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BRAF inhibitor and stereotactic radiosurgery is associated with an increased risk of radiation necrosis

Kirtesh R. Patel^{a,*}, Mudit Chowdhary^{a,*}, Jeffrey M. Switchenko^b, Ragini Kudchadkar^c, David H. Lawson^c, Richard J. Cassidy^a, Roshan S. Prabhu^d, and Mohammad K. Khan^a

^aDepartment of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia

^bDepartment of Biostatistics and Bioinformatics Shared Resource, Winship Cancer Institute of Emory University, Atlanta, Georgia

^cDepartment of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia

^dSoutheast Radiation Oncology Group, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, North Carolina, USA

Abstract

We retrospectively compared the outcomes and toxicities of melanoma brain metastases (MBM) patients treated with BRAF inhibitors (BRAFi) and stereotactic radiosurgery (SRS) with SRS alone. We identified 87 patients with 157 MBM treated with SRS alone from 2005 to 2013. Of these, 15 (17.2%) patients with 32 MBM (21.4%) received BRAFi therapy: three (20.0%) before SRS, two (13.3%) concurrent, and 10 (66.7%) after SRS. Overall survival (OS) was compared between cohorts using the product limit method. Intracranial outcomes were compared using cumulative incidence with competing risk for death. Baseline patient characteristics were similar between groups, except for the SRS cohort, which had higher rates of chemotherapy and more recent year of diagnosis. Radiation characteristics, including dose per fraction, total dose, gross tumor volume size, and prescription isodose, were also similar between cohorts. One-year outcomes – OS (64.3 vs. 40.4%, $P=0.205$), local failure (3.3 vs. 9.6%, $P=0.423$), and distant intracranial failure (63.9 vs. 65.1%, $P=0.450$) were not statistically different between the SRS + BRAFi and SRS-alone groups, respectively. The SRS + BRAFi group showed higher rates of radiographic radiation necrosis (RN) (22.2 vs. 11.0% at 1 year, $P<0.001$) and symptomatic radiation necrosis (SRN) (28.2 vs. 11.1% at 1 year, $P<0.001$). Multivariable analysis showed that BRAFi predicted an increased risk of both radiographic and SRN. SRS and BRAFi predicted for an increased risk of radiographic and SRN compared with SRS alone. Approaches to mitigate RN for patients receiving SRS and BRAFi should be considered until the clinical trial (<http://www.clinicaltrials.gov>: NCT01721603) evaluating this treatment regimen is completed.

Correspondence to Mohammad K. Khan, MD, PhD, Department of Radiation Oncology, Emory University, 1365 Clifton Road NE, Room A1312, Atlanta, GA 30322, USA, Tel: + 1 404 778 3763; fax: + 1 404 778 4139; drkhurram2000@gmail.com.

*Kirtesh R. Patel and Mudit Chowdhary contributed equally to the writing of this article.

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Keywords

BRAF inhibitor; brain metastases; melanoma; radiation necrosis; stereotactic radiosurgery

Introduction

Over the past 10 years, the landscape for metastatic melanoma patients has changed significantly. Immune therapies, including antibodies targeting CTLA-4 and PD-1, have considerably improved overall survival (OS) [1]. Furthermore, 40–60% of melanoma patients also have a mutation in the serine protein kinase – most commonly V600E – that leads to constitutive activation of the oncogene, leading to mutation-specific targeted therapies [2]; prospective studies involving the use of these BRAF inhibitors (BRAFi), vemurafenib and dabrafenib (DAB), have reported remarkable response rates and improvements in OS [2–4]. Although immune therapy and BRAFi have shown improvements in extracranial efficacy, their benefit intracranially has been limited [3,4]. As a result, these agents are often utilized with radiation to maximize intracranial control. Although whole-brain radiation therapy (WBRT) is the historical standard of care, two concerns for melanoma patients have arisen with this therapy: (a) as melanoma patients are living longer because of improvements in systemic therapy, neurocognitive toxicities from WBRT are more significant [5] and (b) melanoma is a radioresistant tumor; low dose per fraction WBRT may not provide adequate local control [6]. As a result, systemic agents, including BRAFi, are commonly being combined with stereotactic radiosurgery (SRS) for melanoma brain metastases (MBM) patients.

