



# Stereotactic radiotherapy for spinal hemangioblastoma — disease control and volume analysis in long-term follow up

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## ABSTRACT

**Background:** This retrospective analysis evaluated the long-term outcome of spinal stereotactic body radiotherapy (SBRT) treatment for hemangioblastomas.

**Materials and methods:** Between 2010 and 2018, 5 patients with 18 Von-Hippel Lindau-related pial-based spinal hemangioblastomas were treated with fractionated SBRT. After precisely registering images of all relevant datasets, we delineated the gross tumor volume, spinal cord (including intramedullary cysts and/or syrinxes), and past radiotherapy regions. A sequential optimization algorithm was used for dose determinations, and patients received 25–26 Gy in five fractions or 24 Gy in three fractions. On-line image guidance, based on spinal bone structures, and two orthogonal radiographs were provided. The actuarial nidus control, surgery-free survival, cyst/syrinx changes, and progression-free survival were calculated with the Kaplan-Meier method. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

**Results:** The median follow-up was 5 years after SBRT. Patients displayed one nidus progression, one need of neurosurgery, and two cyst/syrinx progressions directly connected to symptom worsening. No SBRT-related complications or acute adverse radiation-related events occurred. However, one asymptomatic radiological sign of myelopathy occurred two years after SBRT. All tumors regressed; the one-year equivalent tumor volume reduction was 0.2 mL and the median volume significantly decreased by 28% ( $p = 0.012$ ). Tumor volume reductions were not correlated with the mean ( $p = 0.19$ ) or maximum ( $p = 0.16$ ) dose.

**Conclusions:** SBRT for pial-based spinal hemangioblastomas was an effective, safe, viable alternative to neurosurgery in asymptomatic patients. Escalating doses above the conventional dose-volume limits of spinal cord tolerance showed no additional benefit.

**Key words:** SBRT; hemangioblastoma; myelopathy; Von-Hippel Lindau

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## Introduction

Spinal hemangioblastomas are benign, vascular, pial-based tumors that represent the third most common intramedullary spinal cord tumor. They are most often associated with pain, which may be followed by sensory loss, and less commonly, motor symptoms [1]. Many of these spinal cord tumors are accompanied by syringomyelia, which contribute to neurological sequelae. Hemangioblastomas present either as sporadic lesions or, in 20–25% of cases, manifestations of von Hippel-Lindau disease (VHL), due to a loss-of-function mutation in the VHL tumor suppressor gene. Historically, complete microsurgical removal has been the standard of care for spinal cord hemangioblastomas [2]. However, in the last decade, studies on spinal stereotactic body radiation therapy (SBRT) from the United States and Asia have shown encouraging results, with high rates of disease control [3–6]. Most patients experienced no significant adverse toxicity with a variety of SBRT platforms and prescribed doses, although adverse neurologic events have been reported [5]. It remains unknown whether dose escalation might be an appropriate strategy for treating hemangioblastomas. First, there is a risk of developing additional tumors throughout the individual's lifetime, and repeated SBRT sessions are often necessary. Second, the analogous treatment, intracranial radiosurgery for benign tumors, began with a high dose, but further experiences showed that de-escalating intracranial radiosurgery doses could reduce toxicity, while maintaining excellent rates of tumor control. On the other hand, prior to the development of SBRT, patients that were unsuitable for a resection were treated with conventionally fractionated external beam radiotherapy; however, the doses were inadequate, and outcomes were poor [7]. The present retrospective study aimed to evaluate disease control, toxicity, and tumor volume reductions during a long-term follow-up after spinal SBRT.

## Materials and methods

All follow-up information was obtained in November and December, 2020. After institutional review board approval, all clinical information was retrospectively reviewed. Follow-up radiographic evaluations (myelopathy, progression of nidus

and/or cyst) were performed by one treating team (1 radiation oncologist, 1 radiologist, and 1 neurosurgeon).

