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.
### 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.        | 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.     | Prospective cohort study          | 136          | SL     | 16 (12-20) | No                                                                             | Accurate, safe                               | Low                |
| Choi et al.         | Retrospective study               | 42           | C      | 20 (10-30) | 1 Gr. IV neurotoxicity                                                        | 87/81% at 6/12 months                       | Low                |
| Ryu et al.          | Prospective cohort study          | 62           | N      | 16 (12-20) | Transient grade I esophageal mucositis                                        | 80% response                                 | Low                |
| Gerszten et al.     | Case series                       | 11           | C      | 19 (16-22.5) | No                                                                            | 100% tumor control                           | Very low           |
| Sheehan et al.      | Retrospective study               | 40           | HT     | 17.3 (10-24) | 73% segmental kyphosis                                                        | 82% tumor control                           | Low                |
| Gagnon et al.       | Prospective cohort study          | 151          | C      | 26.4 (no previous RT), 21.05 (previous RT) in 3 fractions | 1 wound breakdown, 2 vertebral fracture | 84% symptom improved                      | Low                |
| Gibbs et al.        | Case series                       | 919          | C      | 12.5-25   | 3 delayed myelopathy                                                        | 96.8% local control                          | Very low           |
| Tsai et al.         | 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 | No difference with RT in pain                 | Low                |
| Levine et al.       | Clinical trial                    | 10           | C      | 30 (20-36) in 3 fractions | No | 9 out of 10 was stable                                                 | 89% in 1 year                                | Very low           |
| Sahgal et al.       | Retrospective study               | 39           | C      | 24 (7-40) in 3 fractions | 3 Gr. I/II nausea, 1 constipation, 3 transient increased pain | All except 4 were controlled                | Very low           |
| Nelson et al.       | Prospective cohort study          | 32           | L      | 18 (14-30) | 7 grade I nausea                                                              | 98% local control                            | Very low           |
| Woonra et al.       | Prospective case series           | 102          | C      | 19.4 (15-24) | 1 hemorraghe, 1 spinal instability                                           | 84% pain control                             | Low                |
| Ryu et al.          | Case series                       | 49           | N      | 10-16     | No                                                                             | 84% pain control                             | Very low           |
| Gagnon et al.       | 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.        | Prospective cohort study          | 74           | C      | 16-25 in 1-5 fractions | 3 myelopathy                                                                  | 84% symptom improved                        | Low                |
| Teh et al.          | Retrospective study               | 80           | N      | 6-12 for 3-5 fractions | No                                                                             | All good pain, very high local control       | Very low           |
| Gerszten et al.     | Prospective cohort study          | 500          | C      | 20 (12.5-25) | No                                                                            | 86% pain improvement, 88-90% local control   | Low                |
| Ryu et al.          | Prospective cohort study          | 177          | N      | 8-18      | 1 myelopathy                                                                  | NA                                            | Low                |

C: Cyberknife (Accuracy Inc., Sunnyvale, CA, USA), N: Novalis (BrainLab 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
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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.40:

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 metastasis5,29, 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 days5,19,29,33.

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 Hospital6,35, and Haley et al.40 reported no statistically significant difference in pain between SRS and RT groups.

Local control

Local control rates are reported to be approximately 90%. De- gen 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-up11. 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-
trol rate in patients, 69% of whom had previously received radiotherapy. Chang et al. 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. 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. 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. Sheehan et al. reported a 100% tumor control rate in lesions that had not previously undergone irradiation, and Ryu et al. 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, such treatments can be given soon after surgery instead of after the usual significant delay before standard external beam RT is permitted. 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.

Rock et al. 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. 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. Currently, there is no evidence to support one regimen over another. In one recent large series, 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), a median dose 35 Gy (range 20-50.4 Gy), a median dose of 20 Gy in 5 fractions (range 20-30 Gy), 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. Although they reported failures in 3 out of 49 patients treated for solitary metastases, no failure was identified in adjacent untreated vertebrae. 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. Based on these findings, Sahgal concluded that it was possible that 1) failure in the epidural space may have been 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.

**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, dysphagia, diarrhea.
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.\(^6\) contained no radiation-induced spinal cord toxicity, and Gerszten et al.\(^1\) found no spinal cord toxicity after a follow-up of over 60 months. Ryu et al.\(^10\) 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\(^7\), 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\(^19\).

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\(^15\). 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 single 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\(^19\). 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 chemoresistant 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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