The Volumetric Response of Brain Metastases After Stereotactic Radiosurgery and Its Post-treatment Implications

**BACKGROUND:** Changes in tumor volume are seen on magnetic resonance imaging within weeks after stereotactic radiosurgery (SRS), but it remains unclear what clinical outcomes early radiological changes portend.

**OBJECTIVE:** We hypothesized that rapid, early reduction in tumor volume post-SRS is associated with prolonged local control and favorable clinical outcome.

**METHODS:** A retrospective review of patients treated with CyberKnife SRS for brain metastases at the University of North Carolina from 2007 to 2009 was performed. Patients with at least 1 radiological follow-up, minimal initial tumor volume of 0.1 cm³, no previous focal radiation, and no recent whole-brain radiation therapy were eligible for inclusion.

**RESULTS:** Fifty-two patients with 100 metastatic brain lesions were analyzed and had a median follow-up of 15.6 months (range, 2-33 months) and a median of 2 (range, 1-8) metastatic lesions. In treated metastases in which there was a significant tumor volume reduction by 6 or 12 weeks post-SRS, there was no local progression for the duration of the study. Furthermore, patients with metastases that did not reduce in volume by 6 or 12 weeks post-SRS were more likely to require corticosteroids (P = .01) and to experience progression of neurological symptoms (P = .003).

**CONCLUSION:** Significant volume reductions of brain metastases measured at either 6 or 12 weeks post-SRS were strongly associated with prolonged local control. Furthermore, early volume reduction was associated with less corticosteroid use and stable neurological symptoms.

**KEY WORDS:** Brain metastases, Local control, Radiosurgery, Volumetric response
It remains unknown whether either could and the relationship control and overall survival (OS). Volume reduction after SRS at approximately 6 or 12 weeks, objectives of this study were to evaluate the associations of as a means of assessing treatment response. The primary follow-up imaging and the sensitivity of post-treatment imaging lead to changes in clinical management insofar as the timing of between these changes and clinical outcomes of interest—could lead to changes in clinical management insofar as the timing of follow-up imaging and the sensitivity of post-treatment imaging as a means of assessing treatment response. The primary objectives of this study were to evaluate the associations of volume reduction after SRS at approximately 6 or 12 weeks, along with other covariates of interest, and the outcomes of local control and overall survival (OS).

PATIENTS AND METHODS
Study Design and Eligibility Criteria
The University of North Carolina at Chapel Hill School of Medicine Institutional Review Board approved this retrospective study of patients treated with CyberKnife (Accuray, Inc, Sunnyvale, California) SRS for brain metastases at the North Carolina Cancer Hospital between August 2007 and June 2009. All patients had biopsy-proven primary malignancy and a clinical diagnosis of brain metastasis confirmed by MRI. Patients with at least 1 clinical and radiological follow-up, minimal initial tumor volume of 0.1 cm³, and a Karnofsky Performance Status score ≥ 60 were eligible for the study. Patients undergoing SRS for metastatic lesions previously treated with focal radiation therapy or receiving adjuvant SRS after surgical resection were excluded. Patients who received WBRT within 4 months before SRS were also excluded.

Treatment Planning, Delivery, and Follow-up
All patients were initially evaluated by a multidisciplinary team that included a radiation oncologist and neurosurgeon certified in the use of SRS. Treatment planning was performed using computed tomography scans with 1-mm slice thicknesses and MRI scans with slice thicknesses between 1.0 and 1.5 mm performed before beginning treatment. Relevant target volumes and critical structures were manually contoured on the planning images, and an inverse treatment-planning algorithm was used to produce a nonisocentric treatment plan. Initial MRI of the brain, as part of clinical follow-up, was first performed at 6 or 12 weeks post-SRS, and then every 3 months for the next 2 years. Most patients with initial MRI at 6 weeks post-SRS also returned at 12 weeks post-SRS for MRI evaluation. Initial post-SRS imaging timing was at the discretion of the treating radiation-oncologist; patients deemed to be at high risk of the development of new, distant lesions in the central nervous system were scheduled for initial MRI follow-up at 6 weeks post-SRS. Patients were followed until death or until lost to follow-up.

