The majority of primary spinal cord tumors are benign noninfiltrative lesions, such as meningiomas or schwannomas, for which microsurgical resection has long been recognized as a standard of care. However, tumor location, patient age, and medical comorbidities can challenge the application of microsurgery. Building on the successful use of stereotactic body radiation therapy (SBRT) for the management of malignant metastatic...
spinal tumors and frame-based stereotactic radiosurgery (SRS) for unresectable benign intracranial lesions, SBRT for benign spinal tumors was initially reported in the late 1990s.\(^2\)\(^5\) Reports from numerous additional single-institution cohort series that highlight the potential safety and efficacy of SBRT as a nonoperative alternative for a variety of benign spinal tumors have since been published.\(^3\)\(^5\)\(^8\)\(^9\)\(^17\)\(^18\) Unlike patients treated with SBRT for malignant metastatic spinal tumors, patients with benign spine tumors have a long natural history. Continuous long-term follow-up is warranted both for the evaluation of tumor control and to address concerns regarding delayed myelopathy caused by the extreme hypofractionation inherent to spinal SBRT.

The majority of the initial experiences with SBRT for benign primary spinal tumors involved a dose similar to that used for malignant metastatic spinal tumors (i.e., 16–30 Gy in 1–5 fractions).\(^3\)\(^5\)\(^8\)\(^9\)\(^17\)\(^18\) Similarly, intracranial application of SRS for benign tumors, such as meningioma and acoustic neuroma, began with a high dose similar to that used to treat malignant intracranial tumors. Additional experience with intracranial SRS dose de-escalation to 12–13 Gy in 1 fraction was found to reduce toxicity while maintaining excellent rates of tumor control.\(^6\)\(^11\)\(^14\) Contemporaneous reports of outcomes with long-term follow-up and use of lower-dose spinal SBRT in patients with benign tumors have been limited.\(^15\)\(^19\) Thus, we aimed to assess the long-term outcomes in patients after spinal SBRT for benign tumors. We hypothesized that lower doses (such as 12–13 Gy in 1 fraction) might provide an efficacy similar to that found with the dose de-escalation commonly used for intracranial radiosurgery to treat acoustic neuroma or meningioma and a lower risk of toxicity.

## Methods

After institutional review board approval, our prospectively maintained institutional radiosurgery database was queried to identify patients treated with SBRT for benign primary spinal tumors between 2004 and 2016. Patients were included irrespective of previous treatments (including surgery) and tumor location (intradural or extradural). Patients with malignant or metastatic tumors were excluded. SBRT consisted of 9–21 Gy in 1–3 fractions using the CyberKnife (Accuray, Inc.), Synergy S (Elekta), or TrueBeam (Varian Medical Systems) radiosurgery platform. Our technique for spinal SBRT was described previously.\(^8\)\(^13\) In brief, SBRT targets included a gross tumor volume without a clinical target volume expansion; gross tumor volume–to–planning target volume expansions of 0–2 mm were based on treatment-delivery platform and physician preference. Daily image guidance was used in all cases with near-real-time 6-D tracking (Xsight Spine, Accuray, Inc.), daily cone-beam CT, and/or the ExacTrac system (Brainlab Novalis). Immobilization for linear accelerator-based radiosurgery-delivery platforms was accomplished by using either the BodyFIX system (Elekta) or a custom thermoplastic mask, depending on tumor location. Follow-up included MRI at 6-month intervals after the completion of SBRT.

Statistical analyses were completed using IBM SPSS 22. For a comparison of SBRT doses, the patients’ lesions were dichotomized into 1 of 2 groups, low-dose SBRT (n = 34) or high-dose SBRT (n = 8), using a cutoff median biologically effective dose (BED\(_{10 Gy}\)) value of 30 Gy. Tumor control was calculated from the date of SBRT to the last follow-up visit using Kaplan-Meier survival analysis, and comparisons between groups were completed using a log-rank method. Local control was defined as either a stable or smaller lesion size. To account for potential indication bias, a propensity score analysis was completed based on the conditional probabilities of SBRT dose selection with nearest-neighbor propensity score matching. Toxicity was graded using Common Terminology Criteria for Adverse Events version 4.0 with a focus on grade 3+ toxicities and the incidence of pain flare.

## Results

For the included 38 patients the most common histological findings were meningioma (15 patients), schwannoma (13 patients), and hemangioblastoma (7 patients). The median age at SBRT was 58 years (interquartile range 25–91 years). The 47 treated lesions were located in the cervical (n = 18), thoracic (n = 19), or lumbosacral (n = 10) spine. Of these lesions, 8 (17%) were previously irradiated, and surgery had previously been performed for 25 (53%). Five (11%) lesions were lost to follow-up after SBRT. Each lesion was treated using the CyberKnife (n = 11), Synergy S (n = 21), or TrueBeam (n = 15) radiosurgery platform. The median spinal cord maximum dose was 11.6 Gy (interquartile range 10–13.2 Gy). Table 1 provides baseline patient and tumor characteristics.

