For the past 30 years, the incidence of malignant melanoma has been increasing at a faster rate than any other cancer in the United States. Advanced disease stage (III or IV) imparts a median survival time of less than 10 months. Among patients with Stage IV disease, the prevalence of brain metastases is as high as 40%–60%. Melanoma constitutes the third most common cause of brain metastases after carcinoma of the lung and breast. Brain metastases have been also shown to contribute directly as a cause of death in up to 95% of patients.

Metastatic melanoma has been argued by some to be relatively radioresistant and also demonstrates less responsiveness to certain chemotherapeutic agents. Melanoma cells can facilitate downregulation of proliferation pathway gene expression, assuming a more aggressive phenotype (“dynamic phenotype switching”), which enables them to metastasize in response to environmental conditions.
stress (e.g., hypoxia, radiation, or chemotherapy). Contemporary intracranial melanoma treatment approaches for oligo-metastatic brain disease employ a combination of surgical excision, systemic therapy, and stereotactic radiosurgery (SRS) to attain local control of brain metastases.

The categorization of the CNS as an immune-privileged site has for a time dampened the hopes for development of immunotherapies for brain tumors. FDA approval of cytokine-based therapy with interleukin-2 in 1998 and checkpoint blockade with ipilimumab in 2011 were major developments in melanoma treatment. Checkpoint blockade–based therapy demonstrates an improved tumor control and reduced toxicity compared with cytokine-based therapy. Ipilimumab was shown to increase survival in patients with unresectable Stage III or IV melanoma, resulting in its increased use and more patients being treated with a combination of SRS and ipilimumab. The exact nature of this interaction has not yet been elucidated. Kies et al suggested that patients undergoing SRS after ipilimumab. We report on a cohort of patients treated for melanoma brain metastases with a combination of ipilimumab and SRS. We specifically evaluated the effect of immunotherapy timing on post-SRS outcomes.

**Methods**

**Patient Population**

This study is a retrospective review of a prospectively maintained database, approved by the institutional review board at the University of Virginia (UVA). The database was assessed for all adult patients consecutively treated with SRS for melanoma brain metastases during 2009–2014. All patients included in the analysis had histologically confirmed melanoma and newly diagnosed brain metastases at the time of the first SRS session. All patients received at least 1 course of ipilimumab (either at UVA or at other facilities for which access to the patient's medical record was attained), with the timing determined by the oncologist. The median clinical and radiological follow-up periods were 7.9 months (range 0.4–42.6 months) and 6.2 months (0.4–34.7 months), respectively. Refer to Tables 1 and 2 for specific patient and tumor attributes.

