In recent years, the incidence of melanoma in all age groups has been increasing in the United States. The cumulative incidence of brain metastases for all patients with melanoma is between 7.4% and 11.1%. Stereotactic radiosurgery (SRS) is an effective treatment option that results in high rates of local control. SRS treatment of brain metastases in select patients with melanoma may be associated with improved survival.

Systemic management of metastatic melanoma has focused on agents that can improve overall survival and intracranial response. BRAF is a protein kinase that has been implicated in cell proliferation and differentiation and is mutated in 70% of patients with melanoma. Mutation in the BRAF gene protects cells from apoptosis. Targeted therapies for the BRAF V600E mutation have been developed. Vemurafenib was shown in a randomized controlled trial to prolong overall survival. In addition, dabrafenib has been shown to improve progression-free survival. Dabrafenib showed an overall intracranial response of 39% in patients with melanoma if they did not have previous local treatment. Vemurafenib was studied in patients with untreated melanoma brain metastases and was associated with an intracranial response of 53%.

Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment

David Ly, MD, Hilary P. Bagshaw, MD, Christopher J. Anker, MD, Jonathan D. Tward, MD, PhD, Kenneth F. Grossmann, MD, PhD, Randy L. Jensen, MD, PhD, and Dennis C. Shrieve, MD, PhD

Department of Radiation Oncology and Division of Oncology, Huntsman Cancer Hospital, and Department of Neurosurgery, University of Utah, Salt Lake City, Utah; and Division of Radiation Oncology, University of Vermont Cancer Center, Burlington, Vermont

OBJECT BRAF inhibitors improve progression-free and overall survival in patients with metastatic melanoma. Brain metastases are common, and stereotactic radiosurgery (SRS) has been used, resulting in excellent local control. Because BRAF inhibitors are associated with intracranial responses, the authors hypothesized that BRAF inhibitors would improve local control in patients with melanoma who are receiving SRS for brain metastases.

METHODS The authors retrospectively identified patients with metastatic melanoma who had been tested for BRAF mutation and treated with SRS for brain metastases. Patients with previous resection, multiple brain metastases, or multiple courses of SRS were eligible. SRS was delivered in a single fraction to a median dose of 2000 cGy. Patients with a BRAF mutation were treated with a BRAF inhibitor on the basis of physician preference.

RESULTS The authors identified 52 patients who were treated in 82 treatment sessions for 185 brain metastases and 13 tumor beds. At a median follow-up of 10.5 months, the 1-year local control rate was 69.2%. At 1 year, the local control rate for brain metastases in patients with BRAF mutation with BRAF treatment was 85.0%, and the local control rate for brain metastases in those without BRAF treatment was 51.5% (p = 0.0077). The rates of distant brain failure, freedom from whole-brain radiation, and overall survival were not different on the basis of BRAF mutation status or inhibitor therapy. The number of new intratumoral hemorrhages after SRS was increased significantly in patients with BRAF treatment.

CONCLUSIONS Treatment with BRAF inhibitors was associated with improved local control after SRS in patients with melanoma and brain metastases. An increased number of intratumoral hemorrhages was associated with BRAF inhibitor therapy.

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KEY WORDS stereotactic radiosurgery; melanoma; BRAF; brain metastases; BRAF inhibitor
Although systemic agents have shown promise, local therapies such as surgery and irradiation remain the mainstay of treatment for brain metastases. In a study of vemurafenib, patients were eligible only if their disease had progressed despite local therapy. In the study, 25% of the 24 subjects underwent SRS. Because of the favorable local control rates provided by SRS and the promise of BRAF inhibitors in the extracranial/intracranial setting, it is likely that many patients with melanoma and brain metastases will undergo both treatments.

We hypothesize that the addition of BRAF inhibitor therapy will improve local control in patients with melanoma who undergo SRS for brain metastases.

