Spine stereotactic radiosurgery for the treatment of multiple myeloma

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OBJECTIVE The objective of this study was to define symptomatic and radiographic outcomes following spine stereotactic radiosurgery (SRS) for the treatment of multiple myeloma.

METHODS All patients with pathological diagnoses of myeloma undergoing spine SRS at a single institution were included. Patients with less than 1 month of follow-up were excluded. The primary outcome measure was the cumulative incidence of pain relief after spine SRS, while secondary outcomes included the cumulative incidences of radiographic failure and vertebral fracture. Pain scores before and after treatment were prospectively collected using the Brief Pain Inventory (BPI), a validated questionnaire used to assess severity and impact of pain upon daily functions.

RESULTS Fifty-six treatments (in 38 patients) were eligible for inclusion. Epidural disease was present in nearly all treatment sites (77%). Moreover, preexisting vertebral fracture (63%), thecal sac compression (55%), and neural foraminal involvement (48%) were common. Many treatment sites had undergone prior local therapy, including external beam radiation therapy (EBRT; 30%), surgery (23%), and kyphoplasty (21%). At the time of consultation for SRS, the worst, current, and average BPI pain scores at these treatment sites were 6, 4, and 4, respectively. The median prescription dose was 16 Gy in a single fraction. The median clinical follow-up duration after SRS was 26 months. The 6- and 12-month cumulative incidences of radiographic failure were 6% and 9%, respectively. Among painful treatment sites, 41% achieved pain relief adjusted for narcotic usage, with a median time to relief of 1.6 months. The 6- and 12-month cumulative incidences of adjusted pain progression were 13% and 15%, respectively. After SRS, 1-month and 3-month worst, current, and average BPI scores all significantly decreased ($p < 0.01$). Vertebral fracture occurred following 12 treatments (21%), with an 18% cumulative incidence of fracture at 6 and 12 months. Two patients (4%) developed pain flare following spine SRS.

CONCLUSIONS This study reports the largest series of myeloma lesions treated with spine SRS. A rapid and durable symptomatic response was observed, with a median time to pain relief of 1.6 months. This response was durable among 85% of patients at 12 months following treatment, with 91% local control. The efficacy and minimal toxicity of spine SRS is likely related to the delivery of ablative and conformal radiation doses to the target. SRS should be considered with doses of 14–16 Gy in a single fraction for patients with multiple myeloma and limited spinal disease, myelosuppression requiring “marrow-sparing” radiation therapy, or recurrent disease after EBRT.

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KEY WORDS spine radiosurgery; multiple myeloma; vertebral metastasis; stereotactic body radiotherapy; oncology

MULTIPLE myeloma is a malignant plasma cell neoplasm and the second most common hematological malignancy.^{2,28,31} The age-adjusted incidence of myeloma in the general population is 6 per 100,000 annually, with a 45% 5-year survival rate.^{2,40} Overall survival

is more favorable with limited disease; however, more than 95% of patients with myeloma have diffuse disease at the time of initial diagnosis. With the advent of newer chemotherapeutic agents, the treatment of this disease is rapidly evolving. Since 2002, the mortality rate has been

ABBREVIATIONS BPI = Brief Pain Inventory; EBRT = external beam radiation therapy; HD-MRI = high-definition MRI; HR = hazard ratio; KPS = Karnofsky Performance Scale; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery.

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decreasing by 1% annually (www.seer.cancer.gov).⁴² As mortality declines due to improved systemic therapies, the prevalence of this disease increases, highlighting the importance of long-term quality of life.

The greatest morbidity among patients with myeloma stems from bone disease.^{30,40} At diagnosis, 80% of patients have radiographic evidence of osteolytic bone lesions.^{3,20,21,27,30} While patients may present with signs and symptoms of renal failure, hypercalcemia, or infection, patients most commonly present with bone pain emanating from the spine or ribs. Ultimately, the prevalence of bone pain approaches 100%, requiring repeat surgical fixation, palliative radiotherapy, and narcotics. As a consequence of bone destruction in the spine, many patients suffer from vertebral fractures (55%–70%) or neurological deficits caused by spinal cord or nerve root impingement (up to 30%).^{2,3,20,21}