## Patients

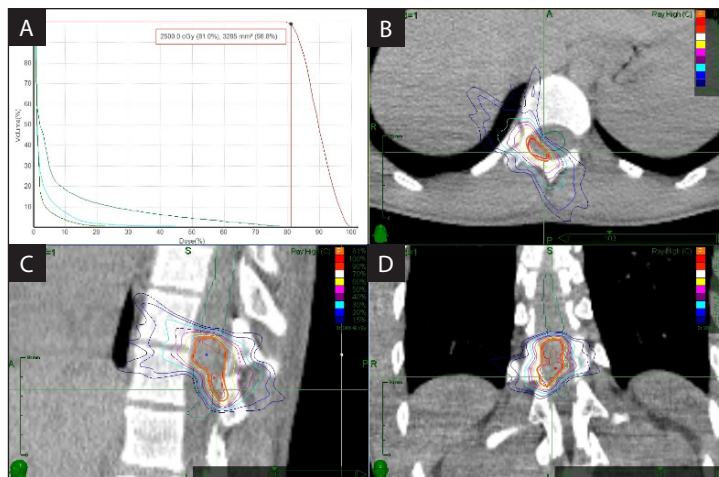
Between 2010 and 2018, 5 patients with 18 VHL-related pial-based spinal hemangioblastomas were treated with fractionated robotic SBRT using the CyberKnife system (Accuray, Sunnyvale, CA) in conjunction with Xsight Spine tracking software. Patients were eligible for radiotherapy, when they had progressive disease, in terms of volume enlargement or symptom severity, with or without previous surgery, and when they had refused surgical intervention or were judged inoperable after an evaluation by a neurosurgeon. All patients received psychological support and underwent psychiatric examinations, when needed. No patient obtained conventional radiotherapy before or after SBRT, and no postoperative adjuvant SBRT was performed. Table 1 displays the patient demographics, hemangioblastoma locations, and symptoms at presentation (i.e., pure motor, pure sensory, or mixed symptoms, or asymptomatic).

## Procedures

Patients with only cervical spine lesions were immobilized with a 3-point thermoplastic face mask. With the patient in a supine position, the spinal region of interest was imaged with 1-mm thick native CT scans and MRI (at least T1 with contrast

**Table 1.** Clinical characteristics

|                                     |                        |
|-------------------------------------|------------------------|
| No. of patients                     | 5                      |
| No. of tumors                       | 18                     |
| No. of patients with solitary tumor | 3                      |
| No. of patients with four tumors    | 1                      |
| No. of patients with eleven tumors  | 1                      |
| Male sex                            | 3                      |
| Median age at treatment (range)     | 22 years (18–60 years) |
| Presenting symptoms                 |                        |
| Motoric                             | 4                      |
| Sensory                             | 4                      |
| Mixed                               | 3                      |
| Asymptomatic                        | 7                      |
| Tumor location                      |                        |
| Cervical                            | 8                      |
| Thoracic                            | 10                     |



**Figure 1.** Example of stereotactic body radiotherapy (SBRT) treatment plan, with 25 Gy in 5 fractions. **A.** The dose volume histogram; **B.–D.** Sose distribution in transversal, sagittal and coronal plane respectively with steep dose gradient to protect the spinal cord

enhancement and T2). After relevant image datasets were precisely registered, the gross tumor volume, spinal cord (including intramedullary cysts and/or syrinxes), and regions of past radiotherapy were delineated. No additional margins were added. Sequential dose optimization using MultiPlan (Accuray, Sunnyvale, CA) was performed for 99% planning target volume (PTV) coverage, spinal cord doses (0.25 mL), and for doses equal to 2% of the spinal cord volume (D2%; this was preferred as an alternative to the maximum absorbed dose to ensure that the maximum dose did not rely on a single computation point). Continuous on-line image guidance was provided, based on the spinal bone structures, in addition to two orthogonal radiographs. The typical treatment plan was 25 Gy, delivered in 5 fractions (Fig. 1).

### Follow-up

Patients were followed up with clinical examinations, neurologic status assessments, and MRI, according to the policy of the referring physician. In general, follow-ups were conducted at 6- to 12-month intervals after SBRT. Nidus or cyst progression was defined as any dimensional enlargement detected with a T1-weighted MRI with intravenous contrast enhancement or with a T2-weighted MRI, respectively. All available follow-up MRI T1 scans with contrast enhancement (performed 1–3 years after SBRT) were imported into the treatment planning system. Residual nidus delineation was provided by the same radiation oncologist.

