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Stereotactic body radiation therapy for benign spine tumors: is dose de-escalation appropriate?

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Abstract

OBJECTIVE—Akin to the nonoperative management of benign intracranial tumors, stereotactic body radiation therapy (SBRT) has emerged as a nonoperative treatment option for noninfiltrative primary spine tumors such as meningioma and schwannoma. The majority of initial series used higher doses of 16–24 Gy in 1–3 fractions. The authors 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 with a lower risk of toxicity.

METHODS—The authors identified 38 patients in a prospectively maintained institutional radiosurgery database who were treated with definitive SBRT for a total of 47 benign primary spine tumors between 2004 and 2016. SBRT consisted of 9–21 Gy in 1–3 fractions using the CyberKnife (n = 11 [23%]), Synergy S (n = 21 [45%]), or TrueBeam (n = 15 [32%]) radiosurgery platform. For a comparison of SBRT doses, patients were dichotomized into 1 of 2 groups (low-dose or high-dose SBRT) using a cutoff biologically effective dose (BED_{10Gy}) of 30 Gy. Tumor control was calculated from the date of SBRT to the last follow-up using Kaplan-Meier survival analysis, with comparisons between groups completed using a log-rank method. To account for potential indication bias, a propensity score analysis was completed based on the conditional

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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.

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Previous Presentations

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probabilities of SBRT dose selection. Toxicity was graded using Common Terminology Criteria for Adverse Events version 4.0 with a focus on grade 3+ toxicity and the incidence of pain flare.

RESULTS—For the 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 (range 25–91 years). The 47 treated lesions were located in the cervical (n = 18), thoracic (n = 19), or lumbosacral (n = 10) spine. Five (11%) lesions were lost to follow-up after SBRT. The median follow-up duration for the remaining 42 lesions was 54 months (range 1.2–133 months). Six (16%) patients (with a total of 8 lesions) experienced pain flare after SBRT; no significant predictor of pain flare was identified. No grade 3+acute- or late-onset complication was noted. The 5-year local control rate was 76% (95% CI 61%–91%). No significant difference in local control according to dose, fractionation, previous radiation, surgery, tumor histology, age, treatment platform, planning target volume, or spine level treated was found. The 5-year local control rates for low- and high-dose treatments were 73% (95% CI 53%–93%) and 83% (95% CI 61%–100%) (p = 0.52). In propensity score–adjusted multivariable analysis, no difference in local control was identified (HR 0.30, 95% CI 0.02–5.40; p = 0.41).

CONCLUSIONS—Long-term follow-up of patients treated with SBRT for benign spinal lesions revealed no significant difference between low-dose ($BED_{10Gy} \leq 30$) and high-dose SBRT in local control, pain-flare rate, or long-term toxicity.

Keywords

SBRT; spine; dose; benign tumors; meningioma; schwannoma; hemangioblastoma; oncology

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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.[1] 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.[3,5,8,17,18] 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).[3,5,8,17,18] 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] Contemporary 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_{10Gy}) 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 identihed; 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-onest 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 [$BED_{10Gy} \le 30$ Gy] vs high [$BED_{10Gy} > 30$ 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).[3,5,8,17,18] 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.[6,11,14] The majority of modern series to date have included a large spectrum of dose schedules without a comparison of outcomes between each of them.[3,5,8,17,18] 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 ($BED_{10Gy} \leq 30$ Gy) treatment and those who underwent high-dose ($BED_{10Gy} > 30$ 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 Stanford[18] and high-dose series from our institution[8,9] (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.

ABBREVIATIONS

BED_{10Gy}	biologically effective dose
SBRT	stereotactic body radiation therapy
SRS	stereotactic radiosurgery