Methods

Patient Selection

We retrospectively identified patients who were 18 years or older with metastatic melanoma who received their first course of radiation for brain metastases with SRS at the University of Utah and completed testing for BRAF mutation between 2009 and 2012. This study was approved by the University of Utah institutional review board, which waived the need for informed consent. Patients who had resection, multiple brain metastases, or multiple courses of SRS were included in this study. Patients with previous brain irradiation were excluded.

Radiation Therapy

SRS was delivered using a frameless linear accelerator–based radiosurgery unit. Target volumes were treated in a single treatment fraction by using a dynamic conformal arc technique with 6-MV photon beams. Stereotactic treatment planning was completed using the iPlan system (BrainLAB). The planned target volume was the brain metastasis or resected tumor bed without additional expansion. The prescription isodose surface was selected such that ≥95% of the target volume was encompassed by the prescription isodose volume and ≥99% of the target volume was covered by ≥95% of the prescription dose. The median dose delivered was 2000 cGy. Salvage treatment for recurrent lesions included SRS and surgery in select cases. Salvage treatment for distant brain disease was based on physician preference and included SRS or whole-brain radiation therapy. Whole-brain radiation therapy was administered using opposed laterals with 6-MV photon beams to a median dose of 3750 cGy in 15 fractions.

BRAF Mutation Testing and Inhibitor Treatment

Patients with metastatic melanoma had their tissue tested for BRAF mutation V600E at the University of Utah between 2009 and 2012. Patients who did not have the BRAF V600E mutation (wild-type BRAF) were not treated with BRAF inhibitor therapy. Patients with the BRAF V600E mutation were treated with a BRAF inhibitor (dabrafenib or vemurafenib) on the basis of physician preference, but it was typically initiated after other systemic treatments had failed (median 2 systemic treatments, range 0–5 systemic treatments). Patients were treated with a BRAF inhibitor for ≥60 days. BRAF inhibitor therapy could be initiated before or after SRS. The majority of the treated lesions (53.9%) were not treated with a BRAF inhibitor within a 30-day period before or after SRS. If the patient was on a BRAF inhibitor or was about to start a BRAF inhibitor (46.1%), a washout period was initiated before and after SRS (median 7 days, range 1–20 days). Of the 17 patients treated with BRAF inhibitor therapy, 9 were treated with 150 mg of oral dabrafenib twice daily, 4 were treated with 720 mg of oral vemurafenib twice daily, 3 were treated with 960 mg of oral vemurafenib twice daily, and 1 had unknown BRAF inhibitor treatment.

Definition of End Points

Patients were followed in multidisciplinary brain tumor clinics with serial contrast-enhanced brain MRI. The primary end point was local control; treatment failure of a brain metastasis was defined as retreatment with surgery and/or radiotherapy and/or an increase in the ratio of the axial, sagittal, or coronal area as noted by the product of the length and width in the given plane by 25% on subsequent T1-weighted post–contrast-enhanced MR images after SRS. Local control was timed from the date of SRS. Patients were censored if they were lost to follow-up, developed a hemorrhage of a treated lesion (as seen on a T1-weighted image), or at the start of any subsequent whole-brain radiation therapy secondary to distant brain disease. Distal brain failure was defined as development of new brain metastases on the T1 post–contrast-enhanced MR images obtained after the date of the SRS. Patients were censored for distant brain failure if they were lost to follow-up. Overall survival was calculated at the time of death from any cause from the time of SRS. Patients were censored for overall survival if they were lost to follow-up. Hemorrhage was identified as a hyperintense signal on the T1-weighted MR images before SRS and on all subsequent MRI scans.

Statistical Analysis

Statistical analysis was completed using StatsDirect 2.7.9 statistical software. The Student t-test (unpaired, 2-sided test) for the comparison of means and the chi-square test for comparisons of proportions were used to assess differences in patient demographics. The chi-square test and the Fisher exact test were used for univariate analyses to examine the association of the end point and given outcome. We used the Kaplan-Meier method to assess the time to the end point. To compare the survival distributions of 2 samples, the log-rank test was used. A p value of ≤0.05 was considered significant.

