SPINAL RADIOSURGERY

STEREOTACTIC RADIOSURGERY FOR THE TREATMENT OF PRIMARY SARCOMAS AND SARCOMA METASTASES OF THE SPINE

OBJECTIVE: Spinal sarcomas pose unique treatment dilemmas because of the difficulty of achieving adequate surgical margins and/or delivering curative radiation doses (65 Gy) in close proximity to the spinal cord. This study used hypofractionated stereotactic radiosurgery (SRS) to deliver higher biologically effective doses to treat primary spinal sarcomas and spinal sarcoma metastases.

METHODS: Twenty-four patients with spinal or paraspinal sarcomas entered an Institutional Review Board-approved registry trial to evaluate SRS efficacy. They were assessed at regular intervals for pain control, disease progression, and complications for a minimum of 12 months or until death.

RESULTS: The median treatment dose for the spinal sarcoma lesions was 30 Gy at the 80% isodose in 3 fractions, with some variation based on tumor size, shape, and dose to adjacent critical structures. Seven patients were treated definitively; all had excellent pain relief and are alive with a mean follow-up period of 33 months. Two patients had complete tumor regression, 3 had partial regression, and 2 experienced recurrences and have been re-treated. Seven patients underwent resection and adjuvant SRS. One of 3 patients treated preoperatively had complete tumor regression, and none of the 4 patients treated postoperatively had a local recurrence with a mean follow-up period of 43.5 months. All 10 patients with sarcoma metastases to the spine (16 lesions) died, with a mean survival of 11.1 months from first spinal metastasis treatment. Complete pain relief was achieved in 8 patients, partial relief in 7 patients, and none in 1 patient. No patient developed radiation myelitis.

CONCLUSION: These preliminary results suggest that SRS may have a role in the definitive treatment of patients with primary spinal sarcomas who are deemed unresectable and as adjuvant treatment in those undergoing surgery and for palliation of sarcoma metastases.

KEY WORDS: Hypofractionated, Metastases, Radiosurgery, Sarcoma, Spine, Stereotactic.

ABBREVIATIONS: BED, biologically effective dose; CT, computed tomographic; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery

Paraspinal sarcomas and primary bony sarcomas of the spine pose particularly unique treatment dilemmas when the goal is to achieve similar oncological results for tumors with the same histology, grade, and size that occur outside of the spinal column (2). The proximity of the dural sac, aorta, vena cava, and esophagus make achieving adequate negative surgical margins difficult, and the consideration of achieving a wide surgical margin is extremely difficult. The en bloc resection of a spinal segment is a relatively recent concept that few surgeons initially appreciated as different from a complete piecemeal corpectomy. Now, however, it is recognized that, with rare exceptions, the rate of local recurrence depends on the adequacy of the resection, even when adjuvant chemotherapy and/or radiation is used (3). Furthermore, inclusion of modalities such as proton beam therapy for relatively low-grade tumors (Grade 1 chondrosarcomas and chordomas) necessitates a “complete” resection of all gross tumor to achieve a local recurrence rate in long-term follow-up of less than 10% for chondrosarcomas and less than 40% for chordomas.

