Spinal radiosurgery: a neurosurgical perspective

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Spine stereotactic radiosurgery (SSRS) is proving to be one of the most significant advances in the treatment of both metastatic and primary spine tumors. High-dose hypofractionated and single fraction radiation appear to convey better local tumor control than conventional radiation for tumors considered radioresistant, such as renal cell carcinoma and melanoma. Multiple series have demonstrated control rates greater than 85% which appears to be histology independent. The markedly improved local control rates compared to conventional radiation techniques are beginning to change the treatment paradigms for spine tumors. Recent evidence in the literature reflects the integration of SSRS in the treatment of metastatic and primary malignant and benign spine tumors as the principle treatment or as a neoadjuvant or postoperative adjuvant therapy. For instance, as confidence grows with the use of SSRS as a postoperative adjuvant, surgical resection of metastatic disease has become less aggressive with the expectation that radiation can control residual disease. Despite high dose radiation delivery within millimeters of the spinal cord, toxicity has been limited with rare cases of radiation-induced myelopathy. The establishment of spinal cord and other critical structure tolerances is essential to the continued evolution of SSRS, as radiation oncologists begin to use this modality to treat spinal cord compression. This paper reviews the neurosurgical integration of SRS into spine practice.

Keywords: Spine stereotactic radiosurgery, spinal cord tolerance, spine tumor, spine radiation, metastatic spine tumor, primary spine tumor

Over the past decade, technologic advances in surgery and radiation have significantly impacted the outcomes for both metastatic and primary spine tumors in terms of palliation and cure. The development of surgical interventions including percutaneous cement augmentation, anterior and posterior segmental fixation, posterolateral decompression for metastatic tumors and en bloc spondylectomy for primary tumors have been part of this treatment revolution. However, the biggest improvement in outcomes has been manifest through the application of stereotactic radiation to spine tumors. Stereotactic body radiotherapy is an extension of the well established radiosurgery used for intracranial tumors. Radiation advances including 3-dimensional localization and intensity modulation have resulted in a high degree of accuracy in achieving dose conformity, providing a therapeutic dose to the tumor while sparing normal tissue tolerance (e.g. spinal cord, esophagus, bowel and kidneys). The ability to deliver a cytotoxic tumoral dose has improved responses of metastatic and primary spine tumors considered resistant to conventional external beam radiation (cEBRT), such as renal cell carcinoma and chordoma. Prior to the development of the spine application for SBRT, proton beam was the only modality that could deliver high-dose conformal radiation. Due to the limited number of facilities and need to use conventional fractionation schemes, proton beam was principally used in an attempt to cure primary spine tumors. The widespread availability of SBRT and
ability to deliver hypofractionated or single dose radiation has increased accessibility to high-dose conformal radiation. Currently, a number of spine applications are being explored including: 1) definitive therapy for metastatic spine tumors, 2) postoperative adjuvant radiation, 3) neoadjuvant for primary tumors, and 4) benign intra- and extra-dural tumors.

DETERMINATIVE THERAPY FOR METASTATIC SPINE DISEASE

The most significant SRS spine application to date has been as definitive local treatment for metastatic spine tumors.2-16 In most series, the use of high-dose radiation has been restricted to tumors that involve the bone or with epidural abutment, but tumors with high-grade spinal cord compression have been considered a relative exclusion criterion. While radiosensitive tumors (eg. hematologic malignancies, breast and prostate carcinoma) can be treated with hypofractionated regimens, the greatest utility of SRS is the improved response of radioresistant tumors. Historically the response rates for RT-resistant tumors using cEBRT techniques were poor and many patients demonstrated tumor progression.1,17 Series reporting spine outcomes without stratifying for radiosensitivity of the tumors often reported excellent results because of the large number of hematologic malignancies, breast, prostate and neuroendocrine tumors.1 When stratified by radiosensitivity to conventional external beam radiation marked differences are seen in tumoral responses.17-26 Maranzano, et al., for example, reported that unfavorable (i.e. radio-resistant tumors) such as hepatocellular carcinoma demonstrated a 20% response rate with a durability of 1 to 3 months. Favorable (i.e. radiosensitive tumors) showed an 80% response at 16 months.19 Multiple series reporting outcomes for SRS have demonstrated radiographic and clinical responses of greater than 85% with over 16 month follow-up that are histology independent. (Figure 1) Currently, a prospective randomized trial is ongoing comparing in an attempt to compare a scheme with comparable outcomes to cEBRT (8 Gy x 1) to high dose single fraction radiation (16 Gy x 1).