The median follow-up duration for the 42 lesions with available follow-up data was 54 months (range 1.2–133 months). Six (16%) patients (with a total of 8 lesions) had a pain flare after SBRT. No significant predictor of pain flare was identified; we found no difference according to dose (low versus high), fractionation (single versus multifractionation), previous radiation, previous surgery, tumor histology, age, treatment platform, planning target volume, or spine level treated. Table 2 lists the incidence of pain flare, and a chi-square analysis revealed no significant correlation between any of the factors. No grade 3+ acute- or late-onset complication was noted; 1 patient who suffered local recurrence that required salvage SRS and surgery had grade 2 myelitis manifested as imbalance and impaired proprioception.

The 5-year local control rate was 76% (95% CI 61%–91%), as found using a Kaplan-Meier survival plot (Fig. 1). We found no significant difference in local control rates according to dose (low [BED\(_{10 Gy}\leq 30\) Gy] vs high [BED\(_{10 Gy}>30\) Gy]), fractionation (single versus multifractionation), previous radiation, previous surgery, tumor histology, age, treatment platform, planning target volume, or spine level treated (p = 0.05). Durable control of pain after treatment was experienced by 80% of the patients. No significant difference between the high- and low-dose groups in baseline patient or tumor characteristics was identified other than an increased use of the CyberKnife platform in the high-dose group. The 5-year local control rates for the low-dose and high-dose groups were 73% (95% CI 53%–93%) and 83% (95% 61%–100%), respectively (p = 0.52).
Fig. 2 shows a Kaplan-Meier survival plot that compares the local control rates in the high- and low-dose groups. A propensity score–matched multivariable analysis identified no difference in local control rates (HR 0.30, 95% CI 0.02–5.40, p = 0.41).

Discussion

Modern radiation treatment-planning and -delivery techniques have enabled a safe escalation of dose per fraction while targeting lesions in close proximity to the spinal cord. Analogous to the initial experiences with intracranial SRS, treatment of benign lesions began by prescribing doses necessary to control malignant/metastatic lesions (i.e., 20–30 Gy in 1–5 fractions). A greater understanding of the natural history and responsive nature of most benign intracranial lesions has prompted a de-escalation of prescribed SRS doses with similar excellent rates of local control and further avoidance of treatment-related toxicity. The majority of modern series to date have included a large spectrum of dose schedules without a comparison of outcomes between each of them. The results of our analysis revealed no significant patient characteristic that was predictive of receiving high- or low-dose SBRT, and we found that patients were less likely to receive a high dose when the TrueBeam or Synergy S platform was used (Table 3). To our knowledge, few data sets have reported parallel findings with de-escalation of SBRT doses for the treatment of benign intraspinal lesions.

Our retrospective review of 38 patients who underwent SBRT for a total of 47 benign spine tumors revealed a 5-year local control rate of 76%, and no significant difference was found among patients who underwent low-dose (BED10Gy ≤ 30 Gy) treatment and those who underwent high-dose (BED10Gy > 30 Gy) treatment or in those with a single-fraction plan and those with a multifractionation plan. Initial dose selection was determined by lesion size and proximity to the spinal cord, with a temporal association with lower dose use (i.e., patients were more likely to receive a lower dose toward the end of our review period). Our threshold for low and high doses was based on the median dose across the entire patient cohort. Several separate analyses using different high- and low-dose thresholds were performed, each of which yielded findings similar to those reported here. Table 4 summarizes the published...
literature that supports the use of SBRT for benign spinal tumors to date. Our local control rate was similar to that found in historical higher-dose series and was associated with durable pain control in 80% of patients. These findings are more compelling when we consider that SBRT served as a salvage modality after surgery for 25 (53%) lesions and previous radiotherapy was provided for 8 (17%) of the lesions in this cohort. Of all the patients treated, no grade 3+ acute- or late-onset complication was experienced, and one grade 2 myelitis was noted in a patient who underwent 2 courses of SRS and previous surgery. This extremely low toxicity rate is in line with those in previous reports from Stanford18 and high-dose series from our institution8,9 (Table 4).

We recognize the limitations of this study, which include its retrospective nature and the potential for selection bias, both when treatment was initiated and when we reviewed the patient records. This study also included significant heterogeneity in lesion histology, similar to most studies of SBRT for benign spine tumors, and standardized follow-up was lacking. In addition, after treatment, 5 lesions were subsequently lost to follow-up. With a small sample size, this study was limited in power to detect small differences in tumor control according to dose levels. Last, high-dose treatment and the CyberKnife platform were used more often based on a temporal relationship of platform selection and high-dose use in our clinic. Aside from these limitations, this cohort represents one of the largest series and longest follow-ups of benign spine tumors treated with SBRT to date. This report highlights effective local tumor control and minimal toxicity irrespective of SBRT dose in a patient population that was previously treated heavily and in 70% of whom previous surgery or radiation had failed.

