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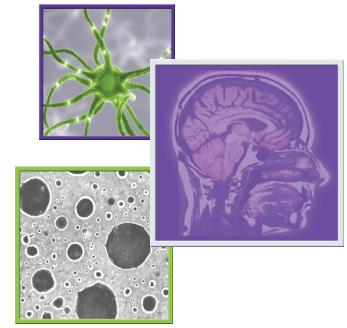

Review of stereotactic radiosurgery for intradural spine tumors

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Practice points

- Surgical resection is the most common treatment for intradural spinal tumors.
- Stereotactic radiosurgery (SRS) may be indicated for patients who are older, have residual disease following surgery or cannot tolerate surgical treatment.
- Research on SRS treatment outcomes for intradural metastases is limited but suggests that SRS may control tumors with minimal toxicity.
- Benign intradural extramedullary tumors have been studied more extensively than other intradural tumor subtypes, with patients demonstrating pain reduction and local tumor control following SRS.
- SRS has been associated with radiation-induced myelopathy in a rare subset of patients.

Stereotactic radiosurgery (SRS) has become an increasingly popular treatment modality for spinal tumors due to its noninvasive and targeted approach. Whether SRS has the promise of relieving pretreatment symptoms and providing local tumor control for patients with intradural spine tumors is still debated. This review explores the current literature on SRS treatment for both metastatic and benign intradural tumors, with a focus on differential use for intramedullary and intradural extramedullary neoplasms. Although mortality rates from underlying malignant disease remain high, SRS may benefit patients with spinal metastatic lesions. Benign tumors have shown a promising response to SRS therapy with low rates of complications. Larger studies are necessary to determine the indications and outcome profile of SRS for intradural spinal neoplasms.

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KEYWORDS
• intradural tumors • spine metastases • stereotactic radiosurgery

Intradural spinal cord tumors represent approximately 30% of spinal cord neoplasms [1]. With its success in treating intracranial lesions, stereotactic radiosurgery (SRS) has been increasingly trialed in patients with intradural spinal tumors [2]. Surgical resection remains the mainstay treatment for these tumors, but among patients who may not tolerate surgical intervention and in those with residual disease after surgery, SRS is considered a potentially beneficial treatment option [3–7]. Due to the differences in radiosensitivity between healthy tissue and tumors, SRS is able to target tumors while still preserving normal tissue [8–12]. Commonly used SRS technologies currently include CyberKnife (Accuray, Inc., CA, USA), Novalis (BrainLAB, Heimstetten, Germany) and Synergy S (Elekta,

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Crawley, UK) [2]. The frame-based nature of early SRS initially limited the treatment to intracranial targets [13,14]. The recent development of image-guided technology has facilitated SRS treatment for extracranial spinal tumors, although evaluation of its use has largely been limited mostly to vertebral lesions and malignancies [15–19]. This narrative review article seeks to summarize the recent trends and outcomes associated with the treatment of intramedullary (IM) and intradural extramedullary (IDEM) spine tumors using SRS.

Methods

A systematic search of the US National Library of Medicine PubMed database was performed to identify English-language articles on the application of SRS for intradural tumors. We searched for combinations of the following terms: stereotactic radiosurgery, SRS, CyberKnife, spine, extracranial, tumors, metastases, intradural, intramedullary, extramedullary and radiation-induced myelopathy. We also performed a hand-search strategy to obtain references from the selected articles as well as from systematic reviews and meta-analyses on the topic (Table 1).

Metastatic intradural tumors

• Metastatic IDEM tumors

Nearly 40% of patients diagnosed with cancer will develop spinal metastases [32,33]. Most spinal metastases develop in the vertebral body, and less than 2% are characterized as IDEM [34]. Frequently, intradural metastases are associated with microscopic malignant cerebrospinal fluid seeding, portending a poor overall prognosis [35,36]. Therefore, SRS may be a method worth considering for patients with intradural metastases as a noninvasive alternative to surgical excision. Despite this potential, very little research has been done elucidating the treatment success and outcomes associated with SRS IDEM metastases. Descriptions of IDEM metastases in general, regardless of treatment modality, are limited to isolated case reports [37–42]. Shin *et al.* reported their experience on four IDEM spinal tumors treated with SRS. The mean treatment dose was 13.8 Gy (range: 10–16 Gy). Of the three patients with four IDEM tumors, two described clinical improvement. One of the four tumors demonstrated a complete response, two showed a partial response and one developed into progressive disease [20].