Recent studies, however, report potential concerns from treatment with radiation and BRAFi. A case report of a patient with metastatic melanoma treated with stereotactic body radiation for a liver lesion, followed by vemurafenib (VMF) 2 days later, led to significant skin necrosis and liver damage in the entrance radiation portal fields [7]. Another case report suggests that the combination is associated with radiation necrosis (RN) [8]. However, multiple studies have investigated the efficacy and toxicity of SRS and BRAFi, reporting no significant increase in side effects [9–12]. Given the controversy between these studies, the aim of our project is to report our own institutional experience with SRS and BRAFi for MBM patients.

Methods

Patients

After receiving Institutional Review Board approval, we retrospectively identified 87 consecutive patients with MBM with a total of 157 brain metastases (BM) treated with SRS from 2007 to 2014.

The half-life of VMF and DAB is 40 h [13] and 8 h [14], respectively. Assuming that it takes five half-lives to clear the drug [15], we included patients treated with VMF 12 days before SRS or DAB 2 days before SRS. We also included patients treated concurrently or after SRS. Patients treated without a BRAFi were included in the SRS-alone group.

All patient charts were reviewed for the following baseline characteristics at the time of initial SRS: age, sex, clinical trial enrollment, number of brain metastases, presence of active systemic disease, primary controlled, Eastern Cooperative Group Oncology performance status, recursive partitioning analysis (RPA), melanoma specific graded performance assessment score, lactate dehydrogenase (LDH) value, previous systemic therapy, and next systemic therapy. Radiation treatment parameters were also recorded, including the number of fractions, dose per fraction, cumulative total dose, treatment to an intact metastasis or resection cavity, conformity index, prescription isodose line, cumulative gross tumor volume (GTV), and planning target volume (PTV) margin.

Radiation treatment

Technical details of SRS have been described previously [16,17]. Briefly, SRS was delivered using a frameless linear accelerator-based radiosurgery unit with 6 MV photon beams. The T1 postcontrast MRI defined lesion constituted the GTV. No margin was used to create a clinical target volume. The GTV was expanded by 1 mm to generate the PTV. The radiation dose was prescribed on the basis of the size of the lesion and its proximity to other structures. Lesions up to 20 mm in diameter were treated to 21 Gy, 21–30 mm in diameter to 18 Gy, and 31–40 mm in diameter to 15 Gy. Patients with large lesions (typically > 40 mm in diameter) were treated with fractionated radiosurgery over three to five fractions using a frameless radiosurgery technique.

Follow-up

Post-SRS follow-up consisted of a clinical examination and brain MRI at 4–6 weeks, followed by clinical exam and MRI brain imaging every 3 months thereafter, unless clinically indicated at an earlier time point. Local recurrence (LR) was defined as the presence of new progressive nodular enhancement within a previous 80% isodose line of the previous SRS treatment. Distant intracranial failure (DIF) was defined as the presence of new enhancing lesions distinctly outside the previous SRS field.

Toxicity

Radiographic RN was defined as the development of a contrast-enhancing mass within previous SRS fields; if there was a question of the nodular enhancement representing LR versus RN, cases were discussed at a multidisciplinary tumor board to develop a consensus. Additional functional imaging was also obtained (e.g. magnetic resonance perfusion, magnetic resonance spectroscopy, or brain PET) to further aid evaluation. For patients who were symptomatic from these adverse events, steroids were initially used. In patients with continued symptoms, hyperbaric oxygen and/or bevacizumab were also considered, whereas surgery was reserved for refractory patients and/or where the diagnosis remained unclear. Patients who underwent salvage surgical resection were deemed to have an LR if there was evidence of any residual disease, whereas patients with only necrosis (and no residual disease) were considered to have RN.