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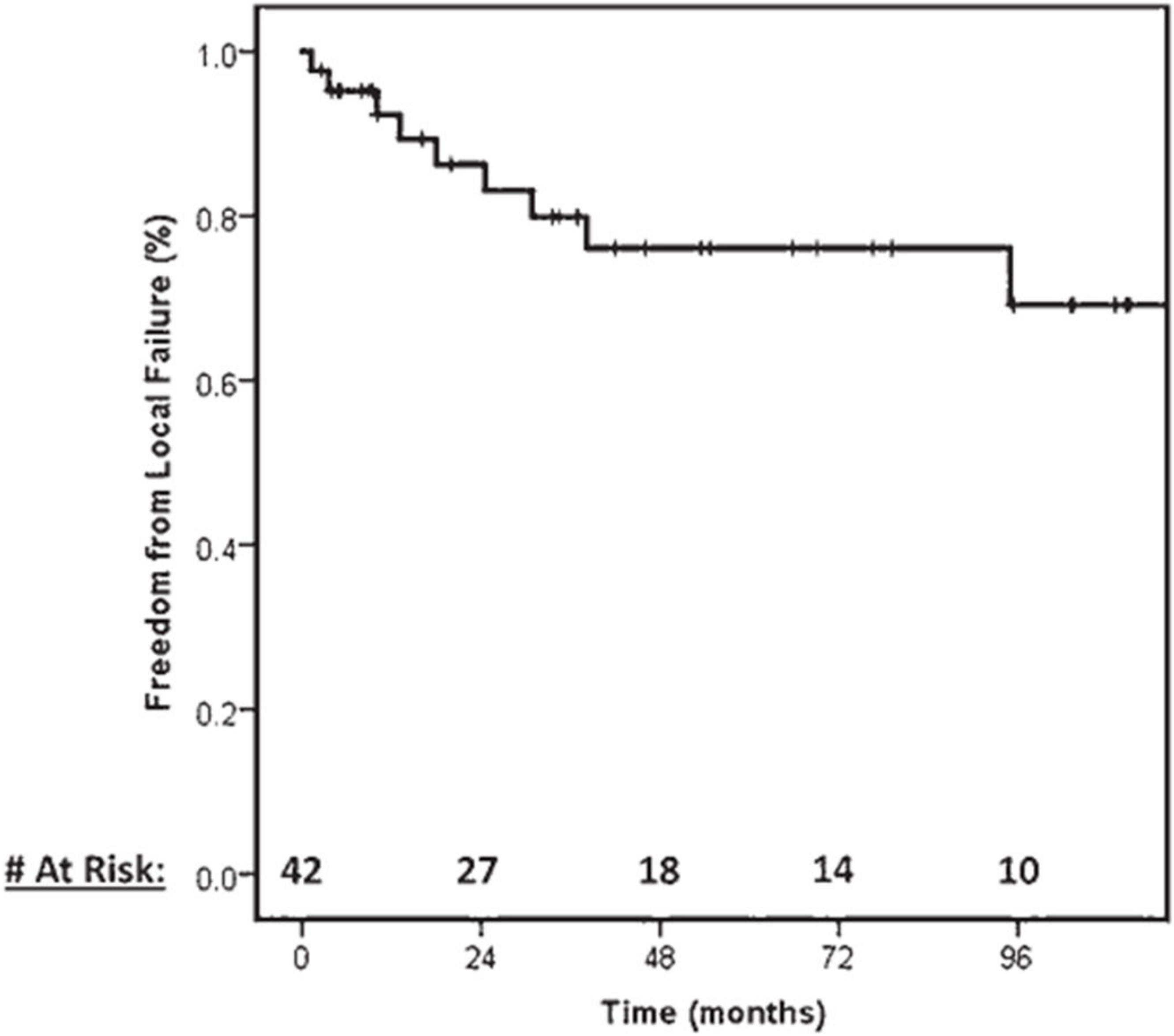

FIG. 1.
Local control of benign spinal lesions treated with SBRT.