Results

Demographics

We identified 52 patients (median follow-up time 10.5 months) who met the study criteria. A total of 198 brain lesions (185 brain metastases and 13 operative beds) were treated in 82 treatment sessions (median 1 session, range 1–6 sessions) with a median dose of 2000 cGy (range 1500–2400 cGy). Complete demographic data are shown in Table 1. Of the 52 patients who were treated, 31 had the BRAF mutation and 21 had the wild-type BRAF gene. Of the patients who were positive for BRAF mutation, 17 (54.8%) were treated with a BRAF inhibitor. Of the 198 lesions treated with SRS, 21 lesions were treated with
BRAF therapy before SRS, 34 lesions were treated with BRAF therapy before and after SRS, 41 lesions were treated with BRAF therapy after SRS, and 102 lesions were not treated with BRAF therapy. There were no significant differences, other than mutation status, between the patients treated with or without a BRAF inhibitor (Table 2).

Local Control

The 1-year local control rate for all the brain lesions was 69.2% (Fig. 1). There were a total of 38 treatment failures; 14 of 59 (23.7%) failures occurred in the lesions of patients with wild-type BRAF, and 24 of 139 (17.3%) failures occurred in the lesions of patients with BRAF mutation. Of the 185 patients with brain metastases, 41 (22.2%) had a complete response. At 1 year, the local control rate for brain lesions in patients with wild-type BRAF was 67.1%, whereas the 1-year local control rate for brain lesions in patients with BRAF mutation was 70.0% (p = 0.12). In patients with BRAF mutation, BRAF inhibitor treatment was associated with improved local control (Fig. 2) (p = 0.0077). At 1 year, in patients with BRAF mutation, the local control rate for brain lesions for those who had BRAF inhibitor treatment was 85.0%, and the local control rate for those who did not have BRAF inhibitor treatment was 51.5%. The significance level for local control did not change when the patients with wild-type BRAF were added to the cohort (Fig. 3). At 1 year, the local control rate for brain lesions in patients who had BRAF inhibitor treatment was 85.0%, whereas the local control rate for patients without BRAF inhibitor treatment was 60.0% (p = 0.013). However, there was no difference in local control when we compared the patients with BRAF mutation who did not have BRAF inhibitor treatment (hazard ratio [HR] 2.44, 95% confidence interval [CI] 1.13–5.32) and the patients with wild-type BRAF (HR 0.99, 95% CI 0.43–2.31). We also evaluated the impact of BRAF inhibitor therapy before SRS versus no BRAF inhibitor therapy and found no association with local control when BRAF inhibitor therapy was initiated before SRS (HR 1.16, 95% CI 0.47–2.86; p = 0.75).

Distant Brain Failure

The 1-year distant brain control rate was 33.0% (median time to failure 5.5 months). At 1 year, the distant brain control rates in patients with wild-type BRAF and those with BRAF mutation were 33.0% and 32.3%, respectively (p = 0.25); there was no association with BRAF mutation status and distant brain control. In patients with BRAF mutation, BRAF inhibitor treatment was not associated with distant brain failure (p = 0.97). Similarly, distant brain failure was not affected when patients with wild-type BRAF who did not have BRAF inhibitor treatment were included in the cohort compared with patients with BRAF mutation who had BRAF inhibitor treatment (p = 0.54).

Freedom From Whole-Brain Radiation Therapy

Patients in this series who experienced distant brain failure were treated with additional courses of SRS or whole-brain radiation therapy. There were 30 additional SRS courses. Whole-brain radiation was administered to 17 (33.0%) of the 52 patients who were treated for brain metastases. The rate of 1-year freedom from whole-brain radiation therapy was 62.0% (median time to whole-brain

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irradiation 23.6 months). The use of BRAF inhibitor treatment did not decrease the use of whole-brain radiation ($p = 0.46$).