The close proximity of the spinal cord also makes delivery of adequate curative or even adjuvant radiation doses difficult. It is well recognized that a preoperative dose of at least 50 to 65 Gy or a postoperative dose of at least 65 Gy is necessary to
achieve local control in most patients with a sarcoma diagnosis. This was demonstrated in a study of 112 patients with high-grade sarcomas who underwent radiation for gross disease. Those receiving less than 63 Gy had a local control rate of 22%, whereas for those receiving more than 63 Gy, the local control rate was 60% (15). Most studies suggest, however, that doses in excess of 50 Gy increase the incidence of radiation myelopathy, especially in fields exceeding 10 cm, in elderly patients, or when large fractional doses are used. Consequently, the limited radiation tolerance of the spinal cord has necessitated the use of technologies such as proton beam, heavy charged particles, and high-dose-rate brachytherapy and brachytherapy implants to approach effective doses even for adjuvant treatment of paraspinal and spinal sarcomas (5, 6, 11, 14, 27). In 1 study, 26 chondrosarcomas of the cranial base and cervical spine were treated with surgical resection, followed by high-dose photon and proton irradiation with a mean of 67 cobalt-Gy equivalents. This treatment resulted in a 3-year local control rate of 91.6% (20). In another study, 200 chondrosarcomas of the cranial base (50% Grade 1) were subjected to high-dose postoperative fractionated proton beam radiation. The dose ranged from 64.2 to 79.6 cobalt-Gy equivalents (median, 72.1 cobalt-Gy equivalents), given in 38 fractions. The resulting local control rate was 98% (22). In addition, there is some evidence that sarcomas in general may have a lower α/β ratio, which suggests that hypofractionation in this tumor histology would increase the effectiveness of radiation as both an adjuvant and a primary treatment option (26).

Tumor localization was achieved through either gold fiducial marker placement or fiducial-less Xsight spinal localization (Accuray, Inc.), both of which have a nominal error of less than 1.0 mm (12, 29). The details of patient setup and accuracy have been described previously (23). All patients underwent computed tomographic (CT) imaging and, in most cases, magnetic resonance imaging (MRI). The 2 imaging studies were subsequently fused using treatment planning software. Contours of the gross tumor volume, spinal canal, and critical structures (kidneys, esophagus, rectum, etc.) were performed by the treating physician. An inverse planning algorithm determined the optimal treatment program, which in most cases used a collimator between 20 and 50 mm (depending on tumor size) to deliver an optimal prescribed dose of 30 Gy in 3 fractions, using 150 to 300 separate beams. The actual delivered dose varied, based on the size and shape of the target tumor, the allowed dose to adjacent critical structures, and the judgment of the radiation oncologist. The optimal prescribed dose for patients who had undergone previous external beam radiation was also 30 Gy in 3 fractions at the 80% isodose line. The 80% isodose line was selected because, in the majority of cases, it would allow optimal coverage with less incongruity of dose to the tumor. In smaller tumors, advances in stereotactic radiosurgery (SRS) have made it possible to approach effective doses even for adjuvant treatment of paraspinal and spinal sarcomas (5, 6, 11, 14, 27). In 1 study, 26 chondrosarcomas of the cranial base and cervical spine were treated with surgical resection, followed by high-dose photon and proton irradiation with a mean of 67 cobalt-Gy equivalents. This treatment resulted in a 3-year local control rate of 91.6% (20). In another study, 200 chondrosarcomas of the cranial base (50% Grade 1) were subjected to high-dose postoperative fractionated proton beam radiation. The dose ranged from 64.2 to 79.6 cobalt-Gy equivalents (median, 72.1 cobalt-Gy equivalents), given in 38 fractions. The resulting local control rate was 98% (22). In addition, there is some evidence that sarcomas in general may have a lower α/β ratio, which suggests that hypofractionation in this tumor histology would increase the effectiveness of radiation as both an adjuvant and a primary treatment option (26).

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a higher isodose line could sometimes be used, and in larger tumors, a lower isodose line was occasionally necessary.

The CyberKnife SRS system was used to perform the robotic radiosurgery. The system and technique have been described in detail by others (5, 23). Briefly, this system uses a 6-MV X-band accelerator with 600 MV/min output to deliver highly collimated radiation beams. The accelerator is mounted on a robotic arm that moves the linear accelerator to multiple predetermined points in an area around the tumor to be treated. A tracking system takes localizing x-rays after every third treatment beam. These images are used to track the tumor location and enable real-time adjustments in the aim of the treatment beam. Implanted fiducials or vertebral element contours may be used as landmarks for the radiosurgical target, which eliminates the need for a stereotactic frame and rigid immobilization of the patient.