**TABLE 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A* (n = 32)</th>
<th>Group B* (n = 14)</th>
<th>Total (n = 46)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yrs, median (range)</td>
<td>62.0 (24.3–83.6)</td>
<td>66.7 (48.4–83.6)</td>
<td>63 (24.3–83.6)</td>
<td>0.088</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>23.9 (71.9:28.1)</td>
<td>10.4 (71.4:28.6)</td>
<td>33.1 (71.7:28.3)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>KPS score at SRS</td>
<td></td>
<td></td>
<td></td>
<td>0.496</td>
</tr>
<tr>
<td>≤50</td>
<td>2</td>
<td>1</td>
<td>6.6% (n = 3)</td>
<td></td>
</tr>
<tr>
<td>&gt;60–80</td>
<td>3</td>
<td>3</td>
<td>13% (n = 6)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>27</td>
<td>10</td>
<td>80.4% (n = 37)</td>
<td></td>
</tr>
<tr>
<td>Melanoma GPA score</td>
<td></td>
<td></td>
<td></td>
<td>0.243</td>
</tr>
<tr>
<td>0–1</td>
<td>12.5% (n = 4)</td>
<td>14.3% (n = 2)</td>
<td>13% (n = 6)</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>53.1% (n = 17)</td>
<td>64.3% (n = 9)</td>
<td>56.5% (n = 26)</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>18.8% (n = 6)</td>
<td>0%</td>
<td>13% (n = 6)</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>15.6% (n = 5)</td>
<td>21.4% (n = 3)</td>
<td>17.4% (n = 8)</td>
<td></td>
</tr>
<tr>
<td>No. of brain metastases treated at 1st SRS (range)</td>
<td>5 (1–22)</td>
<td>4.5 (1–16)</td>
<td>5 (1–22)</td>
<td>0.866</td>
</tr>
<tr>
<td>Extracranial metastases at time of SRS</td>
<td>96.9% (n = 31)</td>
<td>92.9% (n = 13)</td>
<td>95.7% (n = 44)</td>
<td>0.521</td>
</tr>
<tr>
<td>Prior hemorrhage</td>
<td>6.3% (n = 2)</td>
<td>7.1% (n = 1)</td>
<td>6.5% (n = 3)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Prior resection</td>
<td>0</td>
<td>14.3% (n = 2)</td>
<td>4.4% (n = 2)</td>
<td>0.088</td>
</tr>
<tr>
<td>Prior systemic therapy (other than ipilimumab)</td>
<td>46.9% (n = 15)</td>
<td>78.6% (n = 11)</td>
<td>58.7% (n = 27)</td>
<td>0.046</td>
</tr>
<tr>
<td>Prior WBRT</td>
<td>9.4% (n = 3)</td>
<td>7.1% (n = 1)</td>
<td>8.7% (n = 4)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormally elevated LDH</td>
<td>68.8% (n = 22)</td>
<td>71.4% (n = 10)</td>
<td>69.6% (n = 32)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Median no. of ipilimumab treatment cycles (range)</td>
<td>4 (1–8)</td>
<td>3 (1–6)</td>
<td>4 (1–8)</td>
<td>0.666</td>
</tr>
<tr>
<td>Multiple SRS</td>
<td>37.5% (n = 12)</td>
<td>28.6% (n = 4)</td>
<td>34.8% (n = 16)</td>
<td>0.739</td>
</tr>
<tr>
<td>Steroid use at time of SRS</td>
<td>21.7% (n = 10)</td>
<td>13% (n = 6)</td>
<td>34.8% (n = 16)</td>
<td>0.512</td>
</tr>
</tbody>
</table>

LDH = lactate dehydrogenase; WBRT = whole-brain radiation therapy. Boldface type indicates statistical significance.

* Refer to text.
Group A and 31% (n = 72) in Group B. None of the tumor- and treatment-related parameters differed significantly between the groups (Table 2). The patients’ median age was 62 years (range 24.3–83.6 years) for the entire cohort. The median pre-SRS Karnofsky Performance Status (KPS) score as well as disease-specific melanoma graded prognostic assessment (GPA) score showed no significant differences between the groups. Prior systemic therapy (other than ipilimumab) was administered in 57.7% of cases (n = 27); the percentage of patients who received such therapy was significantly greater in Group B (78.6%, n = 11) than in Group A (46.9%, n = 15) (p = 0.046). The median number of ipilimumab treatment cycles administered was 4 (range 1–8). A standard dose of 3 mg/kg was employed.

Radiosurgical Technique
The details of SRS performed at UVA have been reported previously. All SRS was delivered using the Gamma Knife (Elekta AB). Radiosurgical parameters and dose plans were formulated by the treating neurosurgeon in consultation with a medical physicist and a radiation oncologist. The details of stereotactic MRI for radiosurgical planning varied over time, but planning generally included pre- and post-contrast, volumetrically acquired gradient-echo pulse sequences reconstructed into axial and coronal image stacks. In general, dose selection was based on RTOG 95–08 guidelines, but additional parameters, such as the total number of metastases, the tumor volume, and prior or planned whole-brain radiation therapy, were also factored into the dose selection process. The median tumor margin and maximum doses used in the series were 20 Gy (range 14–22 Gy) and 23.7 Gy (range 16.7–45.1 Gy), respectively.