Data Measurement
Tumor volumetry was performed by manual segmentation using the CyberKnife treatment planning software (InView 1.6.0; Accuray, Inc, Sunnyvale, California). T1-weighted post-contrast images with 1- to 3-mm slice thickness were used for volume measurements. All volume measurements were made by the lead author who was blinded to primary tumor type and patient outcomes at the time of measurement. Scans were chosen in a random fashion from a pool of available patients and time points to limit the amount of bias while making measurements. By restricting analysis to the lead author (who was not directly involved in the clinical care of the patients), we sought to reduce interreader measuring errors. For patients with more than 4 treated brain metastases, only the largest 4 metastases were measured. Tumors were further categorized by growth response at each follow-up time point as decreased (≥ 20% volume decrease), stable (volume ± 20% of the initial volume), or increased (≥ 20% volume increase) compared with baseline. These categorization criteria were chosen because we assumed a measurement error of ± 20%, as there are currently no validated categorization schemes for tumor response based on measurements made with computer-assisted tumor volumetry. The primary outcome was local tumor control. Secondary outcomes were OS, corticosteroid dependence, and neurological symptom progression. Local failure was defined as the need for additional treatment for a lesion treated with SRS as deemed by the treating physicians for clinical or radiographic changes. Additional treatment could include WBRT, surgery, chemotherapy, or enrollment in a clinical trial. Moreover, patients who elected palliative care for progressive disease at a treated site were also considered local treatment failures. The differentiation between radiation necrosis and pseudoprogression in patients requiring additional therapy was made by treating physicians in conjunction with a neuroradiologist based on both clinical factors and imaging characteristics on MRI. Typically, a transient increase in size, defined as volumetric increase at a single time point, without clinical symptoms or that responded to corticosteroid therapy, was considered pseudoprogression rather than local failure. Corticosteroid dependence was defined as the use of corticosteroids for neurological symptoms for more than 2 consecutive weeks post-SRS. Neurological symptom progression was defined as worsening of neurological symptoms or development of new symptoms contributable to mass effect of a treated metastatic brain lesion at any time post-SRS.

Statistical Analysis
The Wilcoxon signed rank method was used to test the null hypothesis that a true median score was equal to zero. The Wilcoxon rank sum test or Kruskal-Wallis method was used for continuous variables undergoing 2 or more group comparisons. The nonparametric Jonckheere-Terpstra method was used to test for significant differences across ordered categories for contingency tables where at least 1 of the variables was ordinal and had at least 3 categories. The Fisher exact test was used to test for significant differences between 2-group and/or nominal categorical variable comparisons. Logistic regression modeling was used to investigate the strength of association between covariates of interest and the outcome of local tumor control (ie, the logit of the probability of not having local tumor control). The effective sample size for fitting exploratory models for logistic regression is determined by the number of cases (or controls, if that number is smaller). Using the guideline (to guard against overfitting) that there should be 10 cases for every covariate in a model, we explored 1 and 2 variable models because we had 21 cases. The Kaplan-Meier (or product...
limit) method was used to estimate OS, and Cox regression modeling was used to explore the association of selected covariates of interest on the time-to-event outcome of OS. The effective sample size for fitting exploratory Cox regression models for OS is determined by the number of deaths. Using the same guideline cited previously (to guard against overfitting) and with 33 deaths, we explored 1-, 2-, and 3-variable models of interest.

An approximation to Bayes factors, known as the Schwarz bayesian criterion (SBC), was used to assess the strength of evidence of association for each covariate of interest either local control for the logistic control models or OS for the Cox regression models.\textsuperscript{16,17} The SBC, in the form of a difference measure, may be much more useful than a traditional interpretation of a $P$ value $< .05$ for 2 main reasons. The first is that using the difference in SBCs can give information in support of null hypothesis. The second is that the difference in SBCs may be more interpretable in either very large or very small sample sizes (where an $\alpha$ level of .05 has less of an interpretable value). When comparing differences in SBC, the following measures of the degree of evidence can be used: 0 to 2 is considered weak, greater than 2 and up to 6 is positive, greater than 6 and up to 10 is strong, and 10 or greater is considered very strong. Negative analogs of these numbers provide the same information in support of the null hypothesis.