Statistical analysis

The SRS-alone and SRS + BRAFi groups were compared across categorical covariates using χ^2 or Fisher's exact tests, where appropriate, and were compared across continuous variables using analysis of variance. For OS, death from any cause was defined as the event and patients were censored at the time of last follow-up. OS was estimated using the Kaplan–Meier product-limit method; the log-rank test was used to assess for differences between patients in the SRS-alone cohort and the SRS + BRAFi cohort. A univariate analysis and MVA was carried out using the Cox proportional hazards model.

Nonsurvival outcomes—LR, DIF, RN, and symptomatic radiation necrosis (SRN) were estimated using the cumulative incidence methodology, with death without the event considered a competing risk. For these intracranial outcomes, patients were censored at the time of last brain imaging or salvage WBRT, whichever came first. Cumulative incidence curves for each nonsurvival outcome were compared between groups with death as a competing risk using Gray's test for equality across groups [18]. Univariate and multivariable regression analyses using the semiparametric proportional hazards model in the presence of competing risks were carried out as proposed by Fine and Gray [19]. All potentially prognostic covariates that were statistically significant in the univariate analysis were entered into the multivariable model. All analyses were carried out using SAS, version 9.4.0 statistical software (SAS Institute Inc., Cary, North Carolina, USA). All statistical tests were two sided, with *P*-values less than 0.05 considered statistically significant.

Results

Patient characteristics

Of the 87 MBM patients identified, 15 (17.2%) received BRAFi. Fourteen of 15 (93.3%) patients in the BRAFi cohort were treated with VMF, with the other patient treated with DAB. Three patients (20.0%) received treatment before SRS, one patient (13.3%) received concurrent treatment with SRS, and 10 patients (66.7%) received BRAFi after SRS. The median time between SRS and BRAFi was 40 days. A total of 157 BM were treated, 125 (79.6%) with SRS alone and 32 with SRS + BRAFi (21.4%). Median imaging follow-up was 6.5 (0.4–152.3 months) and 18.9 months (2.13–152.3 months) for all patients and living patients at follow-up, respectively. Table 1 shows that the two groups were statistically similar, except for a higher rate of previous chemotherapy (*P*=0.017), type of next systemic therapy (*P*<0.001), and more recent year of diagnosis (*P*<0.001) for the SRS + BRAFi cohort. The rates of immune therapies were similar between cohorts. Thirty-nine (44.8%) patients were treated for multiple BM. The SRS + BRAFi cohort had a trend toward lower rates of single metastases [(33.3 vs. 59.7%) *P*= 0.062] and melanoma specific graded performance assessment less than 3 [(53.3 vs. 26.4%) *P*=0.063]. In terms of radiation treatment characteristics, patients in the BRAFi group did have a trend toward tighter PTV margin (93.8 vs. 76.2%, *P*= 0.057); there were no other differences in radiation parameters, including number of fractions, radiation dose per fraction, cumulative GTV volume, and prescription isodose (Table 1).

Overall survival

No difference in OS was identified between the cohorts ($P=0.20$) in univariate analysis. Six and 12-months OS for the SRS-alone and SRS + BRAFi groups are 72.8 vs. 78.6% and 40.4 vs. 64.3%, respectively (Fig. 1). Univariate analysis showed LDH as the only statistically significant predictor for survival; however, this was not significant on MVA.

Intracranial control

Fifteen patients (17%) developed LR (Fig. 2). The median time to LR was 4.37 months (0–18 months). There was no difference in the rates of LR between the SRS + BRAFi and the SRS-alone cohorts (3.3 vs. 9.6% at 1 year, $P=0.43$). Univariate analysis showed melanoma-specific GPA ($P=0.019$), RPA ($P<0.001$), and number of BM ($P<0.001$) to be associated with improved LR-free survival. In addition, active systemic disease ($P=0.02$) was associated with increased LR. On MVA, only the presence of two or more BM [hazard ratio (HR) = 0.10; 95% confidence interval (CI), 0.01–0.85; $P=0.035$] and RPA class 1 (HR = 8.89; 95% CI, 1.17–67.46) were significant.

