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Review Article

The Role of Stereotactic Radiosurgery in Metastasis to the Spine

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Objective : The incidence and prevalence of spinal metastases are increasing, and although the role of radiation therapy in the treatment of metastatic tumors of the spine has been well established, the same cannot be said about the role of stereotactic radiosurgery. Herein, the authors present a systematic review regarding the value of spinal stereotactic radiosurgery in the management of spinal metastasis.
Methods : A systematic literature search for stereotactic radiosurgery of spinal metastases was undertaken. Grades of Recommendation, Assessment, Development, and Education (GRADE) working group criteria was used to evaluate the qualities of study datasets.
Results : Thirty-one studies met the study inclusion criteria. Twenty-three studies were of low quality, and 8 were of very low quality according to the GRADE criteria. Stereotactic radiosurgery was reported to be highly effective in reducing pain, regardless of prior treatment. The overall local control rate was approximately 90%. Additional asymptomatic lesions may be treated by stereotactic radiosurgery to avoid further irradiation of neural elements and further bone-marrow suppression. Stereotactic radiosurgery may be preferred in previously irradiated patients when considering the radiation tolerance of the spinal cord. Furthermore, residual tumors after surgery can be safely treated by stereotactic radiosurgery, which decreases the likelihood of repeat surgery and accompanying surgical morbidities. Encompassing one vertebral body above and below the involved vertebrae is unnecessary. Complications associated with stereotactic radiosurgery are generally self-limited and mild.
Conclusion : In the management of spinal metastasis, stereotactic radiosurgery appears to provide high rates of tumor control, regardless of histologic diagnosis, and can be used in previously irradiated patients. However, the quality of literature available on the subject is not sufficient.

Key Words : Radiosurgery · Spinal metastasis · Spine surgery · Radiation therapy · Local control · Spine tumors.

INTRODUCTION

The world health organization estimated that worldwide, 10 million people were diagnosed with cancer in 2000, and that the cancer incidence rate would increase by 50% to 15 million by 2020. Furthermore, as treatment outcomes improve and cancer patients have an increased survival[21], the incidence and prevalence of spinal metastases, which are known to occur in 30-50% of cancer patients[22,27,41], are also set to rise. The majority of these patients will undergo palliative radiation therapy, and the role of radiation therapy for the treatment of metastatic tumors of the spine is well established[7,23,37].

Conventional radiation therapy (RT) is defined as radiation delivered using 1 to 2 beams without high precision or highly conformal treatment. Therefore, the effectiveness of conventional radiation therapy has been limited by the poor radiation tolerance of the spinal cord, which is highly susceptible to radiation. In recent years, advances in imaging technology and computed treatment planning have allowed the safe delivery of high-dose radiation to spinal metastases, even when in close proximity to the spinal cord. These treatments are administered in 1 to 5 fractions of high-dose radiation (to ensure safety), which limit the dose delivered to the spinal cord[12].

The emerging technique of stereotactic radiosurgery (SRS) for spine metastases represents a logical extension of the current state-of-the-art of radiation therapy. Stereotactic radiosurgery has emerged as a new treatment option for the multidisciplinary management of metastases located within or adjacent to vertebral bodies and the spinal cord. The goals of stereotactic radiosurgery parallel those of brain radiosurgery, that is, to improve local control over conventional fractionated radiation therapy and to be effective for the treatment of previously irra-

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Table 1. Summary of the results of the systematic review conducted on stereotactic radiosurgery from 2007

