Australia. Email: m.shanker@uq.edu.au

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.[8–10] 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 χ^2 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).

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
			36.7% of eligible (BRAF-mutant patients)

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.

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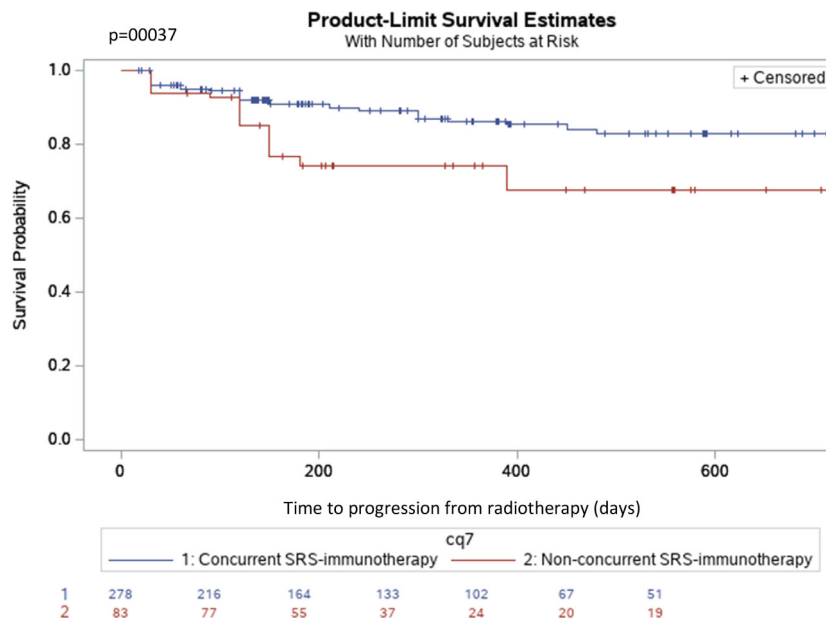
Fig. 1. Kaplan–Meier Curve for time to progression of disease from SRS based on concurrent SRS-IT versus non-concurrent SRS-IT.

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.

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 a ≥ 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

Table 3. Univariate analysis for Progression of Disease (PD)

Explanatory variable	Hazard ratio	95% CI low	95% CI high	P value
Age (continuous)	0.985	0.969	1.002	0.0828*
Gender	0.945	0.557	1.604	0.8337
BRAF-mutant	0.881	0.518	1.497	0.6392
2nd line immunotherapy after BRAF/MEKi	1.232	0.626	2.425	0.5466
Single versus double IT at time of SRS	0.887	0.311	2.527	0.8226
1st versus 2nd line IT at time of SRS	0.825	0.451	1.507	0.5309
Concurrent IT (within 4 weeks) versus non-concurrent IT	0.460	0.267	0.793	0.0037**
BRAF/MEK inhibitor concurrently with SRS	0.543	0.265	1.111	0.2945
Symptomatic at time of SRS	1.251	0.562	2.786	0.5828
Baseline volume (Continuous)	1.052	0.924	1.198	0.4458
ECOG	1.070	0.784	1.461	0.6706
LDH level at time of SRS (continuous)	0.999	0.995	1.002	0.5295
Dexamethasone use at time of SRS	0.724	0.388	1.350	0.3094
Any initial radiological increase in volume of lesion compared to baseline (categorical)	7.586	4.466	12.886	<0.0001**
% Increase in volume compared to baseline (continuous)	1.001	1	1.001	<0.0001**

IT, Immunotherapy; PD, Progression of disease; SRS, Stereotactic radiosurgery. *$P <0.25$ (for inclusion in multivariate model) and **$P <0.05$.

Table 4. Multivariate analysis for long-term treatment response (CR or PR) and progression of disease (PD)

Long-term CR or PR	HR	95% Confidence Interval	P value
BRAF-mutant	0.726	0.424–1.243	0.2431
Concurrent IT (within 4 weeks) versus non-concurrent IT	2.611	1.235–5.52	0.012**
Symptomatic at time of SRS	0.789	0.408–1.527	0.4818
ECOG	0.965	0.681–1.368	0.8418
Dexamethasone use at time of SRS	2.776	1.458–5.285	0.0019**
% Increase in volume at 3-month MRI compared to baseline (continuous)	0.981	0.974–0.988	<0.0001**
Any initial radiological increase in volume of lesion at 3 months compared to baseline (categorical [yes or no])	0.048	0.007–0.345	0.0026**
Long-term PD			
Age (continuous)	1.004	0.967–1.043	0.8271
Concurrent IT (within 4 weeks) versus non-concurrent IT	0.524	0.163–0.596	0.0477**
% Increase in volume at 3-month MRI compared to baseline (continuous)	1.001	1–0.001	<0.0001**
Any initial radiological increase in volume of lesion at 3 months compared to baseline (categorical [yes or no])	3.779	1.666–8.572	0.0015**

ECOG, Eastern Cooperative Oncology Group; IT, Immunotherapy; SRS, Stereotactic radiosurgery. **$P <0.05$.

criteria 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 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).[11–16,26–28,33–35] Our analysis reiterates the synergistic response of SRS-IT but also further strengthens this relationship by performing additional multivariate analyses of individual BM,