**Overall Survival**

Of 52 subjects, 36 (69.2%) had died by the last follow-up. At 1 year, the overall survival rate was 48.0% (median survival 12 months). Survival was not associated with BRAF mutation status; at 1 year, the survival rates for patients with BRAF mutation and those with wild-type $BRAF$ were 50.0% and 45.0%, respectively ($p = 0.30$). BRAF inhibitor treatment in patients who had BRAF mutation was not associated with overall survival. At 1 year, the overall survival rates were 50.2% and 42.9% for patients who had BRAF inhibitor treatment and those who had no treatment, respectively ($p = 0.82$). Overall survival did not change when the patients with wild-type $BRAF$ were included in the analysis ($p = 0.90$). Of the 36 deaths, 6 were attributed to unknown causes, 2 were attributed to infectious etiologies, and 8 were attributed to systemic disease. Twenty (55.6%) of the 36 deaths were related to CNS etiology (metastases, hemorrhage, etc.). Of the 20 deaths attributed to CNS causes, 15 (75.0%) were related to intratumoral hemorrhage.

**Hemorrhage**

Of the 198 treated lesions, 27 (13.6%) were associated with intratumoral hemorrhage before SRS. Hemorrhage before treatment did not differ by $BRAF$ mutation status ($p = 0.86$); of the 50 lesions in patients with wild-type $BRAF$, 8 hemorrhaged before treatment (16%), whereas of the 127 lesions in patients with $BRAF$ mutation, 19 hemorrhaged before treatment (15%). Intratumoral hemorrhage developed in 50 lesions (29.2%) after SRS. The median time to a new hemorrhage was 49 days from SRS. New intratumoral hemorrhage after SRS was not associated with $BRAF$ status ($p = 0.42$). In addition, we did not find an association with hemorrhage and the treated volume of the lesion (HR 1.02, 95% CI 0.99–1.06; $p = 0.17$). Increased hemorrhage risk was associated with BRAF inhibitor treatment in patients with BRAF mutation; in patients who were treated with a BRAF inhibitor and in those who were not, the 1-year rates of freedom from intratumoral hemorrhage were 39.3% and 77.0%, respectively (Fig. 4) ($p = 0.0003$).

**Univariate Analysis**

Univariate analysis was completed to assess the presence of associations between patient/treatment characteristics and local control of the treated volume. $BRAF$ mutation status, treatment volume, age, sex, radiation dose, and whether the patient had surgery before SRS were not associated with local control (Table 3). Because no other variables were significant for local control, a multivariate analysis was not completed.

**Discussion**

The prognosis for patients with metastatic melanoma has improved with newer systemic agents, including BRAF inhibitors. Brain metastases in this patient population continue to be a problem. The treatment of brain metastases requires a multimodal approach. SRS is an effective tool for controlling brain metastases in patients with melanoma; our study shows a local control rate of 69.2% at 1 year. This rate is consistent with those from previous studies, which have estimated 1-year local control rates after SRS of between 49% and 94.3%.4,19,24,26,30,32,38 In our review, patients with melanoma who underwent SRS for brain metastases and BRAF inhibitor therapy had improved local control. At 1 year, the local control rates in patients with $BRAF$ mutation who had BRAF treatment and those who did not have BRAF treatment were 85.0% and 51.5%, respectively. Previous studies of BRAF inhibitors in the intracranial setting assessed the overall response to BRAF inhibitor therapy, but they did not evaluate local control.8,25 Twelve patients who received both radiation and vemurafenib demonstrated a 6-month local control rate of 75%.

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The use of BRAF inhibitors and radiation therapy may have a synergistic effect. Because of the reported dermal reactions from radiation therapy and BRAF inhibitor therapy, BRAF inhibitors may cause radiosensitization.2 It was noted that, in a melanoma cell line, the addition of targeted agents to inhibit BRAF can enhance radiosensitization.34

![Fig. 2. Improved local control rates in patients with BRAF mutation who are treated with a BRAF inhibitor.](image1)

![Fig. 3. Improved local control rates in patients who are treated with a BRAF inhibitor.](image2)
Radiation therapy has been shown to increase permeability in the blood-brain barrier. The enhanced permeability of BRAF inhibitors by radiation can increase radiosensitivity and may improve local control. When BRAF inhibitor therapy was given before SRS, we did not find an association with local control; however, this may solely be a result of the relatively small number of patients who received BRAF inhibitor therapy in that setting. When we added patients who also received BRAF inhibitor therapy in the adjuvant setting, we noted improved local control.