Author	Description	No. of cases	Tech.*	Dose (Gy)	Complications	Outcomes	Quality of evidence
Haley et al.[18]	Retrospective study with matched controls	22 pairs	C	16 (14-20)	1 Gr. II nausea, vomiting	No difference with conventional RT	Low
Gerszten et al.[14]	Prospective cohort study	136	SL	16 (12-20)	No	Accurate, safe	Low
Choi et al.[4]	Retrospective study	42	C	20 (10- 30)	1 Gr. IV neurotoxicity	87/81% at 6/12 months	Low
Ryu et al.[32]	Prospective cohort study	62	N	16 (12-20)	Transient grade I esophageal mucositis	80% response	Low
Gerszten et al.[13]	Case series	11	C	19 (16-22.5)	No	100% tumor control	Very low
Sheehan et al.[36]	Retrospective study	40	HT	17.3 (10-24)	73% segmental kyphosis	82% tumor control	Low
Gagnon et al.[9]	Prospective cohort study	151	C	26.4 (no previous RT), 21.05 (previous RT) in 3 fractions	1 wound breakdown, 2 vertebral fracture	Significant pain improvement	Low
Gibbs et al.[17]	Case series	919	C	12.5-25	3 delayed myelopathy	NA	Very low
Tsai et al.[40]	Case series	69	C	15.5 (10-30)	50% fatigue, 27% nausea, 16% vomiting, 11% esophagitis, 3% diarrhea, 5% sore throat, 1% anemia, 2% thrombocytopenia, 4% neutropenia	96.8% local control	Very low
Levine et al.[24]	Clinical trial	10	C	30 (20-36) in 3 fractions	No	9 out of 10 was stable	Very low
Sahgal et al.[34]	Retrospective study	39	C	24 (7-40) in 3 fractions	3 Gr. I/II nausea, 1 constipation, 3 transient increased pain	85% in 1 year	Low
Nelson et al.[26]	Prospective cohort study	32	L	18 (14-30)	7 grade I nausea	All except 4 were controlled	Very low
Wowra et al.[42]	Prospective case series	102	C	19.4 (15-24)	1 hemorrhage, 1 spinal instability	98% local control	Low
Ryu et al.[31]	Case series	49	N	10-16	No	84% pain control	Very low
Gagnon et al.[8]	Matched pair	18 pairs	C	21-28 in 3 to 5 fractions	1 Gr. II nausea, 2 Gr. I fatigue, 2 Gr. I/II dysphagia, 1 Gr. II L/E numbness	No difference with RT in pain	Low
Gibbs et al.[16]	Prospective cohort study	74	C	16-25 in 1-5 fractions	3 myelopathy	84% symptom improved	Low
Teh et al.[38]	Retrospective study	80	N	6-12 for 3-5 fractions	NA	All good pain relief, very high local control	Very low
Gerszten et al.[11]	Prospective cohort study	500	C	20 (12.5-25)	No	86% pain improvement, 88-90% local control	Low
Ryu et al.[30]	Prospective cohort study	177	N	8-18	1 myelopathy	NA	Low

C : Cyberknife (Accuracy Inc., Sunny vale, CA, USA), N : Novalis (Brain Lab Inc., Germany), L : linac, SL : Synergy S linac (Elekta Synergy S 6-MV LINAC), HT : helical tomotherapy, NA : not available, L/E : low extremity, RT : radiation therapy

diated lesions with an acceptable safety profile. Herein, we present a systematic review regarding the value of spinal stereotactic radiosurgery in the management of spinal metastasis.

MATERIALS AND METHODS

A systematic literature search for stereotactic radiosurgery of spine metastases was undertaken. Case reports or papers describing less than 10 spine metastatic patients and studies that used intensity modulated radiotherapy involving more than 5 fractionations were excluded.

The search was limited to the English literature and was performed using PubMed. References and reviews in identified articles were also examined for potential inclusion. Thirty-one studies met all the study inclusion criteria. Grades of Recommendation, Assessment, Development, and Education (GRADE) working group criteria as described by Guyatt and coworkers[35] was used to critically evaluate the quality of each dataset (Table 1), which was assigned high, moderate, low, or very low qualities based on the GRADE approach[35]. Twenty-three studies were classified as 'low' and 8 as 'very low'. The number of studies using Cyberknife (Accuracy Inc., Sunny vale, CA, USA) was 21. The number of studies using Novalis (Brain Lab Inc., Germany) was 7. The number of studies using LINAC, Synergy S LINAC (Elekta Synergy S 6-MV LINAC) and helical tomotherapy was 1 each.