Statistical analyses were performed using both SAS Version 9.2 (SAS Institute, Inc, Cary, North Carolina) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria). R is an open-source statistical programming language from the R Development Core Team (2008).

**RESULTS**

**Patient and Treatment Characteristics**

Fifty-two patients with 100 metastatic brain lesions of various histologies were identified for this study (Table 1). The group consisted of 32 females and 20 males with a median age of 62 years (range, 36-83 years) and a median Karnofsky Performance Status (KPS) score of 90 (range, 70-100). The median number of metastatic lesions at presentation was 2 (range, 1-8). The mean initial tumor volume was 1.6 cm$^3$ (range, 0.1-22 cm$^3$). Metastatic lesions were treated with a median prescribing dose of 20 Gy (range, 18-21 Gy) at a median isodose line of 79% (range, 69%-84%). Eighty-five of 100 lesions (85%) were treated with 1 fraction, and the remaining 15 lesions (15%) were treated with either 3 (13 lesions) or 5 fractions (2 lesions). Ten patients (19%) had controlled extracranial disease at the time of SRS. Thirty (58%) of 52 patients returned for their initial MRI of the brain at 6 weeks post-SRS; the remaining 22 patients (42%) returned for their initial MRI follow-up at 12 weeks post-SRS. The median follow-up time for survivors was 15.6 months (range, 2-33 months), with 39 patients ultimately dying by the conclusion of the study.

**Tumor Volumetric Response**

A volumetric response occurred by 6 weeks post-SRS with a median absolute volume reduction of 0.80 cm$^3$ (95% confidence interval [CI]: $-0.16$ to $-4.05$, $P = .017$, $n = 64$) compared with baseline. For patients who underwent follow-up MRI at both 6 and 12 weeks, a median absolute volume reduction of 0.23 cm$^3$ (95% CI: $-0.07$ to $-0.77$, $P < .001$, $n = 54$) occurred between 6 and 12 weeks post-SRS. No significant change in volume was detected beyond 12 weeks post-SRS. Median absolute volume change between 12 weeks post-SRS and 6 months post-SRS was +0.12 cm$^3$ (95% CI: +.05 to $-0.1$, $P = .99$, $n = 66$).

Categorization of tumor volume response at each follow-up time interval is reported in Table 2. For example, at 6 weeks post-SRS, a partial decrease in tumor volume was seen in 49 of 52 patients (94%). Median volume change at 6 weeks post-SRS was $-0.5$ cm$^3$ (95% CI: $-0.02$ to $-1.0$, $P < .001$, $n = 54$). When aggregating the follow-up data at 6 and 12 weeks post-SRS, 14 metastatic lesions were categorized as increased in volume. Seven of these lesions (50%) had only a transient tumor volume increase followed by tumor regression, whereas the other 7 lesions (50%) were deemed local failures requiring salvage treatment by the treating physicians. In contrast, of the 9 metastatic lesions with an increase in measured volume either first detected or sustained at the 6 months post-SRS, 7 (78%) were deemed to be tumor progression and required further intervention.

A summary of response categorization at each follow-up time interval is reported in Table 2. For example, at 6 weeks post-SRS, a partial decrease in tumor volume was seen in 49 of 52 patients (94%). Median volume change at 6 weeks post-SRS was $-0.5$ cm$^3$ (95% CI: $-0.02$ to $-1.0$, $P < .001$, $n = 54$). When aggregating the follow-up data at 6 and 12 weeks post-SRS, 14 metastatic lesions were categorized as increased in volume. Seven of these lesions (50%) had only a transient tumor volume increase followed by tumor regression, whereas the other 7 lesions (50%) were deemed local failures requiring salvage treatment by the treating physicians. In contrast, of the 9 metastatic lesions with an increase in measured volume either first detected or sustained at the 6 months post-SRS, 7 (78%) were deemed to be tumor progression and required further intervention.