Product-Limit Survival Estimates
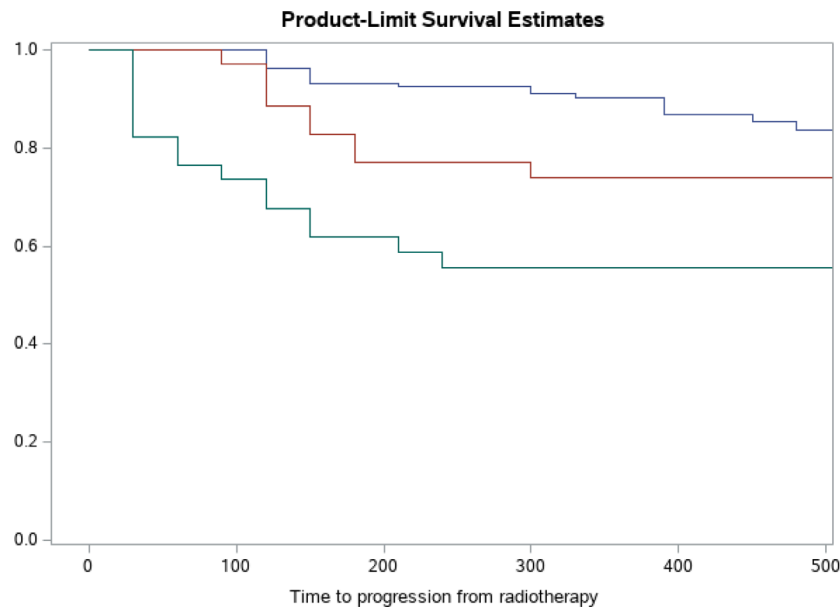
Fig. 2. Kaplan–Meier Curve for time to progression of disease from SRS, stratified by initial change on 3-month post-SRS MRI. Green = ≥20% increase, Red = <30% decrease to <20% increase, Blue = ≥30% decrease in size.

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 (≥20% increase in size, <30% decrease to <20% increase and ≥ 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.[36–40] A recent meta-analysis demonstrated a radiological BM enlargement rate of 8–14% following combined modality treatment compared to 4% in IT alone.[41] 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.[39–41] 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.[42,43] Radiation-

Table 5. Literature review of studies reporting outcomes for patients with melanoma BM receiving SRS and IT

Authors	Year	Study details	Key findings
Moyers J et al.	2021	Database analysis (NCDB) 3008 melanoma BM	Median OS • SRS-IT: 15.77 months • SRS alone: 9.33 months • IT alone: 7.29 monthsLC not reported
Liermann J et al.	2020	Retrospective analysis 36 patients (66 melanoma BM) All patients receiving SRS-IT	OS • 1-, 2-, 5-yr OS rates: 78, 50, 20% respectively.Freedom from local failure • 1-, 2-, 5-yr FFLF rates: 82–85%, 73–80%, 62–80% respectively.
Minniti G et al.	2019	Retrospective analysis 80 patients (326 melanoma BM) Assessed efficacy of SRS + ipilimumab or nivolumab	OS • 1-yr OS rate: 78% nivolumab group, 68% in ipilimumab groupLC not reported
Anderson E et al.	2017	Retrospective analysis 32 patients (21 patients SRS + pembrolizumab and 11 SRS alone)	Median OS: 9 months LC 11% progression for SRS alone versus 4–6% for combination SRS-IT [statistical comparison not reported] • 35% CR, 35% PR
Patel K et al.	2017	Retrospective analysis 54 patients (34 patients SRS and 20 SRS + ipilimumab)	OS • 1-yr OS rate: 37.1% (no statistically significant difference between the subgroups)LC • 1-yr LC rate: 71.4% (no statistically significant difference between the subgroups)
Choong ES et al.	2017	Retrospective analysis 108 patients (339 lesions) (26 SRS alone, 28 SRS + CTLA-4 28, 11 SRS + PDL1)	Median OS: • SRS + CTLA-4: 7.5 months • SRS + PDL1: 20.4 monthsMedian LC (no statistically significant difference between the subgroups) • SRS + CTLA-4: 7.5 months • SRS + PDL1: 12.7 months
Kaidar – Person O et al.	2017	Retrospective analysis 58 patients (29 SRS alone, 29 SRS + IT)	Median OS • SRS + IT: 15 monthsLC (no statistically significant difference between the subgroups) • SRS + IT: 4/29 PD • SRS alone: 14/29 PD
Ahmed KA et al.	2016	Retrospective analysis 26 patients (73 melanoma BM) SRS concurrent with range of systemic therapies	Median OS: 12 months. (no statistically significant difference between the subgroups for concurrent versus prior/after) LC • 6- and 12-month LC rate: 91% and 85% respectively
Mathew M et al.	2013	Retrospective analysis 58 patients (25 patients SRS + ipilimumab and 33 SRS alone)	OS • 6-month OS: 56% (no statistically significant difference between the subgroups)LC not reported

BM, brain metastasis; CR, complete response; FFLF, Freedom from local failure; LC, Local control; LF, Local failure; NCDB, National cancer database; OS, Overall survival; PD, progressive disease; PR, partial response; SRS, Stereotactic radiosurgery; SRS-IT, concurrent SRS and immunotherapy.

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

on MRI after SRS were also predictive of worse outcomes in terms of local control and warrants further investigation. The ABC-X study (NCT03340129) is a current Australian multicentre study exploring the optimal sequencing of IT and SRS in patients with melanoma BM, randomising them to receive either upfront concurrent or salvage SRS.[10] 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 BM[45] could be risk-adapted based on interval MRI response.

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Ethics approval

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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.

Consent for publication

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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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