**Table 2.** Stereotactic body radiotherapy (SBRT) characteristics

|                                 |                     |
|---------------------------------|---------------------|
| Median PTV dose (range)         | 28.6 Gy (27.4–38.3) |
| Median Dmax (range)             | 33.3 Gy (30.9–49.2) |
| Median spinal cord D2%          | 20.7 Gy (19.5–27.8) |
| Median spinal cord Dmax         | 26.3 Gy (24.0–32.2) |
| Median isodose line (range)     | 72% (61–81)         |
| Median Conformity index (range) | 1.4 (1.1–1.9)       |
| Median tumor volume (range)     | 0.21 mL (0.04–3.85) |
| Median Coverage (range)         | 97% (96–100)        |

PTV — planning target volume

### Statistical analyses

We evaluated actuarial nidus control, surgery-free survival, cyst/syrinx and symptom progression-free survival with the Kaplan-Meier method. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. All statistical analyses were performed with Statistica ver. 13.

The one-year equivalent tumor reduction after SBRT was calculated from MRI T1 scans with contrast enhancement. We performed correlation analyses to evaluate associations between the tumor volume reduction and doses (both mean and maximum).

The paired t-test was performed to assess the change in tumor volume over time. The dependence of the change in tumor volume on the dose was assessed with the Pearson correlation coefficient. Volume reductions were compared between

larger and smaller tumors with the Welch two-sample test. All tests were calculated at the 5 % level of significance.