Timing of SRS and Ipilimumab
Patients were assigned to one of 2 groups based on the relationship between the timing of SRS and ipilimumab treatment. Twenty-eight patients were treated with SRS before the first dose of ipilimumab; the median duration of time between SRS and the start of ipilimumab treatment for these patients was 2 weeks (range 3.8–53.6 months). An additional 4 patients were treated with SRS during the ipilimumab protocol (typically consisting of dose cycles every 3 weeks) or within 1 month of the last ipilimumab dose. These 32 patients (the 28 who received SRS before the first dose of ipilimumab and the 4 who received SRS during ipilimumab treatment) together constituted Group A. Another 14 patients were treated with SRS more than 1 month after completing ipilimumab treatment and constituted Group B (Tables 1–4). The patients in Group B were treated with SRS between 1 and 18 months after completing ipilimumab treatment (median 6 months) and typically underwent SRS for lesions discovered during routine follow-up.

Clinical and Radiological Evaluations After SRS
Following SRS, all patients underwent clinical and radiological evaluations at approximately 3-month intervals,

### Table 2. Tumor- and treatment-related parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A*</th>
<th>Group B*</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lesions</td>
<td>160</td>
<td>72</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>Max tumor diameter in cm</td>
<td>0.6 (0.2–6.2)</td>
<td>0.5 (0.2–6.0)</td>
<td>0.5 (0.2–6.2)</td>
<td>0.177</td>
</tr>
<tr>
<td>Radiation vol in cm³</td>
<td>0.2 (0.04–64.5)</td>
<td>0.1 (0.02–22.4)</td>
<td>0.15 (0.02–64.5)</td>
<td>0.183</td>
</tr>
<tr>
<td>Margin dose in Gy</td>
<td>20 (14–22)</td>
<td>20 (15–22)</td>
<td>20 (14–22)</td>
<td>0.731</td>
</tr>
<tr>
<td>Isodose</td>
<td>86.5% (50%–98%)</td>
<td>91% (50%–97%)</td>
<td>90% (50%–98%)</td>
<td>0.427</td>
</tr>
<tr>
<td>Max dose in Gy</td>
<td>24 (18.4–45.1)</td>
<td>23.5 (16.7–44)</td>
<td>23.7 (16.7–45.1)</td>
<td>0.395</td>
</tr>
</tbody>
</table>

Data are given as median (range) except where otherwise indicated. Refer to text.

### Table 3. Treatment-related adverse effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Group A* (n = 32)</th>
<th>Group B* (n = 14)</th>
<th>Total (n = 46)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>37.5% (n = 12)</td>
<td>20% (n = 4)</td>
<td>34.8% (n = 16)</td>
<td>0.56</td>
</tr>
<tr>
<td>Focal neuro deficit</td>
<td>21.9% (n = 7)</td>
<td>26.6% (n = 4)</td>
<td>24% (n = 11)</td>
<td>0.624</td>
</tr>
<tr>
<td>Headache</td>
<td>9.4% (n = 3)</td>
<td>40% (n = 6)</td>
<td>19.6% (n = 9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Seizure</td>
<td>18.6% (n = 6)</td>
<td>13.3% (n = 2)</td>
<td>17.4% (n = 8)</td>
<td>0.71</td>
</tr>
<tr>
<td>Cognitive change</td>
<td>9.4% (n = 3)</td>
<td>30.0% (n = 3)</td>
<td>13% (n = 6)</td>
<td>0.264</td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td>9.4% (n = 3)</td>
<td>6.7% (n = 1)</td>
<td>8.7% (n = 4)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>6.3% (n = 2)</td>
<td>13.3% (n = 2)</td>
<td>8.7% (n = 4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3.1% (n = 1)</td>
<td>13.3% (n = 3)</td>
<td>6.5% (n = 3)</td>
<td>0.158</td>
</tr>
</tbody>
</table>

* Refer to text.

Neuro = neurological.
Boldface type indicates statistical significance.
unless indicated earlier clinically. Some patients received follow-up care outside our institution, and in such instances the clinical information was gathered from patients’ charts and via phone calls. Each neuroimaging study was reviewed by an attending neurosurgeon and neuroradiologist at UVA. The response of the visible tumors was determined to be stable based on volumetry if the tumor was ±10% of the original volume. For small lesions, follow-up volume was assessed via recontouring of the lesions. MRI follow-up studies were reviewed for local tumor control, perilesional edema (new or worsening T2-weighted and FLAIR sequence changes), intraleSIONAL hemorrhage, and tumor necrosis (Tables 3 and 4). MRI studies were evaluated for distant brain metastases as well. Tumor necrosis was defined by either PET (showing reduced glucose uptake) or biopsy. Treatment-related adverse effects were defined as any adverse reaction occurring within 2 months of SRS or ipilimumab treatments. Regional recurrence–free duration (RRFD) was noted, defined as the period of time (in months) from SRS to occurrence of brain (regional) recurrence. Local recurrence–free duration (LRFD) was noted, defined as the period of time (in months) from SRS to occurrence of local (previously treated area) recurrence.

