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STEREOTACTIC BODY RADIOTHERAPY FOR LESIONS OF THE SPINE AND PARASPINAL REGIONS

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Abstract

Purpose—To describe our experience and clinical strategy for stereotactic body radiotherapy (SBRT) of spinal lesions.

Methods and Materials—Thirty-two patients with 33 spinal lesions underwent computed tomography–based simulation while free breathing. Gross/clinical target volumes included involved portions of the vertebral body and paravertebral/epidural tumor. Planning target volume (PTV) expansion was 6 mm axially and 3 mm radially; the cord was excluded from the PTV. Biologic equivalent dose was calculated using the linear quadratic model with $\alpha/\beta = 3$ Gy. Treatment was linear accelerator based with on-board imaging; dose was adjusted to maintain cord dose within tolerance. Survival, local control, pain, and neurologic status were monitored.

Results—Twenty-one patients are alive at 1 year (median survival, 14 months). Median follow-up is 6 months for all patients (7 months for survivors). Mean previous radiotherapy dose to 22 patients was 35 Gy, and median interval was 17 months. Renal (31%), breast, and lung (19% each) were the most common histologic sites. Three SBRT fractions (range, one to four fractions) of 7 Gy (range, 5–16 Gy) were delivered. Median cord and target biologic equivalent doses were 70 Gy₃ and 34.3 Gy₁₀, respectively. Thirteen patients reported complete and 17 patients reported partial pain relief at 1 month. There were four failures (mean, 5.8 months) with magnetic resonance imaging evidence of in-field progression. No dosimetric parameters predictive of failure were identified. No treatment-related toxicity was seen.

Conclusions—Spinal SBRT is effective in the palliative/re-treatment setting. Volume expansion must ensure optimal PTV coverage while avoiding spinal cord toxicity. The long-term safety of spinal SBRT and the applicability of the linear-quadratic model in this setting remain to be determined, particularly the time-adjusted impact of prior radiotherapy.

Keywords

Spinal cord; Spine radiosurgery; Stereotactic body radiotherapy; Normal tissue tolerance

INTRODUCTION

Stereotactic body radiotherapy (SBRT) delivers hypofractionated treatment with high degrees of accuracy and precision. Because of its potential efficacy, low morbidity, and logistical advantages, SBRT is being used for treatment of a variety of sites, including lung, prostate, liver, and spine (1, 2). Lesions in the bony elements of the spine and paraspinal regions are particularly amenable to treatment with SBRT because of relative vertebral column immobility and nominal respiration-related motion. With an estimated 40% of patients with cancer ultimately developing vertebral metastases, the use of SBRT will likely expand as survival from primary malignancies continues to improve (3). SBRT requires meticulous attention to detail in structure delineation and margin selection to maximize tumor coverage and minimize normal tissue exposure, which is particularly important in cases of reirradiation.

Several groups have published their experiences with SBRT for spinal lesions (4–9) in the primary and re-treatment settings. Although these generally reported good palliation with rare toxicity, the tolerance of the spinal cord to hypofractionation using highly conformal high-dose-gradient techniques is largely undetermined. This report presents our initial experience using SBRT for spinal lesions, as well as our strategies for minimizing toxicity.