Although BRAF inhibitor therapy is associated with improved local control, it is not associated with improved distant brain control. Despite significant CNS response rates, vemurafenib and dabrafenib do not cross the blood-brain barrier in high concentrations. The median time to distant brain progression in our cohort of patients was 5.5 months, which compares to the 4.4-month median duration of intracranial response noted by Dummer et al. in patients who received vemurafenib. However, in these previous studies in which the role of BRAF inhibitors was examined, distant brain control was not specifically studied. Because SRS is a targeted treatment, it can likely focally improve the blood-brain barrier penetration of a BRAF inhibitor. We hypothesize that BRAF inhibitors failed to impact distant brain control because the blood-brain barrier remains intact at other sites not treated with SRS. In addition, acquired resistance from BRAF therapy may affect distant brain control. Overcoming resistance may necessitate focusing on molecular targets, such as MEK. The use of combined BRAF and MEK inhibitors has resulted in improved progression-free survival. This study underscores the importance of developing therapies that can overcome the blood-brain barrier or be delivered intracereally.

Chapman et al. previously showed an increase in the overall survival rate from 64% in the dacarbazine cohort to 84% with vemurafenib at 6 months in patients with metastatic melanoma. In our study, patients who were treated with BRAF inhibitor therapy did not experience an improved overall survival. Patients with brain metastases were enrolled onto the study only if those brain metastases were treated definitively more than 3 months before enrollment and had no progression. It was not noted how many of the patients had distant metastatic brain disease. Our population was different, because our patients had known brain metastases that were treated with SRS.

In our cohort, we determined that a new hemorrhage occurred in 50 lesions (29.2%). Hemorrhage was associated with BRAF inhibitor therapy in our study; the rate of freedom from intratumoral hemorrhage was higher in patients who did not have BRAF therapy (77%) than in those who did have BRAF therapy (39%). SRS is not a risk factor for subsequent hemorrhage; a previous study by Ghia et al. found no association between SRS and the risk of subsequent hemorrhage in patients with melanoma brain metastases. Our report of increased risk of hemorrhage from BRAF therapy contradicts previous reports. Twenty-four patients with melanoma brain metastases who were treated with vemurafenib experienced mostly mild to moderate adverse effects, and no intracranial adverse effects were noted. In a study by Long et al., 172 patients received dabrafenib for metastatic brain lesions, and 10 (6%) had an intracranial hemorrhage, although only 1 was attributed to treatment. BRAF therapy with SRS in our cohort was associated with intratumoral hemorrhage.

Intratumoral hemorrhage may be a risk for death; a review of 333 patients with melanoma who were treated with SRS alone for brain metastases showed that 21% of them developed intratumoral hemorrhage. Hemorrhage was associated with decreased patient survival. In our cohort, 15 (75%) deaths of CNS etiology were related to intratumoral hemorrhage of a previously treated tumor. Overall survival was not different between our BRAF therapy groups. Despite the improved local control with BRAF inhibitor therapy, we hypothesize that overall survival was not different because of the higher rates of hemorrhage that were associated with BRAF inhibitor therapy. It is not certain whether there is a causative relationship between BRAF inhibitor therapy and hemorrhage in patients who received SRS. Previous trials in which the use of BRAF inhibitor therapy in the intracranial setting was examined did not have comparison groups to assess the differences in hemorrhage. In a series of 5 patients who received whole-brain radiation or SRS along with BRAF inhibitor therapy, there was no evidence of increased intracranial toxicity, including hemorrhage. Hemorrhage may not be the only intracranial toxicity. In a recent case report, 2 patients developed radiation necrosis of the brain after being treated with SRS followed by vemurafenib 1–2 weeks later. In a separate report, a patient developed radiation necrosis of the brain after receiving SRS while...
on vemurafenib. In our series, all the patients underwent SRS, which may have potentiated the effect of BRAF inhibitors and its toxicity.