Gerszten, et al., reported 393 patients treated for differing tumor histologies differing histologies (eg. breast, lung, and melanoma) treated with SRS at all spinal levels.12 The maximum intratumoral dose ranged from 12.5 to 25 Gy (mean 20 Gy). Pain and radiographic tumor control were achieved in 86% and 90% of cases, respectively, with a median follow-up time of 21 months. Radiographic tumor control differed based on the primary pathology with breast and lung carcinoma showing 100% control, compared to renal cell and melanoma which demonstrated local control rates of 87% and 75%, respectively.

Yamada, et al published a series of 103 patients treated with SRS for RT-resistant oligometastatic tumors.14 The study was a dose escalation from 18 to 24 Gy with spi-

![Figure 1: 68 y.o. male presented with a newly diagnoses kidney mass diagnosed on needle biopsy as renal cell carcinoma. Systemic work-up showed a solitary renal metastasis in the T10 vertebral body with minimal epidural impingement, but no spinal cord compression (a). He underwent 24 Gy single fraction radiation with well controlled disease demonstrated at 20 month follow-up (b). Of note on the follow-up MR, a new metastasis was noted at S1.](image-url)
nual cord constraints defined as a cord Dmax of 14 Gy. Local control was 92% at a median follow-up of 16 months, with the 7 failures occurring at a median time of 9 months. Subgroup analysis demonstrated a dose-response; patients receiving 24 Gy to the planning target volume (PTV) had significantly better local control than those who received less than 24 Gy. Complications were limited to grade 1 and 2 skin and esophageal toxicity. No patient demonstrated new onset post-radiation myelopathy or functional radiculopathy.

Chang, et al., reported 63 patients treated for 74 spinal tumors using SRS with delivered treatment dose of 27 Gy in 3 fractions. The median follow-up was 21 months. The actuarial tumor free progression was 84%. The principle risk of failure was either adjacent segment progression or tumor in the epidural space. No myelopathy or functional radiculopathy was observed. The authors concluded that the liberalization of spinal cord doses may prevent epidural tumor progression.

Complications associated with radiosurgery are generally self-limited and mild including esophagitis, mucositis, dysphagia, diarrhea, paresthesia, transient laryngitis, and transient radiculitis. Radiation-induced spinal cord injury is exceedingly rare, and few cases have been reported in the literature. An early series by Benzil, et al., reported no radiation-induced spinal cord toxicity. Gerszten et al. also did not observe any spinal cord toxicity in a series of renal cell carcinoma spine tumors treated with over 60 months of follow-up. Ryu et al., examined the partial volume tolerance of the spinal cord and complications to single-dose radiosurgery, reporting a single case of radiation-induced spinal cord injury 13 months following radiosurgery. This series concluded the maximum spinal cord tolerance to single-dose radiation is not known, but that partial volume tolerance of the spinal cord is at least 10 Gy to 10% defined as 6 mm above and below the radiosurgery target. Instead of treating to a volume constraint on the spinal cord, Yamada, et.al, treated to a cord Dmax of 14 Gy with no reported myelopathy.

A recent multicenter publication including 1075 cases reported only 6 patients who developed delayed radiation-induced myelopathy at a mean of 6.3 months (range 2 to 9 months) after spinal radiosurgery. Radiation injury to the spinal cord occurred over a spectrum of dose parameters that prevented identification of specific dosimetric factors contributing to this complication.

A newly recognized complication of SRS is delayed vertebral body fracture. In a recent review of 72 SRS cases, 40% of patients developed progressive vertebral body fractures. Risk factors included lytic tumor, thoracolumbar or lumbar tumor location, and greater than 40% vertebral body replacement at the time of surgery. This has led to consideration of prophylactic kyphoplasty in patients at high-risk for post-radiation fractures.

**POST-SURGICAL ADJUVANT**

In current treatment paradigms, surgery for metastatic tumors is used as initial therapy to treat patients with high-grade spinal cord compression with or without myelopathy. As noted, hematologic malignancies, and selected solid tumors (e.g. breast, prostate, germ cell) often respond dramatically to cEBRT, which often represents effective treatment even in the presence of high grade-spinal cord compression. The majority of solid tumors do not respond to cEBRT and may benefit from surgery to decompress and stabilize the spine. Additionally, radiation cannot stabilize an unstable spine. Gross spinal instability often requires open surgery. Axial load pain resulting from a pathologic compression fracture may benefit from percutaneous vertebral body cement augmentation. While surgery is very effective for decompressing and stabilizing the spine, radiation effectiveness is critical for providing local tumor control.