METHODS AND MATERIALS

After multidisciplinary evaluation, 32 patients with 33 spinal lesions were enrolled on a Duke University Medical Center (Durham, NC) Institutional Review Board–approved protocol. All patients underwent computed tomography (CT)-based simulation (GE Light-Speed, Milwaukee, WI) in a customized cradle (10). Initially, patients were simulated using four-dimensional CT with respiratory gating to evaluate the extent of tumor motion. After the first 10 patients showed stable axial skeleton positioning, we subsequently used free-breathing techniques. Treatment was planned using Eclipse (Varian Medical Systems, Palo Alto, CA) with magnetic resonance imaging (MRI)/positron emission tomography fusion as indicated. Gross tumor volume was identified as the involved vertebral body including any paravertebral or epidural soft-tissue component. For lesions within the vertebral body, the entire body and anterior one-third of the pedicles were included in the clinical target volume (CTV). Every attempt was made to avoid completely encircling the cord when applying CTV-to-planning target volume (PTV) margin. In cases of pedicle involvement, the body, involved pedicle, and posterior elements were included, but the uninvolved pedicle was not. Portions of adjacent vertebral bodies were included to provide 6-mm superior/inferior margins, but were not routinely treated in their entirety. Epidural extension was included in the CTV, but no margin was applied to avoid including cord within the PTV. Spinal cord volume was established from the planning CT/MRI; the entire spinal canal was not contoured. The cord volume was extended 6 mm superiorly/inferiorly of the CTV for dose-volume histogram calculations. Prior work has shown that our on-board imaging (OBI) system is accurate to within 1 mm (11), and that the associated immobilization system reduces set-up error to less than 1 mm (12). Therefore, we expanded the cord 2 mm circumferentially and subsequently optimized treatment plans to avoid high doses to this expanded volume.

The SBRT dose selection considered the dose and time elapsed since prior radiotherapy (RT) and proximity of the PTV to the expanded cord. We used the linear-quadratic (LQ) model to calculate the biologic equivalent dose ($BED = nd [1 + d/(\alpha/\beta)]$) delivered to both target and normal structures. Published estimates for spinal cord α/β range from 0.9–4 Gy, with some investigators suggesting different values depending on the region in question (13, 14). In light of the wide range of proposed values, we assumed a uniform α/β of 3 Gy

throughout the spine, midway between the values of 2 and 4 Gy for the cervicothoracic and lumbar spine proposed by Nieder *et al.* (13), respectively. In cases of re-treatment, we limited the SBRT dose based on the following guidelines:

1. 1. Assume cord tolerance of 50 Gy in 2 Gy/fraction ($BED = 83.3 \text{ Gy}_3$), a dose shown to result in a risk of transverse myelitis less than 0.2% (15, 16).
2. 2. Calculate the time-discounted prior BED (BED_{prior}) to the cord by assuming dose recovery of 25%, 33%, and 50% at 6 months, 1 year, and 2 years, respectively (13, 16–18). This is a purposefully more conservative estimate of dose recovery than that predicted from animal models, particularly given that those studies were based on full-thickness conventional reirradiation of the cord, whereas for SBRT, only partial thickness of the cord is exposed to the highest doses (discussed later).
3. 3. Set the maximum tolerable cord dose as the maximum dose to 99% of the contoured cord volume over the region of treatment as $83.3 \text{ Gy}_3 - BED_{\text{prior}}$.

For previously untreated cord, we limit single-fraction dose to 99% of the cord volume in the region of treatment to 12 Gy or less (9).

Treatment techniques included dynamic conformal arcs, multiple conformal static beams, or multiple intensity-modulated beams. Treatment was performed using a Varian (Varian Medical Systems) 21EX linear accelerator with a 120-leaf multileaf collimator equipped with an aSi500 electronic portal imaging device and a gantry-mounted OBI system. Details of the electronic portal imaging device, OBI, and cone-beam CT (CBCT) systems have been previously described (19). The gantry rotates 360° about the patient with the OBI engaged to produce CBCT images in approximately 1 minute; an additional 1–2 minutes are required for image reconstruction with a 512×512 matrix, slice thickness of 1 or 2.5 mm, and axial field of view of either 25 or 50 cm.

The schema used within our institution is shown in Fig. 1. After initial clinical set-up, patients are positioned using orthogonal kilovoltage images registered to the corresponding planning digital reconstructed radiographs. Next, CBCT images are acquired and registered with the treatment planning CT, based primarily on bony landmarks, but with consideration of fiducials and soft-tissue anatomy. Isocenter shifts in the three orthogonal planes are applied remotely. A posttreatment image (kilovoltage or CBCT) is obtained to document any intrafraction motion.