To evaluate for variations in volume response by primary tumor histology, we compared the volumetric responses of breast,
non-small cell lung cancer, melanoma, and renal cell carcinoma (RCC) metastases at 6 weeks, 12 weeks, and 6 months post-SRS. Despite trends suggesting that melanoma and RCC metastases had less robust volume reduction than either non-small cell lung cancer or breast metastases, response categorization differences among these 4 primary types were not statistically significant. This may be due to the relatively small number of patients in some of the histologies, and therefore the interhistology comparisons may not have enough statistical power to detect interhistology differences in volumetric response.

**Primary Outcome: Tumor Volumetric Response and Local Control**

Median tumor volume change at 6 or 12 weeks post-SRS was significantly different between metastases that required further treatment for local progression and those that did not. At 6 or 12 weeks post-SRS, metastases that eventually required further treatment for local progression had a median volume increase of 41% vs a median volume reduction of 61% in controlled tumors ($P < .0001$). This remained consistent on a per-patient basis as well, as patients with primary lesions that achieved a significant tumor volume reduction at 6 or 12 weeks post-SRS did not require salvage treatment for their disease at any later follow-up time point (Figure 1).

Logistic regression models were fitted on a per lesion basis for local control. Covariates that were either strongly or positively associated with local control were extracranial control ($P = .006$), melanoma primary ($P = .004$), and salvage ($P = .01$) therapy. Other covariates that had evidence of association with local control included the presence of neurological symptoms ($P = .02$), previous surgical resection ($P = .02$), and breast primary ($P = .03$). Finally, male patients had worse local control than female patients ($P = .03$).

The best multivariable logistic regression model of local control included the covariates representing lack of corticosteroid dependence and tumor volume change at 6 or 12 weeks post-SRS ($P < .0001$ and $P = .04$, respectively). Models with the covariates representing lack of corticosteroid dependence and melanoma histology ($P < .0001$ and $P = .006$, respectively), and lack of corticosteroid dependence and extracranial control ($P < .0001$ and $P = .009$, respectively) fit almost as well. The best model that did not include the lack of corticosteroid dependence was the model that contained extracranial control ($P = .003$) and tumor volume change at 6 or 12 weeks post-SRS ($P = .0003$).

**Secondary Outcomes: Tumor Volumetric Response and OS, Corticosteroid Dependence, and Neurological Symptom Progression**

Median OS was approximately 12 months (Figure 2A). Overall survival appeared to not be significantly associated with tumor volume change at 6 or 12 weeks post-SRS ($P = .57$, Figure 2B). Sex and primary histology were the only covariates positively associated with OS. Male patients were 2.6 times more likely to

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**TABLE 2. Tumor Volume Response Categorization per Time Interval After Stereotactic Radiosurgery**

<table>
<thead>
<tr>
<th>Time Interval Post-SRS</th>
<th>Decreased Lesions, no. (%)</th>
<th>Lesions With Complete Response, no. (%)</th>
<th>Stable Lesions, no. (%)</th>
<th>Increased Lesions, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 wk</td>
<td>77 (49/64)</td>
<td>25 (16/64)</td>
<td>11 (7/64)</td>
<td>12 (8/64)</td>
</tr>
<tr>
<td>12 wk</td>
<td>78 (57/73)</td>
<td>27 (20/73)</td>
<td>8 (6/73)</td>
<td>14 (10/73)</td>
</tr>
<tr>
<td>6 mo</td>
<td>77 (51/66)</td>
<td>47 (31/66)</td>
<td>9 (6/66)</td>
<td>14 (9/66)</td>
</tr>
<tr>
<td>9 mo</td>
<td>78 (29/37)</td>
<td>41 (15/37)</td>
<td>8 (3/37)</td>
<td>14 (5/37)</td>
</tr>
<tr>
<td>12 mo</td>
<td>90 (16/20)</td>
<td>60 (12/20)</td>
<td>0 (0/20)</td>
<td>20 (4/20)</td>
</tr>
</tbody>
</table>