The outcome assessment was performed in a specified manner by 2 members of the treating team and a nurse practitioner. Assessment of pain, neurological status, side effects, and complications was performed before the initiation of each session and at 2 and 6 weeks after treatment. Subsequent follow-up occurred at 3-month intervals to assess pain relief (patient assessment and pattern of narcotic use before and after treatment) and neurological status. Tumor size viability was followed by appropriate combinations of MRI with gadolinium, CT scan, and/or positron emission tomography/CT scan. Tumor dimensions were recorded where appropriate, and tumor response was classified as either progression, stable, partial regression, or complete regression. Occurrence or progression of other lesions, as well as current chemotherapy treatment, was also recorded at each 3-month interval. The minimum follow-up period was 12 months or until death. All patients either were currently alive and under follow-up or were followed until death. Long-term toxicity was assessed as of the last visit.

RESULTS

Between May 2003 and February 2007, 24 patients with spinal or paraspinal sarcoma involvement of the spine were entered into a trial to evaluate the efficacy of CyberKnife SRS. Fourteen patients had primary sarcomas of the spine; of these, 7 were treated definitively with SRS because they were not candidates for or refused definitive surgical treatment, and 7 had adjuvant treatment in combination with surgery. Of these 14 patients, there were 4 with fibromyxosarcomas, 3 with chondrosarcomas, 2 with leiomyosarcomas, 1 with dedifferentiated liposarcoma, 1 with angiosarcoma, 1 with synovial sarcoma, and 2 with undifferentiated sarcomas, all of which were Grade 2 or higher. Seven of the 14 patients were men, and 7 were women. Patient ages ranged from 29 to 88 years (mean age, 61 years). Ten additional patients with 16 sarcoma metastases to the spine were treated for palliation. The histology of the metastatic lesions consisted of 5 leiomyosarcomas, 2 chondrosarcomas, 2 angiosarcomas, and 1 pleomorphic sarcoma. The 10 patients with sarcoma metastases ranged from 44 to 84 years (mean age, 59 years). Eight were women, and 2 were men. The mean volume of all tumors was 148.4 mL (range, 8.9-601.5 mL). Primary and metastatic lesions were generally treated with the same dosage. The prescribed dose was 30 Gy at the 80% isodose line in 3 fractions, but the actual treatment dose ranged from 20 to 36 Gy (median, 30 Gy); the isodose line ranged from 70 to 85% (80% in 18 of 24 patients) in 1 to 5 fractions, with differences based on tumor size and shape and relationship to adjacent critical structures. The mean conformity index for the group was 1.61 ± 0.23, and the percent coverage with the treatment dose was 98.3 ± 1.2%. The treatment results can be divided into 3 distinct patient groups: 7 patients with primary sarcomas treated definitively, 7 primary sarcoma patients with adjuvant treatment, and 10 patients with sarcoma metastases.

Group 1: Primary Sarcomas Treated Definitively

Seven patients were treated definitively with SRS, because the tumors were unresectable after biopsy, the patients refused definitive surgery, or the patients were thought to be medically unable to tolerate en bloc resection (Fig. 1). Their ages ranged from 29 to 88 years and the mean tumor volume was 239.2 mL.
neurological deficit. Two patients had side effects with treatment: 1 had recovery, and the other had partial recovery of thoracic paraparesis. Two patients with a neural deficit had complete sciatic nerve paresis. Two patients had side effects with treatment: 1 had recovery, and the other had partial recovery of thoracic paraparesis. Two patients with a neural deficit had complete sciatic nerve paresis.