Before treatment, patients completed an intake questionnaire to establish baseline neurologic function, pain level, and analgesic use. Patients were followed up every 2–3 months with physical examination, a similar questionnaire, and imaging studies, as indicated. Treatment failure was defined as evidence of tumor growth in or immediately adjacent to the treated area or worsening pain in the treated area that could not be otherwise explained.

RESULTS

Thirteen men and 19 women (median age, 60 years; range, 45–82 years) were included (Table 1). After initial two-dimensional OBI alignment, CBCT detected residual set-up errors of 0.13, 0.09, and 0.11 cm in the anterior-posterior (AP), cranial-caudal, and medial-lateral directions, respectively. Posttreatment CBCT showed minimal intrafraction motion (0.06 cm AP, 0.09 cm cranial-caudal, and 0.04 cm medial-lateral). Mean total set-up, imaging, and treatment time was typically 45–60 min/fraction. All patients presented with pain in the affected region; 7 had concurrent neurologic symptoms of mild weakness (3 patients), paresthesias (3 patients), or radicular pain (1 patient). Twenty-one patients are alive, whereas 11 patients died of progressive disease. Actuarial 1-year overall survival was

13.5 months. Median follow-up was 7 months (range, 3–21 months) for all patients and 8.2 months (range, 3–21 months) for survivors. Twenty-two patients received prior conventional RT; median prior dose was 35 Gy (range, 20–50.4 Gy; 1.8–3 Gy/fraction). Median interval between courses was 16 months (range, 4–300 months). The most common primary tumor was renal cell carcinoma (31%), followed by breast and lung (19% each; Tables 2 and 3). The SBRT dose and fractionation varied; the median number of SBRT fractions was three (range, one to four fractions). The median dose/fraction and total dose delivered were 7 Gy (range, 5.1–16 Gy) and 18 Gy (range, 14–30 Gy), respectively. The median SBRT BED to the spinal cord (BED₃) and target (BED₁₀) were 70 Gy₃ (range, 41.3–130 Gy₃) and 34.3 Gy₁₀ (range, 23.1–60 Gy₁₀), respectively.

At 1 month post-SBRT, 13 patients reported “complete” and 17 reported “substantial” or “partial” pain relief. Narcotic analgesic use was reduced in all patients. Seven patients with neurologic symptoms at the time of SBRT experienced neither improvement nor worsening during follow-up. The median duration of palliative effect in all patients was 6 months, and in living patients, was 7.6 months (range, 2.7–21 months). There were four treatment failures at a median of 5.8 months (range, 4–12 months), with MRI evidence of progression in the treated vertebral body, paravertebral soft tissues, and/or epidural space (Table 4). Treatment was well tolerated throughout the follow-up period, with Grade 1 nausea reported in 7 patients. There have been no treatment-related neurologic side effects.

DISCUSSION

In cases of symptomatic metastatic disease to the spine, patients have historically been treated with AP-PA or PA fields, with doses ranging from 8 Gy in a single fraction to 40 Gy in 20 fractions, all shown to be equivalent in providing short-term palliation (20–22). Other patients’ cords are treated to “tolerance” during definitive therapy in adjacent areas, with subsequent failure in the in-field spine. In either scenario, if initial attempts fail to control disease, one is faced with the need to re-treat the spine while avoiding the spinal cord.

Spinal cord tolerance dose is not well defined in terms of either the end point definition or the dose/fractionation schedule yielding such damage. With a clinical end point of “myelitis,” Withers *et al.* (23) suggested cord tolerance of 45–50 Gy in 22–25 fractions, a limit widely accepted within the radiation oncology community. The 1991 National Cancer Institute task force report concluded a cord-length-dependent 5% risk of exceeding the tolerance dose at 5 years (TD 5/5) of 50 Gy (5 and 10 cm) and 47 Gy (20 cm) (15). Schultheiss *et al.* (14) published an estimate of tolerance dose (myelitis) of 45–50 Gy (D < 0.2), 57–61 Gy (D5), and 73 Gy (D50). However, these studies did not address dose-constraint issues of primary concern for spinal SBRT, namely cord re-treatment tolerance and partial cord irradiation tolerance.