*SRS, stereotactic radiosurgery. Note that patients with a complete response are included as decreased lesions as well.*

**TABLE 3. Median Tumor Volume Change (%) per Time Interval After Stereotactic Radiosurgery, Reported**

<table>
<thead>
<tr>
<th>Time Interval Post-SRS</th>
<th>Median Volume Change of Decreased Lesions % (95% CI)</th>
<th>Median Volume Change of Stable Lesions % (95% CI)</th>
<th>Median Volume Change of Increased Lesions % (95% CI)</th>
<th>No. of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 wk</td>
<td>−75 (−66 to −96)</td>
<td>−3 (−17 to 20)</td>
<td>+68 (+28 to +430)</td>
<td>64</td>
</tr>
<tr>
<td>12 wk</td>
<td>−79 (−71 to −96)</td>
<td>+4 (−13 to 17)</td>
<td>+175 (+45 to +420)</td>
<td>73</td>
</tr>
<tr>
<td>6 mo</td>
<td>−100 (−95 to −100)</td>
<td>−7 (−17 to 5)</td>
<td>+170 (+35 to +754)</td>
<td>66</td>
</tr>
<tr>
<td>9 mo</td>
<td>−100 (−72 to −100)</td>
<td>−1 (−17 to 6)</td>
<td>+90 (+35 to +590)</td>
<td>37</td>
</tr>
<tr>
<td>12 mo</td>
<td>−100 (−100 to −100)</td>
<td>—</td>
<td>+170 (+38 to +638)</td>
<td>20</td>
</tr>
</tbody>
</table>

*SRS, stereotactic radiosurgery; CI, confidence interval.*
die than female \( (P = .007) \). The median survival time for male patients was 9.5 months (95% CI: 5.4-10.3 months) and 20.5 months (95% CI: 10.6-26.9 months) for females. The median survival time for patients with melanoma was 5.8 months (95% CI: 4.3-9.7 months) compared with 14 months (95% CI: 10-23 months) for those with other primary type tumors \( (P = .01) \). It should be noted that a significant number of those with melanoma were male (7 of 9), and all 7 of those died \( (P = .02) \). To address this possibility of confounding between histology and sex, when those patients with melanoma were removed from the analysis, the association between OS and sex remained significant \( (P = .02) \). When patients with either melanoma or breast cancer were removed, sex again remained significantly associated with OS \( (P = .02) \). When patients with either melanoma or breast cancer were removed, sex continued to appear to be significantly associated with OS \( (P = .03) \). Finally, several 2 and 3 covariate exploratory Cox models of interest were examined. However, by a large margin, the best fitting model was the model that contained only the sex covariate, showing that male patients did much worse than female patients (Figure 2C).

Twenty-nine patients who returned for MRI at 6 or 12 weeks post-SRS had corticosteroid use and neurological symptoms recorded. Of these, 10 patients (34%) required more than 2 weeks of corticosteroids for neurological symptoms related to their metastatic brain disease. Median tumor volume change differed between patients who required corticosteroid treatment(s) and those who did not (9% vs. -69%, \( P = .01 \)) (Figure 3). A smaller, although still significant, difference in median tumor volume change was found in the 10 patients (34%) who experienced neurological symptom progression compared with the 19 patients (66%) who did not experience further neurological deficits post-SRS (20% vs. -67%, \( P = .003 \)) (Figure 4).

Toxicity and Salvage

Two patients reported headaches within 1 week post-SRS; otherwise there were no adverse treatment effects. In 37 patients (71%), additional brain metastases developed distant from treated site(s) that required further treatment, including SRS (\( n = 14 \)), WBRT (\( n = 14 \)), surgery (\( n = 4 \)), chemotherapy/clinical trial (\( n = 4 \)), and supportive care (\( n = 1 \)). Eleven patients (21%) had failure at the SRS-treated site(s). Salvage therapies included supportive care (\( n = 4 \)), WBRT (\( n = 2 \)), surgery (\( n = 2 \)), chemotherapy or clinical trial (\( n = 2 \)), and surgery plus WBRT (\( n = 1 \)).