Ten lesions were treated with 3 fractions, 5 with 1 or 2 fractions because of small lesion size, and 1 with 5 fractions because of recent failure with progression and neural compression of a chondrosarcoma metastasis to T4. The median dose was 30 Gy at the 80% isodose line, with a range of 25–30 Gy) with differences based on tumor and patient characteristics. One patient treated preoperatively had complete tumor necrosis and no viable tumor at subsequent en bloc resection, but 2 had viable tumor at resection and have subsequently died of local and distant disease. All 4 patients treated postoperatively for microscopic positive margins after resection remain alive and disease-free with a mean follow-up of 43.5 months. Two patients have had delayed transient radiculopathy with dysesthesias and partial motor loss, but with resolution of symptoms.

FIGURE 2. Images of an 88-year-old woman who presented with a painful mass protruding against her paraspinal musculature in the lumbar spine that had grown rapidly over the preceding several months. The needle biopsy showed 2 components, with the deeper one being a dedifferentiated liposarcoma. The patient refused definitive surgery but agreed to treatment of the 601-mL lesion with 25.5 Gy at the 78% isodose line in 3 fractions. Pre- (A) and postoperative (C) CT scans. Pre- (B) and postoperative (D) axial MRI scans. She had excellent pain relief and initial slight shrinkage of the lesion, but by 12 months, she had recurrence of pain and slight lesion regrowth. She was re-treated with 30 Gy at the 78% isodose line in 3 fractions to the same field. E, CT scan showing slight shrinkage that is currently durable for an additional 22 months. She again had relief of symptoms. She has no pulmonary metastases, and her only treatment complications were nausea and slight skin irritation on retreatment.

No patient in the study demonstrated any incidence of radiation myelitis, but as noted above, 2 patients developed delayed nausea, and the other had malaise. One of the re-treated patients had skin irritation with the second CyberKnife treatment; this resolved spontaneously. The only significant complications occurred in this group of patients.

Group 2: Primary Sarcomas with Adjuvant Treatment

Of the 7 patients treated with surgery and adjuvant CyberKnife SRS, 3 were treated preoperatively and 4 postoperatively for microscopically positive margins after en bloc resection. The mean treatment volume was 188.9 mL (range, 8.9–407.7 mL). Four had failed a combination of prior surgery and external beam radiation (mean, 55 Gy; range, 45–65 Gy). Patients were treated with a range of 2 to 5 fractions and a median dose of 30 Gy at the 80% isodose line (range, 25–30 Gy) with differences based on tumor and patient characteristics. One patient treated preoperatively had complete tumor necrosis and no viable tumor at subsequent en bloc resection, but 2 had viable tumor at resection and have subsequently died of local and distant disease. All 4 patients treated postoperatively for microscopic positive margins after resection remain alive and disease-free with a mean follow-up of 43.5 months. Two patients have had delayed transient radiculopathy with dysesthesias and partial motor loss, but with resolution of symptoms.

Group 3: Sarcoma Metastases

Of the 10 patients with a total of 16 sarcoma metastases to the spine, the mean volume of the tumors was 99.87 cm³ (range, 9.56–330.3 cm³). Four of the 16 lesions had failed prior external beam radiation (30–35 Gy) and had recurrence of symptoms. Ten lesions were treated with 3 fractions, 5 with 1 or 2 fractions because of small lesion size, and 1 with 5 fractions because of recent failure with progression and neural compression of a chondrosarcoma metastasis to T4. The median dose was 30 Gy at the 80% isodose line, with a range of 20 to 30 Gy. Of the 16 lesions in the 10 patients, complete pain relief was achieved in 8, partial relief in 7, and none in 1. Radiographic evaluation by either MRI or CT scan was obtained for 10 of 16 treated lesions. Nine of the lesions were initially stable (>3 months), and 1 increased slightly. Subsequently, on studies just before the patient’s death, 2 lesions, which had been stable, increased slightly. In the other 6 lesions, the patients survived 4 months or less after treatment, and no follow-up studies were obtained. All 10 patients have died, with a mean survival of 11.1 months (range, 1–21 months) from the time of their first spinal metastasis treatment. There were no major side effects or complications in this group of patients.