The indication for spinal stereotactic radiosurgery in spine metastasis has evolved over time and will continue to evolve as clinical experience increases. However, surgery is usually reserved for spinal instability and significant neurologic deficits from direct tumor progression rather than stereotactic radiosurgery.

The current indications for the use of stereotactic radiosurgery as a treatment modality for metastatic spine disease include pain related to a specific involved vertebral body, radiographic tumor progression as a primary treatment modality for progressive neurologic deficits, and adjuvant therapy after open surgical intervention. These indications were grouped into four general categories, as described by Sahgal et al.[34) :

1. Unirradiated patients : spinal metastases in a previously unirradiated volume treated by SRS.
2. Reirradiated patients : spinal metastases in a previously irradiated volume now containing new, recurrent, or progressive metastatic disease treated by SRS.
3. Postoperative patients : spinal metastases treated with SRS after open surgical intervention, with or without spinal stabilization.
4. Mixed patients : mixed populations involving patients in the three previous categories.

RESULTS

Pain and quality of life

Pain is the most frequent indication for the treatment of spinal metastases, and radiation is well known to be effective as a treatment for pain associated with spinal malignancies. Furthermore, stereotactic radiosurgery has been reported to be highly effective at reducing pain associated with symptomatic spinal metastasis[5,29)], regardless of prior treatment by conventional fractionated radiotherapy, and to have an overall improvement rate of approximately 85-100%. Pain is reported to decrease usually within weeks after SRS and occasionally within days[5,19,29,33)].

Ryu et al.[31)] reported an overall pain control rate of 84% at 1 year after treatment in a series of 49 patients. Gerszten et al.[11)] reported on a mixed population that achieved an overall pain improvement rate of 86% (290 of 336 cases) depending on primary histopathology. Durable pain improvement was demonstrated in 96% of women with breast cancer, in 96% of melanoma cases, in 94% of cases with renal cell carcinoma, and in 93% of lung-cancer cases. Gibbs et al.[16)] reported that 84% of symptomatic patients experienced improvement or resolution of symptoms after treatment. In addition, excellent pain-control and quality-of-life results after spinal stereotactic radiosurgery have been reported by the Georgetown University Hospital[6,8,9)], and Haley et al.[18)] reported no statistically significant difference in pain between SRS and RT groups.

Local control

Local control rates are reported to be approximately 90%. Degen et al.[6)] demonstrated a 95% local control rate for 58 lesions in a mean follow-up of 350 days, and Chang et al.[3)] reported a 1-year 84% progression free incidence in 74 lesions. Overall long-term radiographic tumor control for progressive spinal disease in a series of 500 cases was 88-90% during the median 21-month follow-up[11)]. Radiographic tumor control rates were found to be dependent on primary pathology : breast (100%), lung (100%), renal cell (87%), and melanoma (75%)[11)].

Recurrent spinal metastasis in previously irradiated lesions

Spine SRS is frequently used to treat radiographic tumor progression after conventional RT or after prior surgery. The majority of these lesions have undergone irradiation at significant spinal cord doses. Thus, further conventional irradiation delivery could not be indicated for them. However, currently, spine stereotactic radiosurgery is often being used as a "salvage" technique for those cases in which further conventional irradiation or open surgery are not appropriate.

Choi et al.[4)] recently reported 6 and 12 month local control rates of 87% and 81%, respectively, in previously irradiated patients, and Gerszten et al.[11)] reported an 88% radiographic con-