• Metastatic IM tumors

Due to their location, IM spine tumors that are treated with SRS are at higher risk of causing spinal cord injury and radiation-induced myelopathy as compared with IDEM tumors [12,14,31]. Few studies have assessed SRS treatment outcomes for these tumors [43]. Shin *et al.* considered seven patients with IM metastases among a total sample of 11 patients (four with IDEM tumors). Of the patients with IM tumors, five reported clinical symptom improvement, one experienced no change and one patient was lost to follow-up. The authors found that among all treated tumors (both IDEM and IM), complete tumor control was noted in eight of the nine tumors with appropriate follow-up (89%). The authors reported no radiation toxicity during follow-up (mean time: 10 months) [20]. In a case report, Parikh *et al.* described SRS treatment for a metastatic renal cell carcinoma IM tumor. No complications were noted 26 months following treatment, with the patient reporting normal function, absence of pain and rare paresthesias [21].

Other studies have demonstrated similarly low morbidity associated with SRS, but again these figures are limited by the poor survival inherent to the underlying disease. Veeravagu *et al.* performed a study of nine patients with 11 metastatic IM tumors between 2000 and 2010. Tumor volume ranged from 0.12 to 6.4 cm^3 (median: 0.48 cm^3) and a median dose of 21 Gy (range: 14–27 Gy) was delivered in one to five (median: 3) fractions. The tumors included five breast cancer metastases, two non-small-cell lung cancer metastases, one epitheliod hemangioepithelioma and one cystic adenocarcinoma. Upon follow-up, no patients reported deterioration in neurological status or gait and no local recurrences were noted. One patient experienced presumed radiation-induced myelopathy. Despite an overall low rate of complications, survival was generally poor, with a median survival of 4 months and 4 days (range: 1 month and 2 days–9 months and 6 days) and only one patient alive 14 months after treatment [22]. The available literature suggests that SRS is another potential treatment modality for metastatic IM tumors, and represents an excellent alternative to IM surgery, especially considering the potential morbidity and protracted recovery expected after surgery for excision of an invasive spinal cord tumor in a patient with a limited survival. As these results indicate, SRS may be indicated

for treating IM metastatic spine tumors. Future studies with more subjects will be necessary to evaluate the overall success of SRS in IM metastatic disease.

Benign intradural tumors

The evidence behind SRS in treating metastatic spinal tumors has led to additional investigations into its utility in treating benign spinal intradural tumors such as schwannomas, neurofibromas and meningiomas. Similar to many metastatic lesions, the primary treatment approach to benign intradural tumors is often surgical. However, in patients who may not tolerate the morbidity associated with surgery, early data suggest that SRS may be an effective alternative.

• Benign IDEM tumors

In a prospective study, Dodd *et al.* [23] described radiosurgical outcomes for patients with benign IDEM spinal tumors who underwent CyberKnife radiosurgery between 1999 and 2005. The patient population included 51 individuals with a total of 55 benign tumors: nine neurofibromas, 16 meningiomas and 30 schwannomas. Treatment doses ranged from 16 to 30 Gy and were delivered on consecutive days (range: 1–5 days total) to tumors between 0.136 and 24.6 cm^3 in volume. Within the first year after treatment, three patients (3 of the 55 lesions, or 5%) required surgical resection for progressive symptoms. Only one of these three lesions showed radiographic growth. For those patients who had more than 24 months of follow-up information available (28 of the 51 patients), all lesions were either stable in size or smaller following SRS (61 and 39% of all tumors, respectively). Overall, the authors demonstrated only one instance of radiation-induced myelopathy and an improvement in pretreatment pain symptoms for patients with meningiomas and schwannomas (70 and 50% of patients reporting improvement, respectively) [23].