### Statistical Methods

The patient cohort was stratified based upon the timing of SRS in relation to ipilimumab treatment as described above. Overall survival (OS) was defined as the time interval between the date of diagnosis of brain metastases on the basis of MRI and the date of death or last clinical follow-up. Kaplan-Meier plots were used to analyze patient survival. Tests for statistically significant between-groups differences in survival were computed using the log-rank test. The difference in survival was computed using the log-rank test. RRFD and LRFD were analyzed similarly.

Categorical variables were compared using chi-square or Fisher’s exact tests. Parametric variables between the 2 timing groups (Group A and Group B) were compared using the median test. The comparison regarding age, numbers of metastatic deposits, and the median number of ipilimumab treatment cycles was computed using the Kruskal-Wallis test. A p value of less than 0.05 was deemed statistically significant. All statistical analyses were 2-sided and were performed using IBM SPSS-22 software.

### Results

**Intracranial Disease Response**

The overall median RRFD was 5.4 months (range 0.4–34.7 months), with no significant difference between the 2 timing groups (median 7.2 months [range 1.1–34.7 months] in Group A vs 5.0 months [range 0.4–20.4 months] for Group B, p = 0.487). The 3-, 6-, and 12-month actuarial rates of freedom from regional recurrence for Group A were 77.8%, 50.4%, and 25.8%, respectively. The corresponding 3-, 6-, and 12-month rates for Group B were 74.6%, 33.6%, and 16.8% (Fig. 1B). The overall median LRFD was 8.4 months (range 0.4–34.7). The median LRFD was significantly longer in Group A (19.6 months, range 1.1–34.7 months) than in Group B (3 months, range 0.4–20.4 months) (p = 0.005). The 3-, 6-, and 12-month actuarial rates of freedom from local recurrence for Group A were 96.8%, 72.6%, and 54.4% respectively. The corresponding 3-, 6-, and 12-month rates for Group B were 61.9%, 16.5%, and 16.5%. During the LRFD, 9 patients (28.1%) in Group A and 2 patients (14.3%) in Group B received other systemic therapy (p = 0.31).

**Survival After SRS**

For the entire study cohort, the median duration of survival after SRS was 13.4 months (range 1.2–43.2 months) (Fig. 1A). The median duration of survival for Group A was 13.8 months (range 2.7–43.2 months), and for Group B it was 6.4 months (range 1.2–24.5 months). The 3-, 6-, 12-, 18-, and 24-month actuarial survival rates for Group A were 96.9%, 81.3%, 59.2%, 41.8%, and 31.3%, respectively, and the corresponding rates for Group B were 85.7%, 57.1%, 33.3%, 25%, and 16.7%. The difference between the groups did not reach statistical significance (p = 0.118).

### Treatment-Related Adverse Effects

The most common adverse effects were fatigue (34.8%, n = 16), focal neurological deficit (24%, n = 11), headache (19.6%, n = 9), and seizures (17.4%, n = 8). With the exception of headaches, which were significantly more common in Group B (p = 0.008), there were no significant differences in treatment-related adverse effects be-
Radiosurgery and ipilimumab for melanoma brain metastases

J Neurosurg Volume 127 • November 2017

1011

between these 2 groups. A detailed description is presented in Table 3.

Complications

Post-SRS perilesional edema (T2-weighted or FLAIR sequence perilesional changes) was noted in 26.3% (n = 61), 27.9% (n = 31), 21.8% (n = 17), and 24.1% (n = 13) of lesions at 3, 6, 9, and 12 months post-SRS, respectively. The 2 groups showed a significant difference, mainly in short-term (3 months) and long-term (12 months) perilesional T2-weighted and FLAIR sequence white-matter changes, showing a significantly greater incidence in Group A (31.3% vs 15.3%, p = 0.011 at 3 months and 30.2% vs 0%, p = 0.048 at 12 months, respectively) (Table 4).