Currently the recommendation for high-grade spinal cord compression resulting from RT-resistant tumor is decompression followed by SRS or cEBRT to achieve local tumor control. While a number of centers are attempting to treat high-grade ESCC caused by RT-sensitive tumors with SRS, current spinal cord constraints limit effective therapy. Jin et al. published the results of single fraction SRS used to treat 31 multiple myeloma lesions in 24 patients. Due to the radiosensitive nature of these tumors, the PTV was treated to a median dose of only 16 Gy. The authors noted improved pain control in 86% of patients. Complete radiographic responses were seen in 81% of patients. Of the seven patients who had neurologic deficits at presentation, 5 demonstrated neurologic improvement after SRS. Based on this study, it is feasible to treat high-grade ESCC from radiosensitive tumors with single fraction SRS.

Unfortunately, radioresistant tumors do not typically demonstrate these responses to low dose SRS. Lovelock, et.al, conducted a failure analysis of single fraction patients. All tumor progression occurred in tumors that received less than 15 Gy to some portion of the PTV, often at the dural margin. The cord tolerance constraint used in this study was a cord Dmax of 14 Gy. Any significant degree of spinal cord abutment or compression effectively precludes effective therapy. Lowering the dose at the margin of the spinal cord risks progression of tumor and compression where the greatest measure of control is required, i.e. adjacent to the spinal cord. However, treating to a cytotoxic dose intro-
tumors have led investigators to explore the use of SRS when eradication of the tumor is not feasible. 4 years. Essentially if one lived long enough, the tumor rate for 106 spinal metastases undergoing decompression of the spinal cord, often requiring months to demonstrate a radiographic response. The rationale for surgery to treat high-grade spinal cord compression from RT-resistant tumors is based primarily on a prospective randomized trial conducted by Patchell, et.al which compared cEBRT to decompressive surgery and instrumentation followed by cEBRT for solid tumors causing spinal cord compression.34 Spinal cord compression was defined as displacement of the spinal cord, and neurologic symptoms ranged from pain only to myelopathy resulting in loss of ambulation. Hematologic malignancies and markedly radiosensitive tumors, such as germ cell tumors, were excluded as were patients with other neurologic co-morbidities (e.g. brain metastases). Other exclusion criteria included dis-contiguous epidural disease, an expected survival less than 3 months, and the inability to tolerate the proposed treatment. The protocol defined instability according to the Cybulski criteria, but instability was not an indication for exclusion. In this study, 101 patients were randomized. Patients undergoing surgery and radiation therapy had better outcomes compared to radiation alone in terms of the following: overall ambulation, 84% vs. 57% (p=.001); maintenance of ambulation, 94% vs.74% (p=.024); recovery of ambulation 62% vs.19% (p=.012); bowel and bladder continence 155 vs. 17 days (p=.016); narcotic requirement, 0.4mgs vs. 4 to 8 mgs (p=.002); and survival 122 days vs. 100 days (p=.033). Notably, 57% of patients in the radiation only arm maintained ambulation, but the duration was only 13 days compared to ambulation until death (122 days) in the surgical arm. As the study followed intent to treat analysis, all 3 patients who recovered ambulation in the radiation cohort crossed over to the surgical arm. No patient in the radiation only group recovered ambulation without surgery. The rationale for using SRS as opposed to cEBRT as an adjuvant to surgical decompression is the predicted improvement in tumor control based on radiosensitivity. Klekamp and Samii reviewed local control rates for 106 spinal metastases undergoing decompression followed by cEBRT.35 The overall local recurrence rates as determined by the Kaplan Meier method were 57.9% after 6 months, 69.3% after 1 year and 96% after 4 years. Essentially if one lived long enough, the tumor was bound to locally recur. Among the biggest predictors of recurrence was tumor histology. The poor local control rates using cEBRT for solid tumors have led investigators to explore the use of SRS as a postoperative adjuvant. The ability to deliver cytotoxic doses to even gross residual tumor has changed the aggressiveness of tumor resection. With adjuvant cEBRT, the goal of surgery was to gross totally resect even metastatic tumors due to the high probability of tumor progression. With improved rates of tumor control provided by SRS, the principle surgical goal is epidural tumor decompression and instrumented stabilization. Large paraspinal tumors and even vertebral body tumors can be controlled with SRS, rather than gross total tumor resection, often requiring anterior and posterior decompression and fixation. Edward Benezil and Liliyana Angelov have coined the term “separation surgery” (i.e. posterolateral laminectomy) to describe this limited epidural decompression to provide room for effective SRS (figure 2). Although there are currently no comparison studies, our experience is that most patients are candidates and can tolerate this limited decompression over the previously attempted maximal, gross total tumor resection. Rock, et al., specifically evaluated the combination of open surgical procedure followed with adjuvant radiosurgery in a series of 18 patients. They found this to be a successful treatment paradigm that was associated with a significant chance of stabilizing or improving neurologic function. Local control was 94%. The technique was well tolerated and associated with little to no morbidity.36 Moulding et.al, reviewed 21 patients who underwent “separation surgery” (posterolateral decompression) and posterior segmental instrumentation for radioresistant tumor histologies.37 Of note, the gross tumor volume for radiation was delineated based on the preoperative tumor volume rather than the postoperative residual tumor. The spinal cord and thecal sac contours were established using myelogram/CT, which provides excellent anatomic detail even in the presence of spinal implants. The GTV received 24 Gy in 16 patients and 18 to 21 Gy in 5 patients. Overall local control was 81% with an estimated one-year failure of 9.5%. The local control was significantly better in cohort receiving 24 Gy compared to patients receiving less than 24 Gy, 94% vs. 60%, respectively. In addition to using SRS as an adjuvant to open surgery, patients with pathologic burst or compression fractures can be treated with vertebro- or kyphoplasty prior to simulation and SRS treatment. Percutaneous cement augmentation is effective treatment for pain, but plays no role in local tumor control and is typically combined with postoperative radiation. The pain relief afforded by these minimally invasive procedures often allows patients to tolerate the immobilization required for SRS delivery. Fourney, et.al, reported 84% pain control with visual analogue scores stable up to one year following cement augmentation.38 Gerszten et al., have...
demonstrated the utility of SRS following percutaneous cement augmentation in a series of 26 patients treated with resulting in 92% local tumor control.39