Several additional prospective studies had similar results. Gerszten *et al.* prospectively evaluated 73 benign IDEM tumors treated with CyberKnife SRS (13 meningiomas, 25 neurofibromas and 35 schwannomas) between 2001–2006. The study had a median follow-up period of 37 months with 3, 6 months and annual post-treatment visits. All patients (except for one) underwent a single treatment session. Target volumes ranged from 0.3 to 93.4 cm^3 with a maximum radiation dose of 15–25 Gy (mean dose: 21.64 Gy). The authors reported long-term radiographic tumor control in 100% of patients and pain improvement in 73%. Complication rates were low, with only three patients experiencing radiation-induced myelitis (on the basis of MRI and the development of a Brown–Séquard syndrome) as a result of treatment [24].

Schwannomas in neurofibromatosis-1

Intradural tumors in neurofibromatosis type 1 (NF1) patients were unique in that from the early evidence it appears that they may not benefit from SRS treatment in the same way that the other intradural tumors do [23,24,44]. The neurofibromas in this patient population typically involve numerous nerve roots that complicate the identification of the appropriate radiosurgical treatment target and they may have multiple pain generators acting simultaneously. Additionally, NF-associated tumors may biologically differ from sporadic schwannomas, making them more challenging to treat with radiosurgery. In the study by Gerszten *et al.*, NF1 was the underlying diagnosis for all three patients who experienced no improvement in pretreatment pain levels [24]. Dodd *et al.* noted that, despite an overall association with improved pretreatment symptoms, the seven NF1 patients treated in their study were the only patients not to experience symptom relief. Moreover, despite six of the seven treated lesions demonstrating a stable size upon follow-up, half of these patients reported progressive weakness, numbness and pain that was worse than pretreatment levels [23]. A 2007 retrospective review of 19 benign spinal tumors in 16 patients found that of the three tumors that grew following SRS, two of them had occurred in NF1 patients [25].

SRS complications

Dodd *et al.* were the first to describe a patient who developed myelopathy 8 months after SRS for a spinal IDEM tumor. The authors suspected that trauma resulting from the patient's previous resections may have contributed to her risk for developing myelopathy [23]. Gerszten *et al.* [24] separately described three neoplasms out of 73 for which SRS treatment resulted in radiation-induced myelitis at 5, 12 and 13 months following surgery, respectively. Unlike the patient in the Dodd *et al.* study, these three patients had no prior radiation [23,24]. Marchetti *et al.*, in comparison, identified no occurrences of radiation-induced myelopathy in

Table 1. Reviewed literature on stereotactic radiosurgery for metastatic and benign intradural spine tumors.