While chemotherapy remains the mainstay of treatment in myeloma, radiation therapy has an important role in palliation of symptoms and prophylaxis against cord compression.^{25,33} Because myeloma is inherently radiosensitive, patients have historically been treated with either hypofractionated or single-fraction external beam radiation therapy (EBRT).^{22,26,42} These treatments are generally well tolerated, with few complications and high rates of pain relief.³⁸ As overall survival improves, many patients develop local failure at previously irradiated sites, requiring repeat radiotherapy. Although retreatment of most bone sites may be accomplished safely, retreatment of vertebral metastases requires careful evaluation to ensure tolerance of the spinal cord and/or cauda equina.^{8,39} Therefore, some patients may be well served with spine stereotactic radiosurgery (SRS), which offers the advantage of highly conformal radiation delivery that effectively targets the tumor while minimizing the dose to the spinal cord and adjacent vertebral bodies.^{1,17,41} Although this technique is most commonly used for the treatment of spinal metastases from solid tumors with local control rates of 80%–85%,^{17,18} patients with myeloma and those with minimal spinal disease who previously underwent radiation treatment may be candidates for SRS.^{17,18,33,35,41}

Given the efficacy of spine SRS for alleviation of pain and improvement in quality of life across a spectrum of pathologies, appropriate utilization of this modality for patients with myeloma should be considered.⁵ Moreover, this technique may simultaneously prevent fracture progression and improve local control, especially among those with recurrence after conventional radiotherapy.^{6,19,23} There is a paucity of literature on the utilization of spine SRS in patients with myeloma.^{17,18,33} Therefore, in the present study, we report our experience with spine SRS for the treatment of vertebral metastases from myeloma.

Methods

Patient Selection

All patients who underwent spine SRS were included in a retrospective Institutional Review Board–approved registry. Only patients with confirmed pathological diagnoses of myeloma were included in the present study. Patients with less than 1 month of follow-up or concurrent second

primary tumors were excluded. Primary indications for spine SRS were either symptomatic (pain, neurological deficits) or due to epidural extension of tumor evident on imaging. In general, patients with prior conventional radiotherapy, limited systemic disease burden, or myelosuppression necessitating “marrow-sparing” radiation therapy were eligible for SRS at this institution. In this cohort, 84% of patients met at least one of these primary indications for SRS. Extension of disease into the paraspinal soft tissues was not a contraindication for treatment.

Spine SRS

Patients eligible for SRS initially underwent CT simulation in the supine position. Those with disease at T-4 and above were immobilized in a 5-point thermoplastic head mask, while those with disease below T-4 were immobilized in a Bodyfix mold (Medical Intelligence; Elekta) with a vacuum bag for added immobilization. Simulation CT and high-definition MRI (HD-MRI) were obtained in 1.5-mm slices. MRI sequences were then fused to the treatment-planning CT images using either BrainScan or iPlan software (Brainlab) or MIM (MIM Software Inc.). Target volumes were contoured using HD-MRI according to the bone involvement of the lesion as previously described in detail.³⁵ In each case, the spinal cord was contoured approximately 5 mm above and below each target volume using HD-MRI.^{34,35} Treatment planning was performed using either BrainScan or iPlan software (Brainlab), and more recently, Pinnacle (Phillips). Image guidance during treatment delivery was achieved using cone-beam CT or orthogonal radiography and the ExacTrac system (Novalis). For single-fraction SRS, the spinal cord and cauda equina were constrained to 14-Gy and 16-Gy maximum point doses, respectively; the volume of spinal cord and cauda equina treated to 10 Gy and 12 Gy were both < 10%. Patients were examined in the clinic 1–2 months after SRS and then every 3 months thereafter, with follow-up spine MRI and clinical examination at each follow-up.

Outcome Measures and Statistics

The primary outcome was the cumulative incidence of pain relief after spine SRS.¹³ Pain scores before and after treatment were prospectively collected using the Brief Pain Inventory (BPI), a validated questionnaire used to assess severity and impact of pain upon daily functions.^{4,11,14} The BPI is generally used in populations with chronic diseases such as osteoarthritis or cancer, and has been studied in the context of myeloma-associated vertebral fractures, metastatic bone disease, and SRS.^{10,23,41} BPI scores were recorded as the “worst,” “current,” and “average” pain (ranging from 0 to 10) at each treatment site throughout clinical follow-up. Pain relief and symptomatic failure were adjusted for narcotic usage per Radiation Therapy Oncology Group (RTOG) study 0631.³⁵ Any increase in narcotic utilization was considered pain progression. Pre-SRS BPI scores were compared with 1-month and 3-month post-SRS scores.