The key concept when considering re-treatment of the spinal cord is repair of occult injury over time. A number of small-animal studies support a time-dependent model of repair, but the findings are difficult to scale to human experience (24–26). Perhaps the most clinically relevant study was performed by Ang *et al.* (16). The thoracic and cervical spines of 56 Rhesus monkeys were treated to 44 Gy, then re-irradiated with an additional 57.2 Gy at 1 (*n* = 16) or 2 years (*n* = 20) or 66 Gy at 2 (*n* = 4) or 3 years (*n* = 14; total final doses, 101.2 and 110 Gy). The study end point was lower-extremity weakness or balance disturbances at 2.5 years after reirradiation. Of 45 animals assessable at the completion of the observation period, four developed end point symptoms. A reirradiation tolerance model developed by combining these data with data from a prior study of single-dose tolerance in the same model (27) resulted in an estimated recovery of 33.6 Gy (76%), 37.6 Gy (85%), and 44.6 Gy (101%) at 1, 2, and 3 years, respectively. Using a conservative modeling approach, an

overall recovery estimate of 26.8 Gy (61%) was obtained. Our strategy assumes even more conservative dose recovery of 25%, 33%, and 50% at 6 months, 1 year, and 2 years, respectively.

Nieder *et al.* (13, 18) developed a risk stratification model for myelopathy in human cord re-treatment. Assuming an α/β of 2 Gy (cervical and thoracic spine) or 4 Gy (lumbar spine), they estimated a risk less than 3% provided a total BED₂ less than 135.5 Gy₂, an interval longer than 6 months between courses, and a limit of both courses to less than 98 Gy₂. Using this model, 2 patients in our study were in the high-risk, 2 were in the intermediate-risk, and the rest were in the low-risk categories for development of radiation myelopathy. Both high-risk patients died of progressive disease (at 2 and 11 months) before developing side effects, whereas both intermediate-risk patients are alive (at 10 and 21 months) without treatment-related neurologic sequelae.

In the studies cited, re-treatment included the entire cord circumference. However, with the advent of SBRT, the effect of treating a fraction of the cord with a steep dose gradient is an important consideration (Fig. 2). As such, an appreciation for spinal cord functional anatomy and regional differences in radiosensitivity may be important in predicting and ultimately avoiding clinically significant spinal cord damage with SBRT. As shown in Fig. 3, the spinal cord consists of central grey matter (motor neurons) surrounded by white matter made up of well-defined neuronal tracts, broadly classified as descending motor tracts and ascending sensory tracts (28). There are two principal voluntary motor tracts: the lateral corticospinal tract, located in the posterolateral portion of the white matter, carries 85–90% of all voluntary motor activity from the contralateral cerebral motor cortex, whereas the anterior corticospinal tract carries the remaining signals in an ipsilateral fashion, crossing to control contralateral target muscle groups at the level of action. Although there are no *in vivo* experimental radiation studies establishing the clinical importance of this, it seems plausible that ablative SBRT treatment involving a portion of the cord occupied by a particular tract may not affect the function of untreated tracts at the same level. Although human studies designed to test this theory would not be ethical, appropriately powered animal model studies should be considered.

A number of reports suggest regional differences in radiosensitivity across the spinal cord (29, 30). The clinical end point in most such studies is paralysis, with the spinal cord showing nonspecific white matter necrosis pathologically. The pathogenesis of injury is under investigation, but it generally is believed to be caused primarily by vascular/endothelial damage, glial cell damage, or both (14, 31). In an elegant experiment using high-precision proton irradiation in the rat spinal cord, Bijl *et al.* (32) showed large regional differences in cord radiosensitivity. There was a rightward shift in the dose–response curve from 20.6 Gy iso-effective dose (ED50) with full-thickness irradiation to 28.9 and 33.4 Gy for lateral cord treatment (wide and narrow geometry, respectively) and to 71.9 Gy when only the central portion of the cord was treated. White matter necrosis was observed in all paralyzed rats, with none seen in nonresponders. No damage was observed in central grey matter for doses up to 80 Gy. The investigators attributed their findings to regional vascular density differences, with a potential role for differential oligodendrocyte progenitor cell distribution. However, an equally plausible explanation may be functional differences in the cord white matter regions irradiated, especially given the clinical end point of paralysis, which would not be expected if sensory tracts were preferentially irradiated. No similar reports are available in higher order species, making application of these findings to SBRT difficult.