The use of SRS to treat high-grade spinal cord compression, especially for tumors resistant to cEBRT, is more controversial; however centers are beginning to report outcomes for these tumors. Ryu, et al., recently reported the functional and radiographic outcomes of 62 patients treated with SRS for high-grade spinal cord compression in patients who were not candidates for surgical decompression.40 Patients with hematologic malignancies were excluded, but solid tumors considered RT-sensitive (eg. breast, prostate and neuroendocrine) were included and comprised 40% (25/62) of the study population. Despite ESCC, all patients had strength 4+/5 strength. The median dose was 16Gy, but ranged from 12 to 20 Gy. Cord tolerance doses were maintained below 10 Gy to 10% of the spinal cord. Of the 27 patients with neurologic deficits, 14 (52%) recovered to normal, 3 (11%) improved, and 3 (11%) progressed. Overall, 9 patients progressed of which 7 had RT-resistant pathologies. Failures included 3 infield (ie. dose issues) and 6 out of field (ie. targeting issues). Radiographic follow-up was obtained in 36 patients (58%). Based on T1-weighted post-contrast and T2-weighted scans, the degree of epidural decompression was assessed using a percentage score comparing pre- and postoperative MR images. Of those patients imaged, the reduction in epidural compression was 80% at 2 months. Nine radiographic failures were identified of which 7 had resistant histologies to cEBRT. No spinal cord toxicity was noted in this study. SRS may prove valuable for spinal cord compression, particularly for RT-sensitive histologies or in RT-resistant histologies in which the patient cannot tolerate separation surgery.