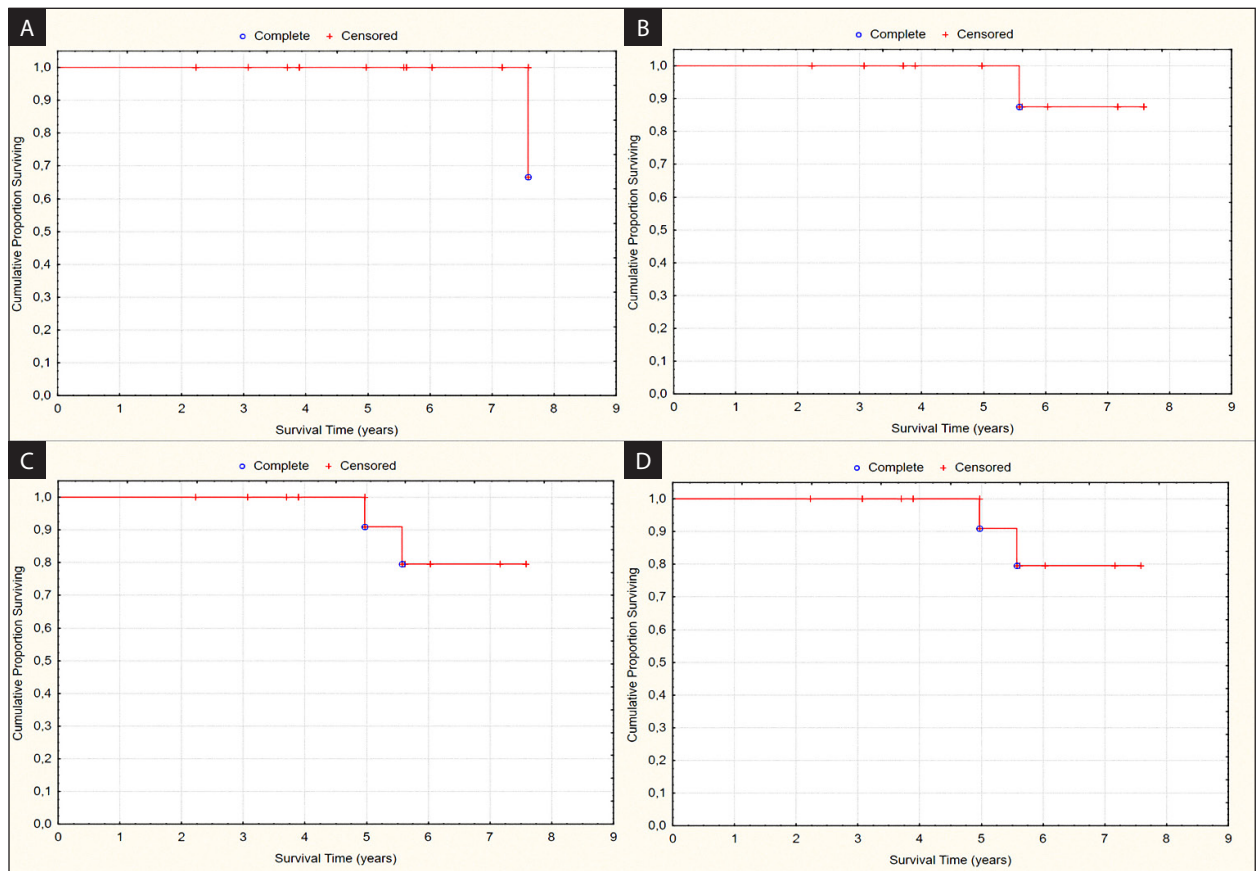
### Results

The mean PTV dose was 29.6 Gy ( $\pm 3.3$ ), and the mean tumor volume was 0.72 mL ( $\pm 1.1$ ). The mean PTV max dose (Dmax) was 35.2 Gy ( $\pm 5.4$ ). Treatment was delivered in 5 fractions for 17 tumors, and in 3 fractions for one tumor. The mean dose in 0.25 ml (D0.25 mL) of the spinal cord was 19.1 Gy ( $\pm 3.8$ ) and only one treatment applied a D0.25 mL above 22.5 Gy. The mean spinal cord D2% and Dmax were 21.6 Gy ( $\pm 2.7$ ) and 27.1 Gy ( $\pm 2.8$ ), respectively. A maximum spinal cord dose >30 Gy (in 0.007 mL) was observed in only one case.

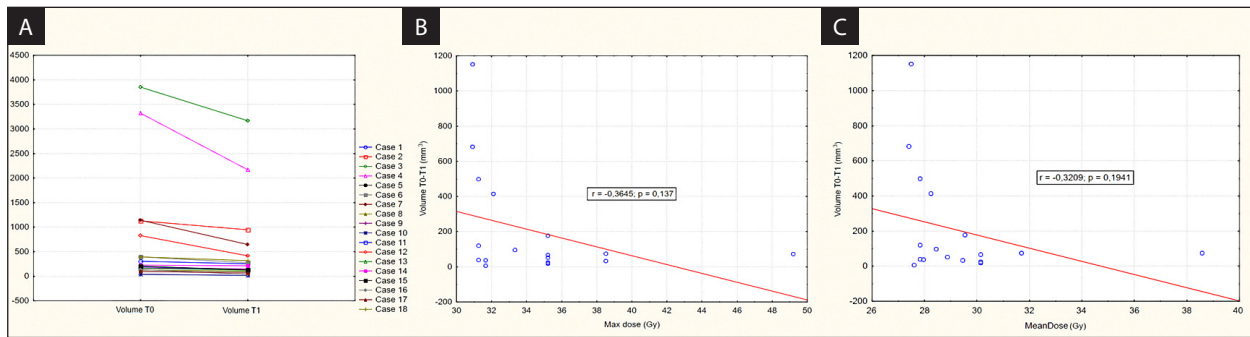
All patients were alive at the time of this report. Figure 2 shows the time courses of one nidus progression, one lesion that required neurosurgery and two cyst/syrinx progressions that were directly connected to symptoms worsening after

the SBRT. No complications or acute adverse radiation events related to SBRT were observed. No late radiation-related toxicity was detected. However, one asymptomatic radiological sign of myelopathy occurred two years after SBRT.

All lesions displayed volume reductions, and no patient was lost during the median follow up of 5 years (range 2–8 years). However, one tumor was not covered with a MRI feasible for volumetric analysis in the predefined interval. The median time to performing the volumetric MRI was 20 months (range 9–40 months). The calculated one-year equivalent tumor volume reduction was 0.2 mL. The mean volume significantly decreased by 28%, from 0.72 mL to 0.52 mL ( $p = 0.012$ ). High volume lesions showed shrinkages, with a median volume reduction of 27%, from 1.3 mL to 0.9 mL. In comparison, small nidus lesions showed significantly higher volume reductions ( $p < 0.001$ ), with a median volume reduction of 33%, from 0.14 mL to 0.09 ml (Fig. 3A). We found no correlation between the tumor volume reduc-



**Figure 2.** Kaplan-Meier analysis of stereotactic body radiotherapy (SBRT) outcomes. Outcomes included: **A.** The time to nidus enlargement; **B.** A need for surgery; **C.** Cyst/syrinx enlargement; **D.** Progression of neurological symptoms



**Figure 3.** Effects of stereotactic body radiotherapy (SBRT) dose on hemangioblastoma volume reduction. **A.** Calculated one-year equivalent nidus volume reduction; **B.** Correlation between nidus volume reduction and maximum dose; **C.** Mean dose of irradiation

tion and either the mean ( $p = 0.19$ ) or maximum ( $p = 0.16$ ) dose (Fig. 3B, C).