DIF was evident in 71.3% (62) of patients. There was no statistical difference in the rates of DIF between the SRS and SRS + BRAFi groups (35.0 vs. 53.2% at 6 months, 63.9 vs. 65.1% at 1 year; $P=0.45$). Controlled primary disease (HR: 0.48; 95% CI, 0.27–0.87; $P=0.016$) and LDH (HR = 1.001; 95% CI, 1.0003–1.00017; $P=0.003$) were significantly associated with DIF on MVA.

We also measured the initial radiographic response to therapy. The mean lesion size at the time of diagnosis was statistically similar between the SRS and the SRS + BRAFi cohorts: 13.18 vs. 9.57 mm, respectively. At 3 months after treatment, the mean lesion size decreased to 12.2 and 8.43 mm in the two groups. A statistically significant difference in the mean percentage change of lesion size was not found between the two groups: 12.2% for SRS vs 15.1% for SRS + BRAFi ($P=0.252$). Figure 3 shows an example of a patient treated with SRS and the related changes to the two lesions in this patient.

Radiation necrosis

RN, measured at the lesion level, was higher in the SRS + BRAFi cohort (at 1 year: 22.2 vs. 11.0%, $P<0.001$). The median time to RN was 8.1 months. Fifteen of the 23 (65.2%) patients who ultimately developed RN were symptomatic; 14 of these patients (93.3%) received steroid treatment. Two (14.2%) patients remained symptomatic despite medical management and required surgical intervention. On comparing the rates of SRN, patients receiving BRAFi correlated with higher rates than the SRS-alone cohort (at 1 year: 28.2 vs. 11.1%, $P<0.001$) (Fig. 4). Of the eight SRS + BRAFi patients developing SRN, three received the BRAFi before SRS, one received it concurrently, and four received the BRAFi after SRS. Table 2 compares the basic side effect profile of the two groups.

The use of BRAFi was associated significantly with RN on univariate analysis (HR: 3.42; 95% CI, 1.68–6.98; $P=0.001$) and MVA (HR: 3.38; 95% CI, 1.32–8.66; $P=0.011$) (Table 3). Patients who had received previous chemotherapy had lower rates of RN on MVA (HR: 0.13; 95% CI, 0.02–0.97; $P=0.046$).

Furthermore, on univariate analysis for SRN, BRAFi and active systemic disease were significant predictors. MVA confirmed the association between BRAFi (HR: 6.10; 95% CI, 2.37–15.70; $P = 0.001$) and SRN. The presence of active systemic disease was associated with decreased SRN on univariate analysis (HR: 0.33; 95% CI, 0.11–0.95; $P = 0.040$) and showed a trend on MVA (HR: 0.34; 95% CI, 0.11–1.02; $P = 0.054$). No radiation parameters – including cumulative radiation dose, number of fractions, GTV volume, nor margin – were found to be significant predictors for RN or SRN on MVA.

Discussion

As recent advances in systemic agents, including BRAFi and immune therapies, have improved OS in metastatic melanoma, measures to improve quality of life are becoming paramount. Although these newer therapies have shown extracranial efficacy, their intracranial potency is often limited by the blood–brain barrier. To overcome this, SRS is often combined with systemic therapies to provide intracranial and extracranial control, respectively. However, studies investigating the safety of these therapies in sequence are needed to verify that patients do not develop significant toxicity and other related detriments to quality of life.

RN is a late adverse side effect of SRS; treatment for symptomatic patients includes steroids, hyperbaric oxygen, bevacizumab, and/or surgical intervention. Although these treatments can be effective, they may result in significant morbidity. Methods to avoid excessive RN and related treatment are therefore crucial. Although preclinical studies suggest minimal penetration of the intact BBB by VMF [20], radiation therapy has been shown to increase permeability of the BBB [21]. Therefore, a transient disruption in the BBB following radiation can potentially enhance the uptake of BRAFi, increase radiosensitivity, and theoretically exacerbate toxicities. In light of this and case reports showing an increased risk of RN, the current NCCN guidelines raise caution on the use of the combination of BRAFi and radiotherapy.