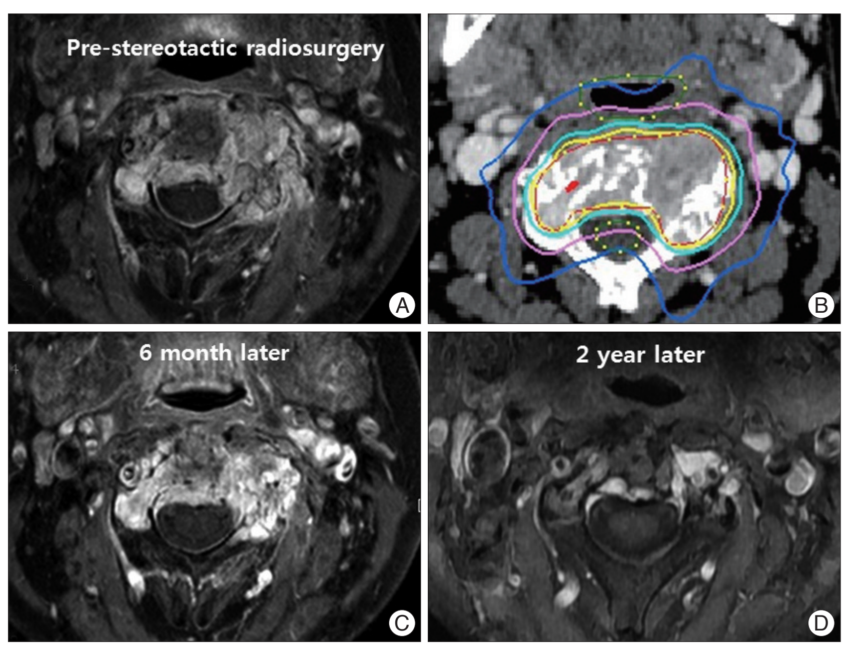

Fig. 1. A representative case of a 48-year-old female with an isolated painful C3 metastasis. The patient experienced pain relief three months after Cyberknife stereotactic radiosurgery. A : Preoperative T1 weighted axial MR image with enhancement. B : Axial projection of the isodose line of the treatment plan. The 77% isodose line represents the prescribed dose of 31.7 Gy (5 fractions), the tumor volume is 14.5 mL, and the spinal cord received a maximum dose of 25.3 Gy. C : Six-month postoperative T1 weighted axial MR image with enhancement. D : Two-year postoperative T1 weighted axial MR image with enhancement showing good response. MR : magnetic resonance.

trol rate in patients, 69% of whom had previously received radiotherapy. Chang et al.[3] reported a 1-year actuarial tumor progression-free incidence of 84% for fractionated SRS treatment; 56% of their patients received SRS as a retreatment.

Primary treatment modality

As greater experience is gained, stereotactic radiosurgery will probably evolve into an initial upfront treatment for spinal metastasis in certain cases, especially for cases of oligometastasis. This is similar to the evolution that occurred over the past decade for the treatment of intracranial metastases by radiosurgery. Additional asymptomatic lesions may be treated by SRS to avoid further irradiation to neural elements and further bone-marrow suppression and to permit subsequent systemic therapy.

Gagnon et al.[8] reported a matched-pair analysis in which 18 patients with breast-cancer spinal metastases treated by SRS were compared to 18 matched patients that received conventional external beam radiation therapy (EBRT) upfront. This study concluded that salvage SRS is as efficacious as initial fractionated RT without added toxicity. Haley et al.[18] recently reported that in terms of pain relief, SRS as a primary treatment modality in spinal metastasis was not different from EBRT. When used as a primary treatment modality, long term radiographic tumor control was demonstrated in 90% of cases of breast, lung, and renal cell carcinoma metastases and in 75% of melanoma metastases[11]. Sheehan et al.[36] reported a 100% tumor control rate in lesions that had not previously undergone irradiation, and Ryu et al.[31] reported the results of a dose-escalation trial in which a series of 49 patients with lesions that had not previously undergone fractionated RT demonstrated good clinical outcomes. Illustrative case showed an example of good response as primary treatment (Fig. 1).

Adjuvant therapy after open surgery

Spinal tumors can be removed from neural structures, allowing immediate decompression. The spine can be instrumented if necessary, residual tumor can be safely treated later by SRS, and thus, the adjunctive SRS can reduce the chance of repeated surgery and possible morbidities from the second surgery. Furthermore, anterior corpectomy with reconstruction procedures in certain cases can be avoided successfully by posterior decompression and instrumentation alone followed by SRS to the remaining anterior lesion. Given the ability to perform spinal SRS effectively, the current surgical approach to these lesions might be changed. As SRS has the stiff falloff gradient of the target dose with negligible skin dose[20], such treatments can be given soon after surgery instead of after the usual significant delay before standard external beam RT is permitted[2,25,39]. Open surgery for spinal metastases will likely evolve in a similar manner, whereby intracranial brain tumors are debulked in such a way as to avoid neurologic deficits and minimize surgical morbidity[12].