Complications

In all of the patient groups, there was only 1 complication related to SRS treatment that required surgical treatment. This patient, who received definitive treatment of a sacral sarcoma, had complete regression of the tumor but developed a rectal tumor cavity fistula, requiring diverting colostomy and drainage. No patient in the study demonstrated any incidence of radiation myelitis, but as noted above, 2 patients developed delayed

(range, 57.3–601.5 mL). One patient, who had undergone previous external beam radiation, had a recurrence. All 7 patients had pain, and 2 had neural deficits (1 had incomplete thoracic paraparesis, and 1 had severe sciatic radiculopathy from a sacral tumor). Six patients were treated in 3 fractions, and 1 was treated in 5 fractions with the median treatment dosage of 30 Gy at the 80% isodose line (range, 24–35 Gy), with differences based on tumor and patient characteristics. All 7 patients had excellent pain relief and are alive, with a mean follow-up period of 33.0 months (range, 20–49 months). Two had complete tumor regression, 3 had partial regression, and 2 experienced recurrences. One had recurrence at 12 months, has been re-treated, and now has stable disease (Fig. 2). The second had recurrence at 45 months and has been re-treated. One patient has slowly progressive pulmonary metastatic disease. One of the patients with a neural deficit had complete sciatic nerve recovery, and the other had partial recovery of thoracic paraparesis. Two patients had side effects with treatment: 1 had...
transient radiculopathy (lasting 3 and 6 months, respectively) in previously irradiated and operated fields.

DISCUSSION

Treatment Dose for Spinal Sarcomas

Several studies, including a report by Ballo et al. (2), have demonstrated that the factors statistically related to higher rates of local recurrence in patients with soft tissue sarcomas include a tumor location within the head, neck, or deep trunk and postoperative radiation doses of less than 64 Gy. In a study of 14 paraspinal sarcomas, Guest et al. (9) suggested 2 problems with achieving an adequate oncological result for paraspinal sarcomas: the inability to achieve a wide margin and the difficulty in delivering adequate radiation in curative doses because of the proximity to the spinal cord. Several categories of studies using radiation treatment for tumors of sarcoma histology have been undertaken. Most of the external beam studies for primary sarcomas of the spine have involved adjuvant treatments after en bloc resection of paraspinal sarcomas or salvage treatments after piecemeal or incomplete resection (9, 19, 28). In tumors such as Ewing’s sarcoma of the vertebral column, radiation and chemotherapy have been combined with curative intent (13, 16). Such studies expend little effort at achieving either an en bloc or even complete piecemeal resection of the tumor, and relatively high local recurrence rates occur because, in most cases, doses have been limited to 50 Gy. In 1 clinical situation in which external beam doses above 50 Gy were used, there was an incidence of spinal cord injury (16). Furthermore, when an en bloc resection was performed with either microscopically positive margins or with negative margins, external ion doses of less than 50 Gy yield unacceptable results in terms of local recurrence.

As more conformal techniques for radiation delivery were devised, early adoption for spinal pathology occurred in an attempt to push the dose to spinal and paraspinal tumors over 65 Gy. However, despite innovative measures such as implanted brachytherapy with 125I seeds in incompletely resected paraspinal sarcomas and lung carcinomas, local failure still occurred within 18 months in most patients (1). Charged particles, such as helium and neon, and some photons have also been used to treat partially resected or recurrent paraspinal sarcomas, with total doses ranging from 60 to 80 Gy (21). After a mean follow-up period of 31 months, the local control rate with these treatments was 50%, with a mean time to recurrence of 7 months. Low-grade chondrosarcomas and chordomas had a slightly better local control rate of about 60% at 3 years. Even for chondrosarcomas and chordomas, it is evident that doses in excess of 65 Gy are necessary (7, 17, 20, 22).