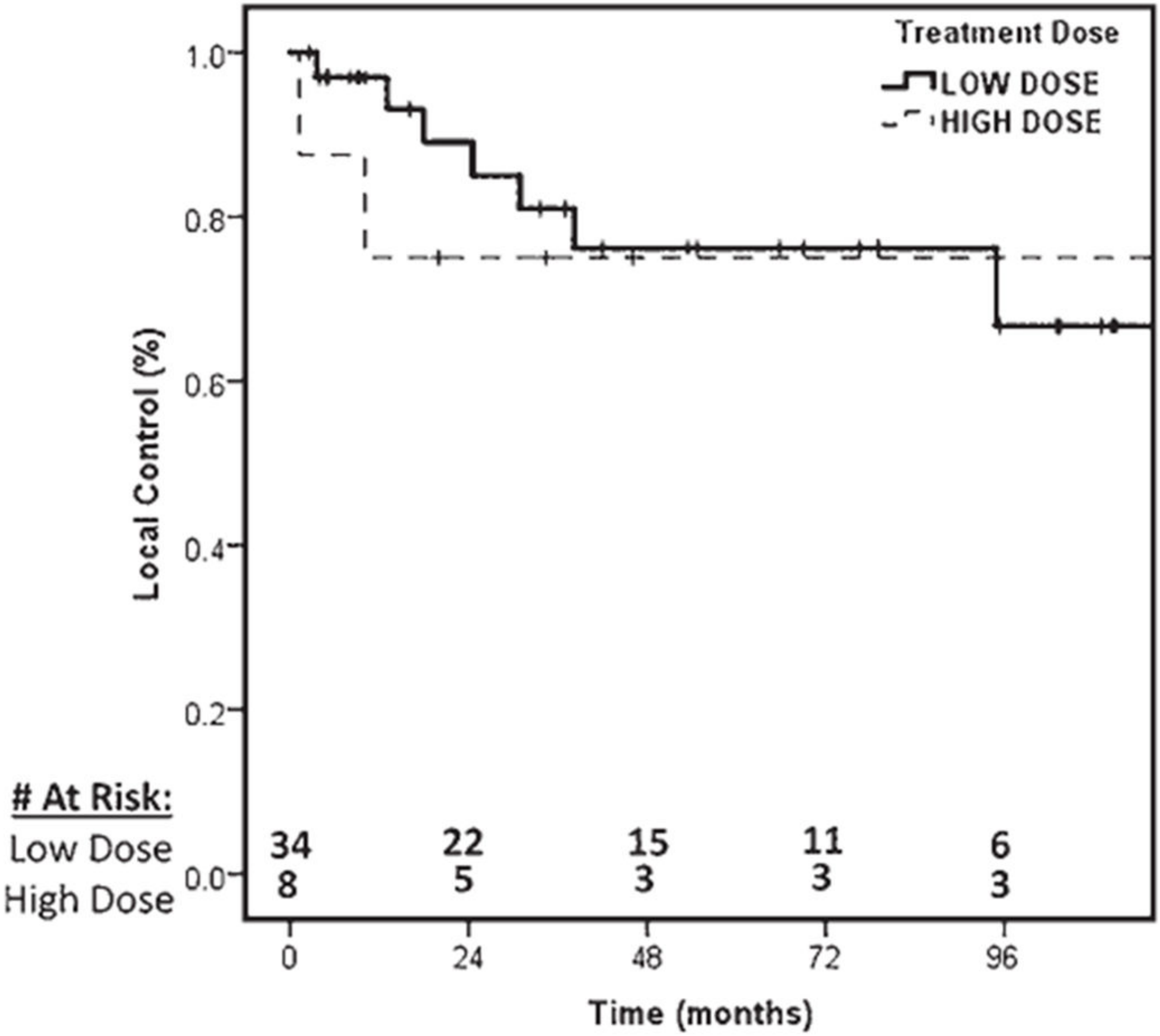

FIG. 2.

Local control of benign spinal tumors treated with low-dose ($BED_{10Gy} \leq 30$ Gy) or high-dose ($BED_{10Gy} > 30$ Gy) SBRT.

TABLE 1.

Patient (n = 38), lesion (n = 47), and treatment characteristics

Characteristic	Value
Patient age in yrs (median [range])	58 (25–91)
Patient sex	
Male	16 (42)
Female	22 (58)
Treatment platform	
CyberKnife	11 (23)
TrueBeam	15 (32)
Synergy S	21 (45)
Histology	
Hemangioblastoma	10 (21)
Meningioma	18 (38)
Paraganglioma	1 (2)
Schwannoma	18 (38)
Spine level treated	
Cervical	18 (38)
Thoracic	19 (40)
Lumbosacral	10 (21)
Previous radiotherapy	
Yes	8 (17)
No	39 (83)
Previous surgery	
Yes	25 (53)
No	22 (47)
SBRT dose in Gy (median [IQR])	13 (12–17)

Values shown are number (%) unless specified otherwise.

TABLE 2.