Study	(Year)	Number of patients and lesions	Number of IDEM/IM	Treatment details	Mean follow-up time	Main clinical/survival outcomes	Radiological observations	Complications	Ref.
Stereotactic radiosurgery for metastatic intradural spine tumors									
Shin *et al.*	2009	7/11	4/7	Mean: 13.8 Gy; range: 10–16 Gy	Mean: 10 months	Two of the four IDEM lesions and five of the seven IM tumors were associated with clinical improvement	89% tumor control	None	[20]
Parikh *et al.*	2009	1/1	0/1	15 Gy in three fractions	26 months	Normal function, decreased head, neck and shoulder pain, rare paresthesias	Stable lesion size	None	[21]
Veeravagu *et al.*	2012	9/11	0/11	Median: 21 Gy; range: 14–27 Gy	–	No deterioration in neurological status or gait, no local recurrences. Median survival of 4 months and 4 days (range: 1 month and 2 days to 9 months and 6 days) and only one patient alive 14 months after treatment	Two patients with reduced size, two with stable size	None	[22]
Stereotactic radiosurgery for benign intradural spine tumors									
Dodd *et al.*	2006	51/55	55/0	Range: 16–30 Gy	Mean: 29 months; range: 24–73 months	Three patients required surgical resection for progressive symptoms; improvement in pretreatment pain symptoms noted for patients with meningiomas and schwannomas (70 and 50% of patients reporting improvement, respectively)	For patients with more than 24 months of follow-up information available (28/51 patients), lesions were either stable in size or smaller (61 and 39% of all tumors, respectively)	One case of radiation-induced myelopathy	[23]
Gerszten *et al.*	2008	73/73	73/0	Mean: 21.64 Gy; range: 15–25 Gy	Median: 37 months; range: 8–71 months	Pain improvement in 73% of patients with pre-operative pain (22/30 patients)	100% tumor control	Three patients experienced radiation-induced myelitis	[24]
Sahgal *et al.*	2007	16/19	–	Median: 21 Gy; range: 10–30 Gy	Median: 25 months; range: 2–37 months	Pain improvement in 46% of patients with pre-operative pain (6/13) unchanged in 38% (5/13), and worsened in 15% (2/13) of tumors 6-month follow-up	Three tumors progressed at 2-, 4- and 36-month post-treatment	None	[25]
Marchetti *et al.*	2013	18/21	21/0	11 lesions single-fraction (10–13 Gy); 10 lesions 4–6 fractions (18.5–25 Gy)	Mean: 43 months; range: 32–73 months	–	No lesions showed progression	None	[26]

IDEM: Intradural extramedullary; IM: Intramedullary.

Table 1. Reviewed literature on stereotactic radiosurgery for metastatic and benign intradural spine tumors (cont.).

Study	(Year)	Number of patients and lesions	Number of IDEM/IM	Treatment details	Mean follow-up time	Main clinical/survival outcomes	Radiological observations	Complications	Ref.
Stereotactic radiosurgery for benign intradural spine tumors (cont.)									
Hernández-Durán *et al.*	2016	52/70	0/70	Mean: 22.14 Gy (95% CI: 20.75–23.53); mean fractionation of 4 (95% CI: 3–5)	Mean: 30.95 months (95% CI: 26.75–35.15)	Symptom improvement or stabilization in 96% of cases	100% radiological stabilization or improvement	One patient with diffuse myelomalacia in the thoracic cord	[27]
Chang *et al.*	1998	13/29	0/29	Mean: 23.2 Gy; range: 18–40 Gy	Mean: 43 months; range: 11–84 months	Symptom improvement in 56% of patients	Of the 23 tumors with more than 2-year follow-up, 22% disappeared, 43% regressed and 35% were unchanged	Three patients with radiation necrosis	[28]
Daly *et al.*	2011	19/27	0/27	17 tumors treated with a single fraction, median: 20 Gy (range: 18–30 Gy); 10 tumors treated with 18–25 Gy in 2–3 treatments	–	–	86% local tumor control at 3 years	One case of Grade 2 foot drop, two cases of Grade 1 sensory deficits	[29]
Ryu *et al.*	2003	10/10	0/10	Mean: 21 Gy; range: 18–25 Gy	Mean: 12 months; range: 1–24 months	–	30% (3/10) smaller; 70% (7/10) stable	None	[30]
Stereotactic radiosurgery for intradural spine tumors (benign & metastatic)									
Gibbs *et al.*	2009	1075 patients	156 patients, benign IDEM; 919 patients, metastatic tumors	Range: 12.5–25 Gy	–	–	–	Six patients developed delayed myelopathy	[31]

IDEM: Intradural extramedullary; IM: Intramedullary.

a sample of 18 patients that underwent SRS for spinal IDEM tumors [26].