The most common histologic type in our series was renal cell carcinoma (RCC), a finding seen in other reports of SBRT spine re-treatment (Table 2). Of the four treatment failures in

our series, three were RCC histologic types (Table 4). RCC comprises only 3–4% of all malignancies in the United States annually (33), with half ultimately developing metastases (34, 35). In a Canadian Phase II trial of palliative conventional RT for patients with RCC (3 Gy $\times$ 10), 83% experienced only a brief period of pain relief (median duration, 3 months) (36), whereas a Swedish Phase II trial of patients with SBRT for RCC metastases (5 Gy $\times$ 5 to 15 Gy $\times$ 3) reported an overall local control rate of 98% with lasting palliation (37). Although no definitive conclusions can be made in the absence of randomized trials, the relatively high percentage of patients with RCC in spine re-treatment series may suggest inadequate treatment using conventionally fractionated RT. SBRT, as either primary treatment or a planned boost, should be explored in this setting.

The use of conventional BED calculations to predict response to SBRT is controversial. The LQ model is widely used to mathematically describe the damaging effects of ionizing radiation on normal and neoplastic tissues (38) and initially was derived to fit experimental observations of the effects of dose and fractionation on cell survival and chromosomal damage. Although many modifications to the LQ model have been proposed to reflect repair kinetics, repopulation rates, volume effects, and radiosensitization by concurrent chemotherapy, all implicitly assume an underlying mechanism of DNA damage/repair in tumor clonogens. However, a number of studies suggest that administration of hypofractionated high-dose radiation *in vivo* has a much greater effect than that predicted from the LQ model. For example, Leith *et al.* (39) calculated the radiation doses required to control metastatic brain lesions using data from *in vitro* survival curves to be at least 25–35 Gy, much greater than that observed to be effective in clinical radiosurgery (15–20 Gy). Similarly, for arteriovenous malformations, single-fraction radiosurgery appears to be far more efficacious than “biologically equivalent” fractionated dose computed from the LQ model (40, 41).

The data suggest that a model of tumor and normal tissue response to SBRT should reflect two different mechanisms: direct cytotoxicity related to DNA damage at all dose levels and vasculature/stromal damage preferentially expressed at increased doses. For the former, *in vitro* cell survival data suggest that the LQ model overestimates radiation-mediated cell killing at increased doses because the model predicts a continuous downward bend while the experimental dose-response data are largely linear at doses greater than 12 Gy (40). Additionally, there is increasing evidence that tumor stem cells are more radioresistant than other tumor cells and may require exceeding a radiation threshold dose before cell death occurs (42), a mechanism not well-described by the LQ formalism. Park *et al.* (43) proposed a “universal survival curve” for SBRT based on a concept of single-fraction equivalent dose derived from a hybridization of the LQ model and the multitarget model. Their *in vitro* validation in the H460 lung cancer cell line is intriguing, although their model may underestimate the enhanced *in vivo* efficacy of radiosurgery because of vascular damage (44).