Lesion-related necrosis was noted at 1 year after SRS in 16.4% (n = 38) of lesions (fluorodeoxyglucose [FDG]-PET–based diagnosis in 34 lesions and biopsy-based diagnosis in 4 lesions). A trend was noted toward a lower incidence of treatment-related necrosis in Group A, but it did not reach statistical significance (19.4% vs 9.7%, p = 0.066), likely due to the small sample size. Intralesional hemorrhage was noted in 12.9% of lesions (n = 30), slightly, but not significantly, more frequently in Group A than in Group B (13.8%, n = 22, vs 11.1%, n = 8, respectively).

Discussion

The relative resistance of metastatic melanoma to conventional external beam radiation therapy and chemotherapy has hampered therapeutic approaches and outcomes. Activation of T-cells occurs in a 2-signal system. CTLA-4 receptor activation interrupts the co-stimulatory signal and restricts T-cell activation. Ipilimumab, a human monoclonal antibody that targets CTLA-4, interrupts this inhibitory checkpoint process, thus facilitating T-cell activation. Ipilimumab was shown to increase survival in patients with unresectable Stage III or IV melanoma. Ipilimumab’s effect in prolonging disease-free survival and OS in melanoma patients with brain metastases.

The use of ipilimumab with SRS in melanoma patients with brain metastases has been increasing in recent years. The exact nature of the interaction and interplay these 2 modalities share with the immune system is unknown. Considering the mechanism by which both treatment modalities exert their therapeutic effect as well as related toxicity (inflammation), one can speculate a synergistic increase of both upon concurrent treatment. One possible reason to combine SRS with ipilimumab is based on the potential CNS immune-priming activity of ipilimumab. Several studies reported a better OS with the combination of SRS and ipilimumab, while others showed no benefit in outcomes. Margolin et al. reported a possible abscopal effect with an increased systemic immune response to ipilimumab. Kiess et al. reported on a series of 46 patients harboring 113 metastatic lesions treated with a combination of ipilimumab and SRS. The authors reported a better OS and reduced regional recurrence in 34 patients treated with SRS before or during ipilimumab cycles as compared with 12 patients treated with SRS after ipilimumab (1-year...
OS 65% vs 56% vs 40%, p = 0.008; 1-year regional recurrence 69% vs 64% vs 92%, p = 0.003, respectively). Schoenfeld et al. recently reported on a small series of 16 patients with melanoma who received 1 to 8 courses of radiation (90% via SRS). Seven patients received ipilimumab before brain-directed radiation, and 5 patients began ipilimumab afterward. Four patients received radiation at some point while undergoing ipilimumab treatment and continued ipilimumab following radiation. The median OS following first radiation treatment among all patients was 14.4 months. Patients who received SRS prior to initiating ipilimumab treatment had superior OS as compared with patients who started ipilimumab treatment prior to receiving SRS (26 vs 6 months, p < 0.001). These findings should be interpreted with caution, considering the small sample sizes, as well as the fact that many reports have shown that the local control of brain metastases has little influence on OS. Knisely et al. reported the outcome of 27 patients with melanoma brain metastases treated with ipilimumab; 59.3% of the patients (n = 16) were treated with SRS before ipilimumab, and 40.7% (n = 11) were treated with SRS after ipilimumab. The median survival, based on Kaplan-Meier analysis, was 21.3 months (95% CI 6.43–26.7 months). No difference was found in the hazard for death with regard to the timing of ipilimumab and SRS (21.3 vs 19.8 months, p = 0.58). Ahmed et al. recently reported on a cohort of 26 patients with a total of 73 brain metastases treated over 30 sessions, with 7 (27%) of the 26 patients receiving nivolumab in an adjuvant setting. Radiation was delivered concurrently, before, or after nivolumab treatment for 17 (23%), 33 (45%), and 23 (32%) lesions, respectively. The authors reported that SRS was well tolerated and that, compared with historical data, brain metastasis local control rates were similar, whereas survival appeared longer.