DISCUSSION

In this study, the lesions that demonstrated local control were those lesions that showed a much larger tumor volume reduction at 6 or 12 weeks \( (P = .0001) \) (Figure 2C).
tumor volume reduction at 6 or 12 weeks. For these early responders, a median volume reduction of more than 90% was achieved by the last available radiological follow-up. These results suggest that a robust, early volumetric response is associated with subsequent local control and parallels findings by Kim et al, who reported an association between a good response, defined as a decrease in total tumor volume by 75% at 4 weeks post-SRS, and local control. Moreover, we found an association between early, robust volumetric response and a decrease in corticosteroid dependence and neurological symptom progression.

A key difference between this study and that of Kim et al is the histological subtypes of tumors. The current study was open to tumor types of any histology, whereas Kim et al analyzed RCC only. The significance of this histological difference is twofold. First, the greater rate of “good responders” at 6 weeks may be due to the more favorable histological subtypes present in the current study on account that RCC is known for its resistance to radiotherapy. Second, these results generalize the research performed by Kim et al to a broader patient population by identifying a general subset of patients with an increased and sustained rate of local control.

The tumor-size time trends delineated in this study not only provide insight into post-SRS outcomes, but may also contribute to the determination of the optimal timing for follow-up imaging. In our patients, tumor volume response occurred within 12 weeks post-SRS, and tumor response at the 6 and 12 weeks post-SRS provided important insight into local control. Our findings suggest that MRI performed at 6 or 12 weeks and 6 months post-SRS, however, would provide clinicians with the most useful patient information to make future treatment decisions. For the select patients with favorable radiographic response up to 6 months post-SRS, reduction in the frequency of imaging may be appropriate. Expanding the imaging interval in favorable responders could reduce the number of MRI scans per year, resulting in significant cost reduction.

Generalizability

Several factors in the design of the study and patient population will allow for generalization to radiosurgery practices elsewhere. Both frameless radiosurgery and the option for either single fraction or hypofractionation are commonly available at most radiosurgery centers. The histological subtypes in this study include the frequent tumors types seen in neuro-oncology practice. The measurement techniques that predicted positive outcomes, early reduction in tumor volume, can be measured with commercial software. The key imaging intervals (6-12 weeks) are also within the commonly accepted practice patterns for radiosurgery patients. Finally, the key patient-centered outcomes measured (local tumor control, steroid dependence, symptom progression) are clinically relevant for patient care and were predicted by the early volumetric response of the lesions.

Limitations

This study has several limitations that must be considered as it is applied to neurosurgical practice. First, it was a retrospective, single-institution study. The sample size, 100 lesions in 52
patients, is only of moderate size. In light of this, statistical methods were selected that conservatively analyzed the data. For example, the sample size, although adequate to support the pooled analysis, was not sufficient to perform detailed histological subgroup analysis. Although the results appear consistent over the major histological subtypes, it would be ideal to have unique subset analyses for lung cancer, melanoma, and each subtype of breast cancer. In addition, detailed corticosteroid dosing was not available for all patients, potentially introducing selection bias. Furthermore, patients with neurological disease progression or those receiving corticosteroids may have had these changes due to increasing total intracranial disease burden as opposed to SRS-treated sites. A further limitation is heterogeneity within the patient cohort with regard to previous treatments, although our exclusion of patients with recent (<4 months) WBRT helped to control for effects secondary to treatments beyond SRS. Last, there are potential inaccuracies with the volume measurement of intracranial lesions, especially for smaller tumor volumes. To combat this, we excluded lesions with an initial tumor volume of less than 0.1 cm³ (6-mm diameter). The ±20% cutoff for volume response categorization was chosen to account for potential volume measurement inaccuracies. Although true volume calculation is available in most commercial imaging software, it frequently requires some degree of manual segmentation or work that currently prevents volume calculations from being widely applied in daily practice. In the near future, advances in such software could overcome this limitation. Several faster techniques for the measurement of brain metastasis volume, including uni- and bidimensional measurements and ongoing advances in automated segmentation software programs, have been validated by comparisons with manual contouring.