To investigate this question further, Gibbs *et al.* [31] retrospectively reviewed 1075 patients with benign or malignant spine tumors treated with CyberKnife. Of these patients, 156 had benign IDEM tumors and 919 patients had metastatic tumors. The authors identified six patients who developed radiation-induced myelopathy, three with IDEM tumors and three with tumors in the vertebral column. The authors were unable to identify a clear dosage pattern responsible for the six patients who were injured, despite animal studies that have shown a correlation between dose strength and radiation toxicity [45]. As the authors explained, three of the patients were given a much larger than average radiation dose, while the other three had small areas of the spinal cord treated with equivalent doses of 8 Gy in single fractions. The authors proposed genetic mutations as a potential mechanism for the toxicities observed in patients. Possible mutations include germ-line mutations associated with ataxia telangiectasia and in *TGF-β1* [31,46]. Of note, the dosing limit for safe treatment of intradural tumors has not yet been determined [47]. As Sohn and Chung describe, fractionation and dose regimens traditionally differ at each institution [47]. Rock *et al.* suggest that single doses of 10 Gy delivered to less than 10% of the cord volume over 2 or fewer spinal segments can be safely tolerated [48]. Gagnon *et al.* report hypofractionated schedules that include 4 Gy in five fractions, 8 Gy in three fractions and 9 Gy in three fractions [49]. Median doses for treating previously irradiated tumors range from 20 to 35 Gy in one to five fractions [17,50,51].

• Benign IM tumors

Only few studies have investigated outcomes following SRS for IM neoplasms. Surgery remains the mainstay treatment approach for these lesions [52], however, surgery may be contraindicated in patients with multiple co-morbidities, and among those with multiple lesions, such as those with multiple hemangioblastomas [28–30,53]. In a meta-analysis of 11 clinical studies that included patients with benign IM tumors, Hernández-Durán *et al.* identified a low incidence of complications (4.5%, 2 of 44 patients) among patients with hemangioblastomas treated with SRS [27]. Chang *et al.* demonstrated that among patients with von Hippel–Lindau disease and hemangioblastomas, SRS resulted in five tumors disappearing (17%), 16 regressing (55%) and only one (3%) progressing. Radiation necrosis occurred in three patients [28]. Daly *et al.* found similar results among 27 hemangioblastomas treated with SRS. The rate of 3-year local tumor control was 86%, with one report of foot drop and two reports of sensory deficits [29]. Ryu *et al.* treated seven hemangioblastomas and three ependymomas with SRS between 1998 and 2003. The mean treatment dose was 21 Gy (range: 18–25 Gy) delivered to a tumor volume ranging between 0.47 and 9.8 cm^3. Upon follow-up imaging, two hemangioblastomas and one ependymoma decreased in size. The seven remaining tumors were similar in size. One patient with a hemangioblastoma developed new hemangioblastomas distant to the treatment site. No radiation myelitis or neurologic deterioration was reported [30].

Conclusion

SRS is a promising treatment modality for the management of intradural spine tumors. For older patients, those with significant comorbidities, or for whom surgery may be contraindicated, SRS may provide good local tumor control and relief of pretreatment symptoms. The few existing studies on intradural metastases suggest that SRS has the potential to aid in tumor control with minimal radiation toxicity. Benign IDEM tumors have been more thoroughly studied and have shown a relatively consistent improvement following SRS. Local tumor control and symptom alleviation are commonly reported for these benign neoplasms. Radiation-induced myelopathy remains a rare but possible complication from SRS. Future studies with larger patient populations are necessary to better understand the indications and complication profile associated with SRS for intradural spine tumors.

Future perspective

Future directions for the field will require additional investigations regarding the use of SRS for the treatment of IDEM metastases and IM lesions. Further data need to be generated comparing clinical and quality of life outcomes of SRS versus surgery, SRS versus SRS + surgery, and SRS versus fractionated radiotherapy. Predictive tools need to be generated identifying clinical variables important for successful SRS treatment, including appropriate dosing levels, ideal timing of treatment and follow-up imaging, and radiographic characteristics of responsive tumors. These results will allow clinicians to identify optimal candidates for

SRS therapy, anticipate potential complications and guide patients as they weigh the expected benefits and risks associated with treatment.

Disclosure

The manuscript submitted does not contain information about medical device(s)/drug(s).

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