### Discussion

In this retrospective study of patients with VHL-related spinal cord hemangioblastomas, we confirmed that long-term SBRT treatment provided local control and displayed a feasible safety profile. We also found that a dose escalation above the spinal cord tolerance limit did not provide a clear benefit.

In general, the prescribed dose in our case series was 25 Gy in 5 fractions, which should not have exceeded the dose-volume limit of the spinal cord. This dose was comparable to that applied by Pan et al. who reported a median peripheral dose at the level of 21.6 Gy [3]. Similarly, Kalash et al. preferred a dose de-escalation strategy, with 21 Gy delivered in three fractions; however, they only evaluated seven hemangioblastomas, among 47 benign tumors [8]. On the other hand, Selch et al. applied single fraction radiosurgery at 12 Gy delivered to the 90% isodose line, in 20 hemangioblastomas<sup>4</sup>. Finally, Daly et al. treated 27 hemangioblastomas with median doses that ranged from 18 to 25 Gy, delivered in one to three fractions [5].

One nidus enlargement was observed in our cohort. An asymptomatic progression in the C1 site was detected after more than 7 years in a patient with multiple lesions; however, there was no need of intervention. Additionally, the same patient underwent neurosurgery, due to progression of a neurological deficit in the T3/4 site, 6 years after SBRT. There were no signs of radiological progression or myelopathy. The high control of nidus in our series was consistent with previous SBRT studies. For ex-

ample, Selch et al. reported a 4-year, local control of 95% in solid tumors [4]. Daly et al. showed a 3-year local control of 86% [5]. In the largest series of 34 evaluable tumors among 46 lesions, Pan et al. demonstrated a 5-year local control of 92% [3]. These results were similar to those reported for neurosurgery, where outcomes of deterioration occurred with an incidence of 15% [9].

We detected two cyst/syrinx progressions during a 5-year median follow up. However, we found no evidence of a syrinx volume reduction after SBRT, consistent with previous reports. Selch et al. observed one syrinx enlargement out of 20 treated hemangioblastomas [4]. Daly et al. described three patients that displayed progression in cysts surrounding the tumor; of those, two ultimately required surgical resections at 2 and 11 months [5]. Several other studies dealing with intracranial hemangioblastomas have reported the tendency of cysts to progress and, overall, cysts were relatively insensitive to radiation treatment [10, 11]. On the other hand, two previous studies reported post-operative effects on tumor-associated syrinxes. Deng et al. and Mehta et al. demonstrated reductions in 83% and 96% of syrinxes, respectively [9, 12]. Currently, surgical resection remains the definitive treatment for symptomatic cystic tumors, despite complications, on the order of 11% [13], in cases of symptomatic and/or large syrinxes. The potential complications include cerebrospinal fluid leakages, superficial wound infection/dehiscence, and both intra- and extradural hematomas. Moreover, surgical resections are required when tumors remain symptomatic after SBRT.

In the present study, before SBRT, 11 of 18 lesions were associated with symptom progression. After

SBRT, all symptomatic patients reported that symptom progression had stopped. However, neurological symptom regression was difficult to confirm, even in patients that presented with pain. Seven asymptomatic lesions remained free of neurological signs after SBRT. In two cases, neurological symptoms progressed, due to cyst/syrinx enlargement. This finding was consistent with findings by Selch et al. who confirmed symptom regression in only one of seven symptomatic lesions [4]. In contrast, in a study by Chang et al., symptom improvement was noted in all patients that experienced tumor reductions, and in some cases, where no change in tumor size was noted [6]. Similarly, Pan et al. found that symptoms improved in 81% of patients [3]; however, clinical evaluation follow-ups were only available for 16 out of 46 tumors. Lastly, intracranial symptom improvement was reported in 55% of patients in a study by Chang et al. [14] and in 64% of patients in a study by Asthagiri et al. [15].