Rock et al.[28,31] specifically evaluated the combination of open surgery followed by adjuvant SRS in a series of 18 patients and achieved a local control rate of 94%, whereas Gerszten et al.[10] reported a series of 26 patients treated by SRS after vertebral body cement augmentation and achieved a local control rate of 92%.

Dose recommendation for spine stereotactic radiosurgery

The prescribed radiation dose to the tumor is determined based on tumor histology, spinal cord, or cauda equina tolerance and previous radiation dosage to normal tissue, especially to the spinal cord. No large-scale study has yet developed an optimal dose for spinal SRS, and no appropriate dose or fractionation schedule for metastatic tumors have been firmly established. However, spinal SRS has been found to be safe at doses comparable to those used for intracranial radiosurgery without the occurrence of radiation-induced neural injury.

Dose and fractionation schedules are different in each institution. Single-fraction SRS doses range from 8 to 24 Gy, while hypofractionated regimens consist of 4 Gy×5 fractions, 6 Gy×5 fractions, 8 Gy×3 fractions, or 9 Gy×3 fractions[9]. Currently, there is no evidence to support one regimen over another[34]. In one recent large series[9], 26.4 Gy in 3 fractions was prescribed to the 75% isodose surface for radiation naïve lesions. Previously irradiated lesions were treated with a mean maximum dose of 20 Gy (range 12.5-25 Gy)[11], a median dose 35 Gy (range 20-50.4 Gy)[3], a median dose of 20 Gy in 5 fractions (range 20-30 Gy)[43], and a median dose 20 Gy (range 10-30 Gy) in 1-5 fractions (median 2).

Adjacent level failure after stereotactic radiosurgery

One concern that has been raised regarding SRS for spinal metastases is whether adjacent levels are included in the radiation field. In the report of University of Pittsburgh Medical Center, no cases of tumor progression were encountered at immediate adjacent levels, thus justifying the treatment of the involved spine only[11,33]. Although they reported failures in 3 out of 49 patients treated for solitary metastases, no failure was identified in adjacent untreated vertebrae[33]. The implication of these findings is that progression in adjacent vertebral bodies is rare, and thus, they support SRS treatment of involved spinal levels only[3,34]. Based on these findings, Sahgal concluded that it was possible that : 1) failure in the epidural space may have been be due to underdosing of the tumor because of strict spinal cord constraints, 2) uninvolved adjacent posterior elements should have been included in the target volume, and 3) encompassing one vertebral body above and below diseased vertebrae was unnecessary[34].

Safety and complications of stereotactic radiosurgery

Complications associated with SRS are generally self-limited and mild. The minor and limited toxicities reported for spine radiosurgery include esophagitis[18,19], dysphagia[6], diarrhea[3,6], paresthesia[6], transient laryngitis[1], compression fracture[9], and transient radiculitis[1].

Radiation induced spinal cord injury is exceedingly rare, and only a small number of cases have been reported. An early series by Benzil et al.[1] contained no radiation-induced spinal cord toxicity, and Gerszten et al.[11] found no spinal cord toxicity after a follow-up of over 60 months. Ryu et al.[30] specifically addressed the partial volume tolerance of the spinal cord and complications of single-dose SRS. They reported a single case of radiation-induced cord injury 13 months after SRS and concluded that, whereas the maximum spinal cord tolerance to single-dose radiation is unknown, partial volume tolerance of the human spinal cord is at least 10 Gy to 10% of the spinal cord volume, defined as 6 mm above and below the SRS target. In a recent multicenter study of 1075 cases[17], only 6 patients developed delayed radiation-induced myelopathy at a mean of 6.4 months (range, 2-9 months) after spinal SRS. Recently, Haley et al.[18] reported that RT had higher acute toxicity rates than SRS but encountered no late complications after either treatment modality.