Secondary outcome variables included the cumulative incidences of vertebral fracture and radiographic failure after SRS. A neuroradiologist reviewed all follow-up spine

MR images, which were compared with treatment-planning MR images to determine radiographic outcomes. Radiographic failure was defined as progression at the site of treatment as reported by a neuroradiologist and confirmed by a radiation oncologist or neurosurgeon. Post-SRS fracture was defined as new vertebral body height loss exceeding 20%, or progressive height loss of 10%. Wilcoxon signed-rank tests were used to compare paired continuous data. Kaplan-Meier analysis was used to determine estimates of overall survival, while cumulative incidence analysis was used to determine estimates of radiographic failure, pain relief, pain progression, relief of neurological deficits, and vertebral fracture. Differences in overall survival were compared using log-rank tests, while all other actuarial outcomes were compared with Gray's tests.¹⁵ Multivariate competing-risks regression was used to control for the following covariates, with death as a competing risk: Karnofsky Performance Scale (KPS) score, extent of spinal disease, systemic disease status, concurrent medical therapies, treatment location, number of treated levels, epidural disease, preexisting vertebral fracture, spinal cord compression, prior in-field irradiation, prior surgery, degree of pain, treatment volume, and maximum target dose. Covariates demonstrating association ($p \leq 0.10$) with outcome variables on univariate analysis were evaluated in a multivariate model. Covariate inclusion into the final multivariate model required a p value ≤ 0.10 . Analyses were conducted using the R statistical software package (R Core Team 2015; R Foundation for Statistical Computing).

Results

Patient and Treatment Characteristics

Fifty-six treatments (in 38 patients) were eligible for inclusion. The median patient age at the time of SRS was 59 years old (range 37–87 years old), and the median KPS score was 80 (range 50–90). Twenty-six patients (68%) had extraspinal bone disease. More than half of the patients were receiving concurrent chemotherapy (63%) or steroids (61%; Table 1). At the time of SRS, 38% of patients were leukopenic, 66% of patients were anemic, 29% of patients were thrombocytopenic, and 73% of patients had a decrease in at least 1 cell line.

Characteristics of the 56 treatment sites are presented in Table 2. The majority (66%) of treatment sites were located in the thoracic spine. Epidural disease was present in nearly all treatment sites (77%). Moreover, preexisting vertebral fracture (63%), thecal sac compression (55%), and neural foraminal involvement (48%) were common. Many treatment sites had undergone prior local therapy, including EBRT (30%), surgery (23%), and kyphoplasty (21%). At the time of consultation for SRS, the worst, current, and average BPI pain score at these treatment sites was 6, 4, and 4, respectively. Among 9 sites (16%) associated with a neurological deficit, numbness/radicular pain was most common (66%), followed by weakness (55%) and bladder incontinence/retention (22%). All but 3 sites (5%) were treated with a single fraction. The median prescription dose was 14 Gy (range 10–24 Gy) in a single fraction (range 1–4 fractions).

TABLE 1. Patient characteristics

Characteristic	Value*
No. of patients	38
Median age in yrs (range)	59 (37–87)
Males (%)	22 (58)
Median KPS score (range)	80 (50–90)
Median Neurologic Function Scale score (range)	1 (0–4)
Prior smoker (%)	22 (58)
Comorbid disease (%)	
Mean BMI $\pm$ SD	29 $\pm$ 6
Hypertension	16 (42)
Hyperlipidemia	8 (21)
Diabetes	2 (5)
Spinal disease characteristics (%)	
Single-level disease	7 (18)
Multilevel disease (2–5 VBs)	14 (37)
Diffuse disease (>5 VBs)	17 (45)
Extraspinal bone disease (%)	26 (68)
Concurrent medical therapies (%)	
Chemotherapy	24 (63)
Steroids	23 (61)
Bisphosphonates	16 (42)
Median prior chemotherapy regimens (range)	2 (0–12)
Median clinical follow-up in mos (range)	26 (1–78)
Median radiographic follow-up in mos (range)	17 (1–67)
Median overall survival in mos (range)	26

BMI = body mass index; VB = vertebral body.