Four studies have suggested that the delivery of SRS and BRAFi is a regimen not associated with an increased risk of RN (Table 4). The first published study by Narayana *et al.* [11] reported on 12 patients treated with SRS and/or WBRT and VMF, with one patient developing RN; another series by Ahmed *et al.* [9] reported on 24 patients treated with only SRS and VMF and also found that one patient developed SRN that required surgery. Gaudy-Marqueste *et al.* [12] reported on 30 patients treated with SRS and BRAFi. Similar to our study, their BRAFi cohort included patients treated concurrently, after, or five half-lives before SRS was delivered. These authors did show that 13.3% of lesions had a greater than 20% decrease in size; however, minimal toxicity was noted. From these three series, the rates of RN do appear low. Nevertheless, the rates of RN compared with a contemporaneous cohort of BRAFi alone or SRS alone remain unclear.

To directly compare the outcomes of patients and to account for differences in baseline characteristics, Ly *et al.* [10] reported on their institutional experience of SRS alone and SRS and BRAFi for MBM. The authors found that the BRAFi cohort was associated with a higher risk of hemorrhage, but they did not report on RN. Furthermore, all of these studies

have used Kaplan–Meier statistics to determine rates of RN or adverse events; however, the cumulative incidence method with death as a competing risk for intracranial outcomes, including RN, has been suggested to be a more accurate model [18,19] in the brain metastases population that has a high-risk of death within 1 year.

In this study, we attempted to directly compare our BRAFi patients with SRS to SRS alone. We first included patients treated with BRAFi before the drug was potentially cleared (i.e. five half-lives) [13,14], during, or after completion of SRS. The median time between SRS and BRAFi in our study was 40 days. We then compared the incidence of RN in MBM patients treated with SRS and BRAFi with a cohort of SRS-alone patients. Using cumulative incidence model statistics, we found that BRAFi delivered in proximity to SRS was associated with significantly higher rates of SRN at 1 year (28.2 vs. 11.1%, $P<0.001$); furthermore, the BRAFi cohort was a significant factor in univariate and multivariate analyses for SRN. Treatment cohorts had similar patient baseline characteristics, except that the non-BRAFi cohort had higher rates of previous chemotherapy. Chemotherapy has been suggested to increase the risk of RN [22] and as such may be a potentially confounding factor to our results. However, the non-BRAFi group received higher rates of chemotherapy, suggesting that this group may have higher rates of RN; this is in contrast to our result that the BRAFi group had higher SRN. Furthermore multiple prospective studies [23–25] and a large retrospective study [26] investigating predictors for RN showed that chemotherapy is not a predictor for radiographic nor SRN.

The SRS alone cohort did have more patients with margin higher than 2 mm; PTV margin expansion, which reflects the amount of normal irradiated brain tissue, is a known predictor for RN [26]. However, PTV margin higher than 1 mm was not a significant predictor for RN on univariate analysis ($P=0.296$).

Although our study suggests that RN may be elevated with BRAFi treatment, one limitation is that we do not have a cohort of BRAFi alone – which itself may cause intracranial toxicity – to directly compare with. Two prospective trials have investigated BRAFi alone, the first with VMF (2) and the second with dabrafanib (4), with both showing no incidence of CNS grade 2 toxicities or higher. In light of these reports, we believe that our finding of SRS and BRAFi to be associated with RN is provocative.

Our study, however, has multiple limitations, including its retrospective design, small sample size, and nonrandomized cohorts, which could contribute toward selection bias. Another limitation of our study is the variety in treatment sequence and timing of delivery between treatments. Finally, distinguishing RN from LR can be quite challenging. The five patients requiring surgical resection highlight this: two were found to have pathologic evidence of RN only, whereas three had RN and locally recurrent tumor. The strengths of this study include its homogenous follow-up/surveillance schedule, statistical model accounting for the cumulative incidence of the outcome with death as a competing risk, and the use of multivariate analysis to adjust for potential confounding variables.