DISCUSSION

From a historical viewpoint, modern LINAC is equipped for a wide variety of treatment modalities, including intensity-modulated radiation therapy, stereotactic treatment, and image-guided radiation therapy. These advances allow more precise target definition and conformality, which makes hypofractionation more feasible, and provide a potential means of reducing the toxicities often observed after administering large fraction sizes[18].

The development of Gamma Knife SRS and LINAC-based radiosurgery allow the delivery of highly conformal doses of radiation in a single fraction. The first Cyberknife (Accuray) prototypes were used in the 1990s, and in 2001 the FDA granted clearance for treatment of extracranial lesions[15].

The metastatic disease population is an inherently difficult group of patients to study, and patients typically have multiple disease sites, poor health, and quality of life. With limited follow-up and survival and other probable confounders such as high dose steroid use, retrospective datasets generally report better outcomes than reported by randomized trials.

This systemic literature review reveals the relative safety and efficacy of spinal SRS. Despite the significant clinical experience and widespread utilization of conventional RT for spinal metastases, stereotactic radiosurgery offers several theoretical advantages as a treatment modality for spinal tumors. Early treatment of these lesions before a patient becomes symptomatic and the stability of the spine is threatened is obvious advantageous[5]. Furthermore, conformal SRS avoids the need to irradiate large segments of the spinal cord. In addition, the early SRS treatment of spinal lesions may obviate the need for extensive spinal surgery for decompression and fixation in these already debilitated patients and may also avoid the need to irradiate large segments of the spinal column, which is known to have a deleterious effect on bone marrow reserve in these patients. The avoidance of open surgery and the preservation of bone-marrow function facilitate continuous chemotherapy in this patient population. Furthermore, improved local control, such as that demonstrated for intracranial radiosurgery, could translate into more effective palliation and potentially longer survival.

One advantage to patients offered by single-fraction SRS is that treatment can be completed in a single day rather than over the course of several weeks, which is not inconsequential for those with a limited life expectancy. Furthermore, the technique may be useful for capitalizing on the possible advantages of radiosensitizers[12]. In addition, cancer patients may have difficulty with access to a radiation-treatment facility for prolonged, daily fractionated therapy. Also, for certain tumors such as sarcomas, melanomas, and renal cell metastases, a large single fraction of irradiation may be radiobiologically advantageous compared to prolonged fractionated RT. As opposed to responses to conventional EBRT, responses to high-dose single-fraction radiation or SRS have been demonstrated to be histology independent, and excellent responses have been observed for radioresistant tumors. Clinical responses such as pain or neurologic deficit improvement might also be more rapid after SRS[12].

Stereotactic radiosurgery for spinal metastasis has several limitations. First, the quality of literature on spinal SRS is poor; no randomized controlled study has been conducted. Second, SRS is more expensive than conventional RT; according to the US Medicare system, the cost of RT is about 80% that of SRS[18]. In the South Korea system, when Cyberknife stereotactic radiosurgery was done in 3 fractions and RT was done in 10 fractions, stereotactic radiosurgery is two times more expensive than 2D RT and similar to 3D RT. Although specific costs are likely to differ in other countries, a cost benefit study is required before the widespread adoption of SRS. Therefore, we suggest that SRS be initially used to treat spinal metastasis and chemo resistant tumors. Nonetheless, we believe that the usage of SRS will progress in the same manner as brain radiosurgery and that eventually it will be routinely used to treat spinal metastasis. However, further randomized controlled studies are required to compare spine SRS to conventional RT for the treatment of spinal metastasis.

CONCLUSION

In the management of spinal metastasis, stereotactic radiosurgery appears to provide high rates of tumor control, may be less affected by histology, and can be used in previously irradiated patients. However, the quality of available literature on spine SRS for metastasis is low or very low. Further high quality studies on SRS for spine metastasis are warranted.

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