* Subtotals may exceed 100% if patients had, for example, multiple medical therapies.

Outcomes and Toxicity

Clinical and radiographic outcomes after SRS are presented in Table 3. The median clinical follow-up duration after SRS was 26 months (range 1–67 months), while the median overall survival after SRS was 26 months (Fig. 1A). The 6- and 12-month cumulative incidences of radiographic failure were 6% and 9%, respectively (Fig. 1B). Among painful treatment sites, 41% achieved pain relief adjusted for narcotic usage (Fig. 2 upper). The median time to pain relief was 1.6 months. The 6- and 12-month cumulative incidences of adjusted pain progression were 13% and 15%, respectively (Fig. 2 lower). After SRS, 1-month and 3-month worst ($p < 0.01$), current ($p < 0.01$), and average ($p < 0.01$) BPI scores significantly decreased. Among 9 patients with neurological deficit at the time of treatment, 5 (56%) achieved improvement following SRS, with a median time to relief of 1.2 months (Fig. 1D).

Vertebral fracture occurred following 12 treatments (21%); 10 of 12 were due to progression of preexisting fractures, while 2 were de novo fractures (Fig. 1C). The 6- and 12-month cumulative incidences of fracture were each 18%. Two (4%) patients developed pain flare following spine SRS.

The incidences of post-SRS fracture in the up-front versus salvage settings were 21% versus 24% ($p = 0.80$),

TABLE 2. Treatment site characteristics

Characteristic	Value (%)
Treatments	56
Location	
Cervical	4 (7)
Thoracic	37 (66)
Lumbar	12 (21)
Sacral	3 (5)
No. of vertebral levels treated	
1	36 (64)
2	13 (23)
≥3	7 (13)
Treatment site characteristics	
Epidural disease	43 (77)
Preexisting vertebral fracture	35 (63)
Thecal sac compression	31 (55)
Neural foraminal involvement	27 (48)
Posterior elements disease	22 (39)
Adjacent-segment disease	18 (32)
Paraspinal extension	16 (29)
Spinal cord compression	8 (14)
Role of SRS	
Primary	29 (52)
Salvage	19 (34)
Adjuvant	8 (14)
Indications for SRS	
Pain alone	37 (66)
Asymptomatic*	10 (18)
Pain w/ neurological deficit	9 (16)
Prior local therapy	
EBRT	17 (30)
Any surgery	13 (23)
Kyphoplasty	12 (21)
Surgery w/ instrumentation	4 (7)
Mean pre-SRS BPI score ± SD	
Worst pain	6.1 ± 3.1
Current pain	3.8 ± 2.8
Average pain	4.0 ± 3.0

Subtotals may exceed 100% if patients had, for example, multiple prior local therapies.

* Asymptomatic epidural disease or radiographic progression.

respectively. Comparable rates of adjusted pain relief (38% vs 41%, $p = 0.85$) and local failure (15% vs 12%, $p = 0.72$) were also observed. However, the incidence of adjusted pain progression was lower in the up-front setting (10% vs 29%, $p = 0.08$), although given the limited number of events, the origin of this difference is uncertain.

Multivariate analysis identified several significant independent predictors of radiographic failure and pain relief (Table 4). Prior in-field EBRT (hazard ratio [HR] 0.02, $p < 0.01$) was protective against local failure, while larger target volumes (HR 1.46, $p < 0.01$) were associated with local progression. After adjusting for narcotic usage,

TABLE 3. Radiographic and symptomatic outcomes and toxicity

Characteristic	Value (%)
Radiographic failure	8 (14)
Median time to failure (mos)	Not reached
Adjusted pain progression	9 (16)
Median time to failure (mos)	Not reached
Adjusted pain relief*	19 (41)
Median time to relief (mos)	Not reached
Mean 1-mo BPI score ± SD	
Worst pain	3.3 ± 3.0
Current pain	1.9 ± 2.5
Average pain	2.4 ± 2.4
Mean 3-mo BPI score ± SD	
Worst pain	3.1 ± 3.4
Current pain	1.9 ± 2.9
Average pain	2.2 ± 3.0
Neurological deficit relief†	5 (56)
Median time to relief (mos)	1.2
Post-SRS complications	
Vertebral fracture‡	12 (21)
Median time to fracture (mos)	Not reached
Progressed fracture	10 (18)
De novo fracture	2 (4)
Pain flare	2 (4)
Any local failure requiring retreatment	5 (9)
EBRT	3 (5)
SRS	2 (4)
Characteristics of radiographic failure	8 (14)
Site of failure	
Vertebral body	4 (7)
Epidural space	3 (5)
Neural foramen	2 (4)
Paraspinal	1 (2)

* Among patients with pain at consultation ($n = 46$).