CONCLUSION

Significant tumor volume reduction by 6 or 12 weeks post-SRS was associated with long-term local control. For patients at low risk of distant intracranial failure (such as those with systemic disease control) with early, robust volumetric response, it may reasonable to shorten imaging intervals to maximize clinical utility. Although it is necessary to validate the findings of this study in a larger, prospective series, the results are encouraging that a robust early volumetric response is associated with sustained local control for metastatic brain lesions.

Disclosures

Dr Morris is a stockholder in the St. Louis CyberKnife Center as well as a consultant for the Radiosurgery Center Corporation. The other authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article. Portions of this work were presented in poster form at the 9th Annual CyberKnife Society Merit Meeting, Dallas, Texas, March 26, 2010.

REFERENCES


COMMENTS

This paper admirably attempts to define the radiographic response of brain metastases to radiosurgery. In a retrospective series of patients treated at a single institution, the authors tried to define the changes in volume that predict long-term control of a treated lesion. Its main value lies in the definition of a volume response beyond which they did not see any evidence of tumor progression (~61%). However, the paper does not help in understanding the true dilemmas of these treatments, “early detection of recurrent disease” and distinguishing treatment effects from progressive tumor, but hopefully represents a step in understanding that lesions do not require further concern.

Rabia Qaiser
Matthew A. Hunt
Minneapolis, Minnesota

This carefully analyzed, small retrospective series makes the interesting observation that metastases that shrink on early post-radiosurgery (RS) imaging are likely to maintain good long-term local radiographic and symptom control. A majority of patients underwent repeat MRI at 6 weeks post-RS; the authors indicate that MRI timing was at the discretion of the treating radiation oncologist, and patients deemed at high risk of remote intracranial failure underwent reimaging at 6 weeks. This seems not to represent judicious use of technology, and arguably patients deemed at high risk of remote intracranial failure over such a short time period might be better served with whole-brain radiotherapy. Imaging at 12-week intervals in the absence of neurological decline would seem more sensible.

These findings may not translate readily into clinical practice. This study requires replication, and the differentiation between local failure and radiation reaction remains fraught with difficulty. Moreover, identifying a numerically meaningful subset of patients with a favorable early imaging response to RS who have such a low risk of remote intracranial metastasis that MRI can be obtained less frequently than every 3 months may be challenging.

David Schiff
Charlottesville, Virginia

The authors of this study are to be commended for a thorough retrospective review of 59 patients with 111 brain metastases treated with CyberKnife radiosurgery. The authors determined that treated metastases achieving relative volume reduction of 61% by 6 or 12 weeks experienced no progression for the duration of the study and that acute volume reduction is associated with less corticosteroid use. Although larger multi-institution studies will be needed to better determine whether there is a volume reduction cutoff above which eventual treatment failure never occurs, the notion of such a cutoff is certainly logical. What would be more beneficial would be a way to identify treatment failures early, and, unfortunately, in this study, early failures (≤12 weeks) were just as likely to be treatment effects as tumor progression, whereas late failures were more likely to be tumor progression, which would suggest that it will be difficult based on conventional MRI to improve on the practice of waiting and watching until imaging changes declare themselves. Regardless, this study adds to the literature and was a well-designed approach to this challenging issue.

Manish K. Aghi
San Francisco, California

CME Questions:

1. What outcome is predicted by a significant decrease in volume 3 months after treatment of a metastatic tumor with stereotactic radiosurgery (SRS)?
   A. Local control at 6-12 months
   B. Increased corticosteroid dependence
   C. Increased neurological symptoms
   D. Pseudoprogression
   E. Improved overall survival

2. What is the optimal time frame for imaging following treatment of a metastatic lesion with stereotactic radiosurgery (SRS) in order to assess the efficacy of treatment?
   A. 1-5 weeks
   B. 6-12 weeks
   C. 13-19 weeks
   D. 20-26 weeks
   E. 27-33 weeks

3. What is the median volumetric reduction 6-weeks following SRS of brain metastases?
   A. 25%
   B. 50%
   C. 75%
   D. 100%
   E. No change