In the present study, we observed no complications or acute adverse radiation events related to SBRT and no late radiation-related toxicity. However, two years after SBRT, one asymptomatic radiological sign of myelopathy was detected. In the largest case series to date, Pan et al., confirmed the safety of radiation treatment; no patient developed any complications related to radiosurgery [3]. Additionally, Selch et al. found no clinical or imaging evidence of spinal cord injury [4]. On the other hand, Daly et al. used a dose escalation strategy, and found four potential radiation-related toxicities. They found two cases of grade 2, unilateral foot-drop symptoms at 5 months after treatment and two cases of grade-1 sensory deficits [5]. SBRT can be potentially risky, as described by Moss et al., in case series using an older radiation technique, where 5 of 31 patients developed radiation necrosis [16]. Nevertheless, SBRT appeared to be safe, based on a comparison with results discussed post-operative complications of 6–23% [12, 13, 17].

In the present study, all tumors regressed; the mean nidus volume significantly decreased, from 0.72 mL to 0.52 mL (28%,  $p = 0.012$ ). In our series, the pretreatment tumor volume was the same as that reported by Selch et al.; however, the majority of tumors in their case series showed no volume reduction after SBRT [3]. In a study by Pan et al., the median pretreatment tumor volume was 0.26 mL (range 0.03–70.90 mL), and 20 of 46 tumors

remained unchanged in size [3]. Daly et al. reported a median target lesion volume of 0.16 mL (range 0.06–9.80 mL), but they did not comment on the volume response to SBRT [5]. In a series of 74 intracranial hemangioblastomas treated with gamma knife radiosurgery, Kano et al., at the University of Pittsburgh, reported a 50% reduction in the volume of enhancing solid tumors, in 38 of 74 tumors [18]. Our results were inconsistent with those of Asthagiri et al., who reported low 10-year local control rates (51%), and concluded that an early volumetric response was not always predictive of the final outcome [15].

We found no correlation between tumor volume reductions and either the mean ( $p = 0.19$ ) or maximum ( $p = 0.16$ ) dose. In contrast, several authors have reported a significant effect of dose on the tumor response rate, after radiosurgery for intracranial hemangioblastomas [18]. We lack similar studies in spine hemangioblastomas, but Daly et al. reported a local tumor control rate comparable to ours, despite their dose escalation protocol [5] which exceeded the dose constraints commonly cited for the spinal cord [19, 20]. Kalash et al. studied de-escalated scenarios for benign spinal tumors, and they found no significant difference between low-dose and high-dose SBRT in the rates of local control, pain flares, or long-term toxicity [8]. As low number of tumors were analyzed in such rare diagnosis, it is not possible to recommend optimal radiation dose. Nevertheless, when long survival is expected, maintaining low radiation toxicity should be a primary endpoint and, thus, dose escalation above spine dose-volume limits seems to be controversial.

To the best of our knowledge, there is no study comparing results of stereotactic and conventional radiotherapy in patients with spinal hemangioblastomas. However, stereotactic radiotherapy minimizes the amount of normal tissue and in indirect comparison improves local control by delivering large cumulative doses as reported by Moss et al. [16]. Smalley et al. reported improved in-field disease control when more aggressive treatment was performed between 1963 and 1983 [7]. Patients treated to a dose of 50 Gy manifested local control in 4/7 (57%) vs. 4/12 (33%) in patients treated to less than 50 Gy. In the brain, Koh et al. reported 5-year disease-free survival of 80% when external beam radiotherapy schedules ranged from 50.0 to

55.8 Gy in 1.8–2.0-Gy daily fractions [21], such doses seem to be less efficient and could potentially harm the spine.

Our study strengths included the homogeneous SBRT technique, the homogeneous patient population, the long follow up, and the volumetric analysis. Our study limitations included the low number of patients, even considering the rarity of VHL-related pial-based spinal hemangioblastomas. Moreover, the timing of the contrast enhancement MRI was somewhat inconsistent for the volumetric analyses, due to attempts to avoid potential toxicity related to intravenous contrast enhancement.

## Conclusions

This study showed that SBRT was effective and safe for treating VHL-related pial-based spinal hemangioblastomas. Thus, the SBRT approach represents a viable alternative to neurosurgery in asymptomatic patients. However, symptoms rarely regressed after SBRT; therefore, microsurgery remains the standard of care for symptomatic patients. We also found that escalating doses above the conventional dose-volume limits of spinal cord tolerance did not indicate any additional benefit.

## Conflict of interest

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