Fractionation/Comparison of Results

CyberKnife robotic SRS not only allows the delivery of BEDs in excess of 65 Gy to these paraspinal and spinal sarcomas, but also allows the dose to be hypofractionated. This may potentially be an advantage if the assumption of a low α/β ratio for sarcomas is correct (26). To our knowledge, our study is the first to segregate patients with primary sarcomatous involvement of the spine for treatment with hypofractionated SRS. Other studies have combined varying grades of chondrosarcoma with chordoma or combined sarcomas with giant cell tumors and plasmacytomas, which makes the response to the radiation difficult to interpret (10, 22). In this series, we demonstrate that, for 7 unresectable patients with a sarcoma diagnosis of at least Grade 2, hypofractionated SRS gave satisfactory relief of symptoms and control of the tumor. Although the number of patients is small, the relatively long mean survival of these patients suggests that this may be a viable treatment option. In addition, a similarly high rate of success was observed in the second group of 7 patients, in whom hypofractionated radiosurgery was used either adjuvantly for microscopic margins or neoadjuvantly to make surgical excision more feasible.

Our fractionation schedule and applied dose were extrapolated from our growing experience and that of others in the treatment of radioresistant metastatic disease of the spine (i.e., renal cell carcinoma), combined with our desire to deliver a BED in excess of 75 Gy while limiting the dose to the adjacent spinal cord (23). Over time, we escalated the dose from 3 × 8.5 Gy to 3 × 10 Gy with no apparent increase in toxicity, but also without a demonstrated improvement in response. Two long-term surviving patients have been re-treated with similar doses without toxicity, suggesting further room for dose increase, although many factors may go into cord tolerance to total radiation dose (25). Others have used similar fractions and doses to the cranial base and upper cervical spine for 2 patients with radiation myelopathy who had both prior surgery and radiation (10). The optimal method for determining the cytological effectiveness of the treatment remains to be determined. Although an estimation of the tumor volume can be obtained from measurements on the MRI or CT scans, and percent shrinkage can be calculated, recent data from positron emission tomography/CT studies suggest that tumor volume may not change dramatically, yet the tumor will still be nonviable. The relative stability of the tumor mass observed in this study may correlate with a marked decrease in standardized uptake value on PET/CT scans or decreased uptake of gadolinium on MRI scans, but insufficient data exist to draw conclusions. Perhaps parameters for tumor death should be used other than decreased tumor volume.

Treatment of Spinal Metastases

The final group of patients evaluated in this study had spinal metastases from primary tumors of sarcoma histology. For spinal metastases, it has been shown that doses in excess of 65 Gy are necessary to control the primary tumor (4, 6, 15). As a result, few studies have considered the problem of treating spinal metastases with external beam doses of less than 45 Gy in a histological diagnosis (18). Instead, studies of external beam radiotherapy and radiosurgery for spine metastases generally combine these highly radioresistant lesions with more sensitive lesions such as metastases from breast, prostate, and colon. In the study of Merimek et al. (18), it is difficult to com-
Disclosures

These preliminary results suggest that hypofractionated SRS may have a role in the definitive treatment of patients with primary spinal sarcomas who are deemed to have unresectable tumors and as both pre- and postoperative adjuvant treatment in those undergoing surgery. Although the empirical use of a 30-Gy dose at the 80% isodose line in 3 fractions was based on an estimated α/β ratio, tumor size, and the relative insensitivity of these tumors, optimal dose strategy needs further investigation. Despite the small size of this hypofractionated SRS series, our fractionation schedule and dose are clearly more effective than standard external beam strategies for palliation of sarcoma metastases to the spine. Response and mean survival from treatment of the metastases exceeded previously published results. Whether alone or in combination with surgery, hypofractionated SRS should be considered the first-line treatment for sarcoma metastases to the spine. As a result of hypofractionation, BEDs in excess of 70 Gy were delivered in close proximity to the spinal cord without any occurrence of radiation myelitis, with up to 4 years of follow-up in some patients.

Disclosures

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