We report on a cohort of 46 patients treated for melanoma brain metastasis deposits with a combination of ipilimumab and SRS, reviewing the effect of SRS timing on outcome parameters. Group A comprised 28 patients treated with SRS prior to ipilimumab and 4 patients treated with SRS during ipilimumab treatment cycles. With the exception of the timing of the treatment modalities, the 2 patient groups were comparable. Patient-related attributes, tumor-related features, and ipilimumab protocols delivered were similar (Table 1), with the exception of prior systemic therapy (other than ipilimumab), which showed a slightly higher incidence in Group B. The SRS treatment parameters were comparable between the groups (Table 2). Treatment-related adverse effects were comparable as well, with the exception of headache, which was experienced by a greater proportion of patients in Group B (9.4%, n = 3, vs 40%, n = 6) (Table 3).

An overall median survival of 13.4 months (range 1.2–43.2 months) was noted, better (although not significantly) in Group A (Fig. 1A), which was comparable with previously reported findings. A similar trend was noted for RRFD (Fig. 1B, p = 0.487). A statistically significant difference was demonstrated for the LRFD outcome parameter (Fig. 1C, p = 0.005). A clear local control advantage was shown for Group A and appears consistent with the immune-priming effect postulated. Reviewing the incidence of treatment-related local complications (Table 4), patients in Group A suffered a higher incidence of all measured complications, namely radiation- or tumor-induced necrosis at 1 year, intralesional hemorrhage at 1 year, and post-SRS perilesional edema at different time points post-SRS. The 2 outcome parameters for which a statistical significance was reached in comparing the groups were early and late post-SRS perilesional edema (3 and 12 months post-SRS). Figure 2 presents a representative case.

It is possible that the same immune-mediated mechanisms that result in better tumor control may also translate to a higher local complications rate. A possible explanation for the lower rate of complications in Group B is that the radiosurgical dose may damage or kill the tumor infiltrating radiosensitive T-cells (TILs), whose functions and tumor homing features have been enhanced by ipilimumab. This may dampen TIL activity, resulting in a slower local antitumor response as well as a weaker local inflammation. When SRS is given prior to ipilimumab stimulation of lymphocytes, fewer TILs are present in the tumor milieu. In addition, the SRS effect on the T-cell-mediated response can be lessened, since radiation is more potent on metabolically active cells. Kiess et al. reported a 50% incidence of tumor swelling in patients treated with SRS before/during ipilimumab, as compared with only 13% in patients treated with SRS after ipilimumab.

This study was not aimed at understanding the molecu-
Radiosurgery and ipilimumab for melanoma brain metastases

J Neurosurg Volume 127 • November 2017

The effect of these modalities on LRFD seems superior when SRS is performed before or during ipilimumab treatment. Partially beneficial local tumoral effects but also elicits peritumoral changes in the surrounding brain parenchyma. This holds true for the multifactorial etiology on LRFD as well. The quality of the medical records and clinical assessments was limited by the nature of a multidisciplinary treatment team. One such limitation is the lack of a thorough and continuous neurocognitive follow-up to correlate with findings of perilesional white matter changes. The small cohort size and sample groups and the inability to perfectly match systemic disease load at the time of SRS serve as additional limitations of this report.

Conclusions

Targeted therapies such as immunotherapy and SRS may interact when administered in patients with brain metastasis. The timing of each treatment may produce potentially beneficial local tumoral effects but also elicits peritumoral changes in the surrounding brain parenchyma. The effect of these modalities on LRFD seems superior when SRS is performed before or during ipilimumab treatment cycles, as compared with SRS performed after ipilimumab.

References

melanoma brain metastases. Am J Clin Oncol [epub ahead of print], 2015


Disclosures
Dr. Schlesinger reports receipt of support for non–study-related clinical or research effort from Elekta Instrument AB.

Author Contributions
Conception and design: Sheehan, Cohen-Inbar. Acquisition of data: Shih. Analysis and interpretation of data: Cohen-Inbar. Review of submitted version of manuscript: Sheehan, Cohen-Inbar. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Shih, Xu. Correspondence: Jason P. Sheehan, Department of Neurological Surgery, University of Virginia, Box 800212, Charlottesville, VA 22908. Email: jsheehan@virginia.edu.