Conclusions

Stereotactic radiation therapy represents an effective
treatment for benign primary malignancies of the spine. After 5 years of follow-up, we report no significant difference in pain control, local control, pain flare, or long-term toxicity between patients in the high-dose group and those in the low-dose treatment group. Akin to the de-escalation of SRS dose used for benign intracranial tumors, such as meningioma or acoustic neuroma, de-escalation of SBRT to a lower dose might be a reasonable approach for treating benign spinal tumors, even in a salvage setting.

References

11. Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC:

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TABLE 4. Summary of previous series of SBRT for benign spinal lesions

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>No. of Patients</th>
<th>Dose (Gy)/No. of Fractions</th>
<th>Histology (no. of tumors)*</th>
<th>Median Follow-Up (mos)</th>
<th>Previous Treatment</th>
<th>Local Control</th>
<th>Late Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al., 1998</td>
<td>3</td>
<td>21/3 (hemangioblastoma); 21/1 (AVM)</td>
<td>Hemangioblastoma (2); AVM (1)</td>
<td>18</td>
<td>None</td>
<td>33%–70% size reduction</td>
<td>None</td>
</tr>
<tr>
<td>Dodd et al., 2006</td>
<td>51</td>
<td>16/1–30/5</td>
<td>Schwannoma (30); meningioma (16); neurofibroma (9)</td>
<td>36</td>
<td>Surgery (51%)</td>
<td>Partial response at all sites</td>
<td>Grade 2+ radiation myelopathy (n = 1)</td>
</tr>
<tr>
<td>Ryu et al., 2001</td>
<td>11</td>
<td>11/1–25/5</td>
<td>Hemangioblastoma (1); AVM (6); schwannoma (2); meningioma (1); chordoma (1)</td>
<td>6</td>
<td>Surgery (n = 4); XRT (n = 2)</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>De Salles et al., 2004</td>
<td>3</td>
<td>12/1</td>
<td>Neurofibroma (2); meningioma (1)</td>
<td>6</td>
<td>Surgery (n = 3); XRT (n = 1)</td>
<td>70%</td>
<td>0%</td>
</tr>
<tr>
<td>Marchetti et al., 2013</td>
<td>18</td>
<td>10/1–25/5</td>
<td>Schwannoma (9); meningioma (11); neurofibroma (1)</td>
<td>43</td>
<td>Surgery (n = 14); XRT (n = 1)</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Gerszten et al., 2012</td>
<td>45</td>
<td>12/1–24/1</td>
<td>Schwannoma (16); meningioma (10); neurofibroma (14)</td>
<td>32</td>
<td>Surgery (n = 21); XRT (n = 2)</td>
<td>NR</td>
<td>0%</td>
</tr>
<tr>
<td>Gerszten et al., 2012</td>
<td>40</td>
<td>11/1–21/3</td>
<td>Schwannoma (15); meningioma (8); neurofibroma (7)</td>
<td>26</td>
<td>Surgery (n = 18); XRT (n = 4)</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Gerszten et al., 2008</td>
<td>73</td>
<td>15/1–25/3</td>
<td>Schwannoma (35); meningioma (13); neurofibroma (25)</td>
<td>37</td>
<td>Surgery (n = 19); XRT (n = 6)</td>
<td>100%</td>
<td>Grade 2+ radiation myelopathy (n = 3)</td>
</tr>
<tr>
<td>Gagnon et al., 2009</td>
<td>13</td>
<td>21/3–37/5</td>
<td>Schwannoma (6); meningioma (5); neurofibroma (2)</td>
<td>12</td>
<td>63% surgery; XRT</td>
<td>NR</td>
<td>0%</td>
</tr>
<tr>
<td>Sahgal et al., 2007</td>
<td>16</td>
<td>10/1–30/5</td>
<td>Meningioma (2); chordoma (4); hemangioma (2); neurofibroma (11)</td>
<td>25</td>
<td>Surgery (n = 5); XRT (n = 2)</td>
<td>89%</td>
<td>0%</td>
</tr>
<tr>
<td>Current cohort</td>
<td>38</td>
<td>9/1–21/3</td>
<td>Schwannoma (13); meningioma (15); hemangioblastoma (7)</td>
<td>54</td>
<td>Surgery (n = 25); XRT (n = 8)</td>
<td>76%</td>
<td>Grade 2+ radiation myelopathy (n = 1)</td>
</tr>
</tbody>
</table>

AVM = arteriovenous malformation; NR = not reported; XRT = conventional radiotherapy.

* Some patients had more than 1 tumor.


Disclosures
Dr. Vargo receives speaking honoraria from Brainlab.

Author Contributions
Conception and design: Vargo, Kalash, Flickinger. Acquisition of data: Vargo, Kalash, Glaser. Analysis and interpretation of data: Vargo, Kalash, Glaser, Flickinger. Drafting the article: all authors. 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: Vargo. Statistical analysis: Vargo, Kalash, Glaser, Flickinger. Study supervision: Vargo.

Supplemental Information
Previous Presentations
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