CONCLUSIONS

Re-treatment of spinal lesions using SBRT appears to provide effective palliation with minimal morbidity to date, although the long-term toxicity has yet to be determined. Patients with neurologic symptoms should be considered for surgical intervention because no patient in this study with neurologic deficits experienced resolution after SBRT. Because of the highly precise nature of SBRT, target and normal structures (especially the spinal cord) must be carefully identified and contoured. Volume expansion must be based on actual treatment system parameters, recognizing the need for a balance between tumor coverage and normal tissue dose to simultaneously ensure adequate tumor coverage and avoid long-term spinal cord toxicity. Although careful planning and a steep dose-gradient inherent in SBRT should

limit high-dose irradiation to only a partial thickness and small volume of the spinal cord, the clinical benefit of this improved dose distribution is unproved. Re-treatment for durable palliation is possible, with both primate and human studies available to guide selection of a minimally toxic SBRT dose. Recurrent RCC is a common indication for re-treatment and should be the subject of future trials aimed at optimizing treatment in this setting. Finally, more work needs to be done to clarify the biologic effectiveness of hypofractionated RT and the kinetics of recovery of radiation-induced damage to normal tissues, specifically the applicability of conventional LQ-based calculations in this setting.

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Fig. 1.

General imaging schema. Pt = patient; kV = kilovoltage; DRR = digital reconstructed radiograph; CB = cone beam; CT = computed tomography; SBRT = stereotactic body radiotherapy; tx = treatment.

Fig. 2.

Axial and sagittal images for a patient treated to C5–T3 for metastatic breast cancer with recurrent back pain. The central light blue contours represent the in-field portion of the spinal cord plus 2-mm axial margin, with extension 6 mm superior and inferior from the identified gross tumor volume/clinical target volume (CTV; in red). Note the steep dose gradient at the CTV-cord interface. Also, note the cord-sparing effect shown on the axial image. This patient had received 32.5 Gy in 13 fractions in a single posterior-anterior field 9 months earlier. An additional 18 Gy in three fractions was delivered using stereotactic body radiotherapy. At 11 months, she has substantial, although not complete, pain relief without narcotic analgesia.

Fig. 3. Axial view of a human cervical spinal cord shows central grey matter (light stain) surrounded by white matter containing motor (dark gray) and sensory tracts (light gray).

Table 1

Patient demographics and clinical characteristics

Total patients	32
Men/women	13/19
Median age (y)	61 (45–82)
Total lesions treated	33
Primary lesions	1
Metastatic lesions	32
Primary disease	
Renal cell	10
Breast cancer	6
Lung	6
Gastrointestinal: various	5
Pheochromocytoma	1
Multiple myeloma	1
Eccrine	1
Head and neck	1
Schwannoma	1

Table 2

Histologic types

	Present study	Gerszten <i>et al.</i> (4)	Gibbs <i>et al.</i> (6)	Ryu <i>et al.</i> (9)
Lesions with prior radiotherapy	67%	69%	68%	0%
Renal cell	31%	19%	27%	8%
Breast	19%	16%	23%	15%
Lung	19%	16%	14%	25%
Melanoma	—	8%	14%	25%
Colon	4%	7%	11%	—
Sarcoma	4%	6%	8%	—
Prostate	—	6%	3%	10%
Multiple myeloma	—	4%	3%	10%
Other	23%	18%	—	36%

Table 3

Spine segment, vertebral body location treated

	Present study	Gerszten <i>et al.</i> (4)	Benzil <i>et al.</i> (7)	Ryu <i>et al.</i> (9)
Involved segment				
Cervical	9%	15%	14%	16%
Thoracic	64%	42%	60%	48%
Lumbar	24%	22%	23%	30%
Sacrum	3%	21%	3%	6%
Location within segment				
Body	70%	NS	NS	"Most common"
Body + lateral + post	19%	NS	NS	
Lateral + post	11%	NS	NS	

Abbreviation: NS = not stated.

Table 4

Treatment failure characteristics

Patient no.	Primary	Area treated	Prior dose (Gy)	Interval (mo)	SBRT dose (Gy)	No. of fractions	Sites of failure [*]
1	RCC	T2	0	—	14	1	VB, epidural space
2	RCC	T10–11	37.5	8	21	3	Epidural space
3	RCC	T3	0	—	21	3	VB, pedicles
4	SCLC	T10	30	18	21	3	VB, pedicles

Abbreviations: SBRT = stereotactic body radiotherapy; RCC = renal cell cancer; SCLC = small-cell lung cancer; VB = vertebral body.

^{*} All failures were within the treatment field.