Pain-flare correlation chi-square analysis

	No. of Lesions		
	No Pain Flare (n = 32)	**Pain Flare (n = 8)**	**p Value**
Fractions			0.245
1	26	5	
3	6	3	
Previous surgery			0.118
Yes	18	2	
No	14	6	
SBRT dose			0.487
High (BED_{10Gy} >30 Gy)	7	1	
Low (BED_{10Gy} ≤30 Gy)	25	7	
Histology *			0.383
Meningioma	11	2	
Schwannoma	14	3	
Hemangioblastoma	5	2	
Age			0.118
≤57 yrs	14	6	
>57 yrs	18	2	
Spinal segment			0.487
Cervical	11	3	
Thoracic	11	4	
Lumbosacral	10	1	
Radiosurgery platform			0.230
CyberKnife	8	1	
TrueBeam	12	2	
Synergy S	12	5	

Complete background (pretreatment) data were available for only 40 of the 47 treated lesions.

* Meningioma, schwannoma, and hemangioblastoma represented the 3 most common tumor histology types but were not the only types found.

TABLE 3.

Patient characteristics and SBRT dose analysis

Patient or Dose Characteristic	No. of Lesions: Low-Dose Group (BED_{10Gy} ≤ 30 Gy) (n = 34)	No. of Lesions: High-Dose Group (BED_{10Gy} > 30 Gy) (n = 8)	p Value
Patient age			0.132
≤57 yrs	15	6	
>57 yrs	19	2	
Spinal segment			0.707
Cervical	12	2	
Thoracic	14	3	
Lumbosacral	8	3	
Histology			0.418
Meningioma	11	3	
Schwannoma	15	3	
Hemangioblastoma	7	0	
Other	1	2	
Previous surgery			0.881
Yes	18	4	
No	16	4	
Previous radiation			0.604
Yes	7	1	
No	27	7	
Radiosurgery platform			0.047
CyberKnife	3	6	
TrueBeam	13	2	
Synergy S	18	0	

TABLE 4.

Summary of previous series of SBRT for benign spinal lesions

Author & Year	No. of Patients	Dose (Gy)/No. of Fractions	Histology (no. of tumors)*	Median Follow-Up (mos)	Previous Treatment	Local Control	Late Toxicity
Chang et al., 1998	3	21/3 (hemangioblastoma); 21/1 (AVM)	Hemangioblastoma (2); AVM (1)	18	None	33%–70% size reduction	None
Dodd et al., 2006	51	16/1–30/5	Schwannoma (30); meningioma (16); neurofibroma (9)	36	Surgery (51%)	Partial response at all sites	Grade 2+ radiation myelopathy (n = 1)
Ryu et al., 2001	11	11/1–25/5	Hemangioblastoma (1); AVM (6); schwannoma (2); meningioma (1); chordoma (1)	6	Surgery (n = 4); XRT (n = 2)	100%	None
De Salles et al., 2004	3	12/1	Neurofibroma (2); meningioma (1)	6	Surgery (n = 3); XRT (n = 1)	70%	0%
Marchetti et al., 2013	18	10/1–25/5	Schwannoma (9); meningioma (11); neurofibroma (1)	43	Surgery (n = 14); XRT (n = 1)	100%	0%
Gerszten et al., 2012[9]	45	12/1–24/1	Schwannoma (16); meningioma (10); neurofibroma (14)	32	Surgery (n = 21); XRT (n = 2)	NR	0%
Gerszten et al., 2012[10]	40	11/1–21/3	Schwannoma (15); meningioma (8); neurofibroma (7)	26	Surgery (n = 18); XRT (n = 4)	100%	0%
Gerszten et al., 2008	73	15/1–25/3	Schwannoma (35); meningioma (13); neurofibroma (25)	37	Surgery (n = 19); XRT (n = 6)	100%	Grade 2+ radiation myelopathy (n = 3)
Gagnon et al., 2009	13	21/3–37.5/5	Schwannoma (6); meningioma (5); neurofibroma (2)	12	63% surgery; XRT	NR	0%
Sahgal et al., 2007	16	10/1–30/5	Meningioma (2); chordoma (4); hemangioma (2); neurofibroma (11)	25	Surgery (n = 5); XRT (n = 2)	89%	0%
Current cohort	38	9/1–21/3	Schwannoma (13); meningioma (15); hemangioblastoma (7)	54	Surgery (n = 25); XRT (n = 8)	76%	Grade 2+ radiation myelopathy (n = 1)

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

* Some patients had more than 1 tumor.