Conclusion

Our retrospective institutional experience use of BRAFi with SRS was not associated with improved survival or intracranial control. Furthermore, patients treated with this regimen developed increasing rates of RN and SRN. Prospective studies investigating BRAFi therapy and SRS for MBM should consider incorporating methods to decrease potential RN in high-risk patients, including fractionated radiosurgery [27] or preoperative radio-surgery [28].

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Figure 1.

Kaplan–Meier curve showing the comparison of stereotactic radiosurgery (SRS) with BRAF inhibitor (solid line) to SRS alone (dashed line) with respect to overall survival. BRAFi, BRAF inhibitor.

Figure 2.

Competing risk model showing the comparison of stereotactic radiosurgery (SRS) with BRAF inhibitor (square) to SRS alone (triangle) with respect to local control (white) and death (black). BRAFi, BRAF inhibitor.

Figure 3.

Change in the size of lesion 3 months after stereotactic radiosurgery. MRI, T1 before (top panels) and after (bottom panels) contrast. Images on the left are 3 months after treatment; images on the right are at the time of initial stereotactic radiosurgery. The lesion in the right temporal lobe is stable in size; the lesion in the left medial occipital lobe develops hemorrhage, as can be seen by increased intensity on T1 precontrast MRI scans. This patient was in the non-BRAF inhibitor cohort.

Figure 4. Competing risk model showing the comparison of stereotactic radiosurgery (SRS) with BRAF inhibitor (square) to SRS alone (triangle) with respect to symptomatic radiation necrosis (white) and death (black). BRAFi, BRAF inhibitor.

Table 1

Baseline patient and treatment characteristics between SRS-alone and SRS + BRAFi cohorts

Covariates	SRS alone (72 patients or 125 lesions)	SRS + BRAFi (15 patients or 32 lesions)	P-value*
Performance status [<i>n</i> (%)]			
0	22 (30.6)	5 (33.3)	1.000
1	32 (44.4)	7 (46.7)	
>1	18 (25)	3 (20)	
Age [<i>n</i> (%)]			
65	48 (66.7)	11 (73.3)	0.765
>65	24 (33.3)	4 (26.7)	
Sex			
Male	55 (76.4)	11 (73.3)	0.751
Female	17 (23.6)	4 (26.7)	
Melanoma-specific GPA [<i>n</i> (%)]			
<3	19 (26.4)	8 (53.3)	0.063
3–4	53 (73.6)	7 (46.7)	
Active systemic disease [<i>n</i> (%)]			
Yes	49 (68.1)	11 (73.3)	0.769
No	23 (31.9)	4 (26.7)	
Primary controlled [<i>n</i> (%)]			
Yes	41 (56.9)	8 (53.3)	0.798
No	31 (43.1)	7 (46.7)	
Number of BM [<i>n</i> (%)]			
1	43 (59.7)	5 (33.3)	0.062
>1	29 (40.3)	10 (66.7)	
RPA			
1	11 (15.3)	1 (6.7)	0.683
>1	61 (84.7)	14 (93.3)	
Previous systemic therapy [<i>n</i> (%)]			
Yes	40 (55.5)	11 (73.3)	0.203
No	32 (44.5)	4 (26.7)	
Previous chemotherapy [<i>n</i> (%)]			
Yes	21 (29.2)	0 (0)	0.017
No	51 (70.8)	15 (100)	
LDH [<i>n</i> (%)]			
200	33 (45.8)	9 (60)	0.512
>200	22 (30.6)	3 (20)	
NR	17 (23.6)	3 (20)	
Year of diagnosis [<i>n</i> (%)]			
2000–2009	44 (61.1)	1 (6.7)	<0.001
2010–Later	28 (38.9)	14 (93.3)	
Next systemic therapy [<i>n</i> (%)]			