PRINCIPAL MALIGNANT SPINE TUMORS

Primary malignant spine tumors, such as chordoma, chondrosarcoma, and osteogenic sarcoma, represent significant treatment challenges due to the difficulties of achieving wide or marginal en bloc resections in the spine. The difficulties arise in part from anatomic constraints of multi-compartmental tumor involvement and the priority of preserving neurologic function. The other major concern is that malignant tumors often demonstrate significant seeding outside the gross tumor volume. For extremity sarcomas, this extensive seeding outside the radiographically identified tumor can be treated with wide or even radical excision by amputation. A review of extra-sacral spine sarcomas showed that only 15% of spine sarcomas were candidates for en bloc excision for attempted marginal or wide margins without jeopardizing neurologic function or other critical structures.41 Rao, et al., reported a series of 80 spine sarcomas, in which only 12 were attempted en bloc excision.42 With this in mind, a number of centers have begun to explore the use of neoadjuvant radiation followed by resection. The precedent for using neoadjuvant chemotherapy and/or radiation in tumors involving the spine is high-risk neuroblastoma and superior...
sulcus tumors.

The outcomes using surgery to treat primary sarcomas of the spine have been poor. Bilsky et al reported outcomes of 59 sarcoma undergoing intralessional resection with postoperative radiation at a median dose of 40 Gy delivered in conventional fractions. The majority of tumors (90%) were high-grade. The median survival for primary tumors was 26.2 months.41

Rao et al., reported the outcomes of 80 patients treated for sarcoma. 29 (36%) primary and 51 (64%) metastatic. The overall median survival was 20.6 months. The survival of patients undergoing en bloc excision was 26.2 months vs. 18.6 for intralional curettage, which was not statistically significant.42

Delaney et al. reported the outcomes of a phase II clinical trial exploring the utility of neoadjuvant radiation for extra-cervical spine or paraspinal chordomas and sarcomas.43 Fifty patients were treated preoperatively with conventional fraction proton radiation treated to 50.4 Gy in 1.8 Gy/fraction. Of note, the tumor volume was not only the gross tumor volume, but also clinical target volume to include the areas where marginal recurrences were historically most likely to occur. For instance, sacral chordomas have a high propensity to locally recur in the piriformis muscle, which was therefore included in the CTV. Patients underwent resection 5 weeks post radiation followed by the delivery of proton beam radiation 19.8 Gy RBE in conventional fractions. Patients demonstrated local control rates of 98% at 1-year, 84% at 3-years, and 78% at 5-year.

Single fraction radiation may be very effective for treating primary spine malignancies. Wu et al., reported a case of a patient who received 24Gy single fraction to an L1 chordoma.6 The radiation was offered as definitive therapy due to medical co-morbidities. The patient underwent kyphoplasty at 2 months at which time biopsy showed which viable tumor. At 4 months, the tumor was resected for suspected radiographic tumor progression. Pathology showed 99% necrosis of the tumor. This type of response has led to the initiation of a prospective trial to assess the utility of neoadjuvant radiation in chordoma. Given the poor responses of high-grade sarcoma, we are beginning to explore neo-adjuvant radiation in this setting as well. The trajectory of beam delivery is soft tissue sparing, so there is little risk of wound dehiscence from operating in an irradiate bed.

Benign Tumors

The treatment of benign spine tumors mirrors the treatment of intracranial lesions. Gerszten et al, reported the treatment of 73 benign intradural, extramedullary spine tumors with a follow-up of median 37 month.47 The tumors were predominantly located in the cervical spine in 43 patient, followed by lumbar in 19, sacral in 6 and thoracic in 5. Tumor histologies included schwannomas in 35 cases, neurofibromas in 25, and meningiomas in 13. Syndromic tumors, NF1 orNF2, were present in 30 cases. Prior treatment was surgery in 19 patients (26%) and failed cEBRT in an additional 6 (8%). The mean tumoral dose was 2164 cGy (range1500 to 2500 cGy). Indications for SRS were principally tumor progression or as a postoperative adjuvant. The outcomes showed significantly improved pain control in 22 of 30 patients who presented with pain and long-term radiographic control in all patients. Of note, patients treated for neurofibromatosis had less consistent pain relief. Three patients demonstrated radiation-induced spinal cord toxicity at a range of 5 to 13 months. While this study represents preliminary data, SRS may play a role in the control of benign tumors, particularly for those unresectable.

CONCLUSION

SRS represents a great advance in the treatment of both malignant and benign spine tumors. The ability to deliver cytotoxic doses to the tumor while sparing normal tissue tolerance offers a better chance at significant palliation and durable tumor control for metastatic patients and potentially cure for benign and malignant primary tumors. The evolution of this technology will require standardized contouring and reporting of tumor volumes and dosing prior to the design of prospective randomized trials to answer the questions being raised by data being presented in a number of centers.

REFERENCES