Increased toxicity, including hemorrhage, has been noted in other organ sites with BRAF inhibitor therapy both with and without radiation therapy. In one case report, a patient with melanoma developed a splenic hematoma and capsule laceration without evidence of metastases after vemurafenib therapy. In another case report, Trappe et al. noted a patient with melanoma who developed disseminated intravascular coagulation after vemurafenib therapy. It was speculated that rapid regression of melanoma may have led to disseminated intravascular coagulation and proteolysis. In a case report by Anker et al., a patient with melanoma who was treated with vemurafenib experienced in-field hepatic injury with fatal hepatic hemorrhage after palliative spine radiation. Others have reported varying skin, lung, and bowel toxicities in patients after treatment with both radiation and BRAF inhibitors. The degree and length of the duration of these toxicities are concerning. Because of these reports and our findings, future studies should examine the relationship of BRAF inhibitor therapy and the use of radiation therapy in the intracranial setting. We recommend discontinuation of BRAF inhibitors for 1–2 weeks both before and after SRS treatment, provided systemic disease is controlled. We await data from a recently completed Phase II study of vemurafenib (ClinicalTrials.gov identifier NCT01378975), in which the efficacy and safety of treatment in patients with metastatic melanoma with brain metastases were assessed.

Our study is limited in that it was a retrospective review of our treated patients. BRAF inhibitor therapy was not initiated in a prospective manner but was typically given after failure of previous systemic agents. In our study, BRAF inhibitor therapy could have been given before and/or after SRS after a washout period. Because this was a retrospective study, the initiation of BRAF inhibitor therapy may have been biased and given to healthier patients. However, comparisons of demographics including age, Karnofsky Performance Scale scores, and recursive partitioning analysis classifications did not reveal significant associations between the BRAF-inhibitor-treatment group and the no-BRAF-inhibitor-treatment group. Another limitation of this study is that the initiation of BRAF therapy could have been given before or after SRS. When we evaluated the use of BRAF therapy when given only before SRS, there was no significant association; however, this may have been a result of the lack of patients in that cohort. The use of BRAF inhibitor therapy along with radiation should warrant a formal clinical trial based on the likelihood of radiosensitization with BRAF inhibitor therapies along with our finding of an association with improved local control with BRAF inhibitor therapy. Future clinical trials should randomly assign patients with BRAF mutation who have melanoma and brain metastases to receive SRS with BRAF inhibitor therapy or SRS alone.

Conclusions

To our knowledge, this is the first study to show an association for improved local control with the addition of BRAF inhibitors in patients with melanoma brain metastases treated with SRS. The addition of BRAF inhibitor therapy to SRS in melanoma brain metastases was found to be associated with an increased risk of intratumoral hemorrhage. Because of the potential toxicity of BRAF inhibitors, we recommend discontinuation for 1–2 weeks before and after SRS treatment, provided systemic disease is controlled.

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Author Contributions
Conception and design: Shrieve, Ly. Acquisition of data: Ly, Bagshaw. Analysis and interpretation of data: all authors. Drafting the article: Shrieve, Ly. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Shrieve. Statistical analysis: Shrieve, Ly, Bagshaw, Anker, Jensen. Administrative/technical/material support: Tward, Grossmann. Study supervision: Shrieve, Anker, Tward, Grossmann, Jensen.

Supplemental Information
Previous Presentation
 Portions of this work were presented in poster form at the American Society for Radiation Oncology 55th Annual Meeting held in Atlanta, Georgia, on September 22–25, 2013.

Correspondence
Dennis C. Shrieve, Department of Radiation Oncology, University of Utah, Huntsman Cancer Hospital, 1950 Circle of Hope Dr., Ste. 1570, Salt Lake City, UT 84112. email: dennis.shrieve@hci.utah.edu.