Covariates	SRS alone (72 patients or 125 lesions)	SRS + BRAFi (15 patients or 32 lesions)	<i>P</i> -value*
Yes	59 (81.9)	13 (87.7)	1.000
No	13 (18.1)	2 (13.3)	
Type of next systemic therapy [<i>n</i> (%)]			
None	13 (18.1)	2 (13.3)	<0.001
Chemo	41 (56.9)	4 (26.7)	
Immune	17 (23.6)	4 (26.7)	
Targeted therapy	1 (1.4)	5 (33.3)	
Number of systemic therapies [<i>n</i> (%)]			
0	32 (44.4)	4 (26.7)	0.445
1	29 (40.3)	8 (53.3)	
2	11 (15.3)	3 (20)	
Number of fractions [<i>n</i> (%)]			
1	119 (95.2)	30 (93.8)	0.666
>1	6 (4.8)	2 (6.2)	
Margin (mm) [<i>n</i> (%)]			
0–1	96 (76.8)	30 (93.8)	0.057
>1	25 (20.0)	2 (6.2)	
Unknown	4 (3.2)	0 (0)	
Median cumulative radiation dose (Gy) (range)	21 (15–30)	21 (15–30)	0.122
Median radiation dose per fraction (Gy) (range)	21 (6–24)	21 (6–24)	0.732
Median GTV volume (range) (cm ³)	0.49 (0.02–33.70)	0.12 (0.01–17.90)	0.267
Median prescription IDL (range) (%)	80 (80–100)	80 (80–96)	0.705

BM, brain metastases; BRAFi, BRAF inhibitor; GPA, graded prognostic assessment; GTV, gross target volume; IDL, isodose line; LDH, lactic dehydrogenase; NR, not recorded; RPA, recursive partitioning analysis; SRS, stereotactic radio-surgery.

Bold *P* values indicates statistical significance, *P* < 0.05.

Table 2

Side effects between SRS-alone and SRS + BRAFi cohorts

Side effects	SRS alone (125 lesions) (%)	SRS + BRAFi (32 lesions) (%)
Radiation necrosis	12	34.4
Acute hemorrhage	3.2	0

Rates of both adverse events are not statistically different between the two cohorts.

BRAFi, BRAF inhibitor; SRS, stereotactic radiosurgery.

Table 3

Univariate & multivariate factors for radiation necrosis

Covariate	Univariate analysis					Multivariate analysis				
	Time to radiation necrosis					Time to radiation necrosis				
	Level	[n (%)]	HR (95% CI)	HR P-value	Type3 P-value	Level	HR (95% CI)	HR P-value	Type3 P-value	
BRAF ⁱ	Yes	32 (20.4)	3.42 (1.68–6.98)	<0.001	<0.001	Yes	2.44 (1.19–5.03)	0.015	0.015	
	No	125 (79.6)	–	–	–	No	–	–	–	
Previous chemotherapy	Yes	36 (23.0)	0.09 (0.01–0.69)	0.020	0.020	Yes	0.13 (0.02–0.97)	0.046	0.046	
	No	121 (77.0)	–	–	–	No	–	–	–	

BRAFⁱ, BRAF inhibitor; CI, confidence interval; HR, hazard ratio.

Bold P-values indicates statistical significance, *P*<0.05.

Table 4

Studies investigating the safety of SRS and BRAFi for melanoma brain metastases patients

References	Type of BRAFi	Sequence of therapy	Number of SRS + BRAFi patients	Statistical model used for intracranial outcomes	% RN (at 12 months)	
					SRS + BRAFi cohort	SRS cohort
Narayana <i>et al.</i> [11]	VMF	Concurrent	12	KM	8.3 ^a	NR
Ly <i>et al.</i> [10]	VMF, DAB	Concurrent and sequential	17	KM	NR	NR
Ahmed <i>et al.</i> [9]	VMF	Concurrent (held 2–3 days before/after)	24	KM	4.2	NR
Gaudy-Marqueste <i>et al.</i> [12]	VMF, DAB	Concurrent, before, or after ^a	30	KM	0.0	NR
Present study	VMF, DAB	Concurrent, before or after ^a	15	Cumulative incidence, competing risk for death	22.2	11.0

BRAFi, BRAF inhibitor; DAB, dabrafenib; KM, Kaplan–Meier; NR, not reported; RN, radiation necrosis; SRS, stereotactic radiosurgery; VMF, vemurafenib.

^aBefore specifically refers to delivering the SRS within five half-lives of stopping the BRAF inhibitor.