† Among patients with neurological deficits at consultation ($n = 9$).

‡ New or worsened fracture.

bisphosphonate use (HR 2.02, $p < 0.01$), spinal cord compression (HR 2.23, $p < 0.01$), and higher maximum target doses (HR 1.29, $p < 0.01$) were associated with more rapid pain relief. No independent predictors of pain progression or post-SRS fracture were identified after multivariate analysis.

Discussion

This series represents the largest of any prior investigation of SRS in the myeloma population. Outcomes for a series of 38 patients undergoing 56 treatments are reported, with a particular emphasis on pain relief and time to symptomatic and radiographic failure. We observed excellent radiographic and clinical outcomes following SRS: at 12 months, 85% of treatment sites were free from adjusted pain progression (Fig. 2 lower), with a radiographic control rate of 91% (Fig. 1B). Pain relief was rapid, with a

FIG. 1. Actuarial curves depicting proportion of cohort surviving (A), free from radiographic failure (B), free from post-SRS fracture (C), and achieving improvement of neurologic deficit (D).

median time to relief of 1.6 months in a cohort of patients with extensive prior local therapy. Importantly, spine SRS was efficacious in the salvage setting, with prior in-field radiotherapy protective against local failure. These results demonstrate that rapid and durable pain relief is routinely achieved, and that few patients experience radiographic and symptomatic progression following spine SRS. The observed rate of pain control is comparable to pain control after conventional radiation (76%) for any sites of bone disease (axial and extraaxial); more limited data are avail-

able for pain control after conventional radiotherapy for spinal lesions exclusively.¹⁶ The low rate of pain progression and excellent radiographic control translated into a low retreatment rate (5 patients, 9%). Among patients that required retreatment, 3 (5%) underwent conventional EBRT (due to poor performance status) and 2 patients (4%) underwent repeat spine SRS.

Data reported by Lecouvet et al.¹⁹ suggest that radiation has a protective effect against subsequent fractures in the myeloma population, with an observed fracture incidence

FIG. 2. Actuarial curves depicting proportion of cohort achieving adjusted symptomatic relief (upper) and free from adjusted symptomatic failure (lower).

TABLE 4. Multivariate competing-risks regression analysis

Covariates	Time to Radiographic Failure				Time to Adjusted Pain Relief			
	Univariate p Value	Multivariate			Univariate p Value	Multivariate		
		p Value	HR	95% CI		p Value	HR	95% CI
KPS score*	0.15	0.15	2.08	0.78–7.51	0.62			
BPI current pain	<0.01	0.52			0.65			
Bisphosphonate use	0.58				0.03	<0.01	2.02	1.24–5.53
Epidural disease	0.70	0.16	4.74	0.55–85.68	0.74			
Spinal cord compression	0.72				0.02	<0.01	2.23	1.34–3.59
Prior kyphoplasty	0.19	0.86			0.26			
Prior fracture	0.02	0.79			0.72			
Prior radiotherapy at site	0.14	<0.01	0.02	0.01–0.34	0.96			
Max target dose (Gy)	0.19	0.12	1.39	0.91–2.19	0.07	<0.01	1.29	1.11–1.49
Target volume (cm ³)*	<0.01	<0.01	1.46	1.19–1.99	0.26			

CI = confidence interval.

Boldface type indicates statistical significance.

* Per 10-unit change.

of 5% in patients who underwent radiation and 20% in patients who did not. However, high-dose radiation may also induce fractures.³⁷ Jin et al. suggested that these fractures may be related to the collapse of bone into the tumor cavity after ablation.¹⁷ To protect against vertebral collapse, Chen et al. highlight the complementary roles of radiation and vertebral augmentation in the setting of multiple myeloma-associated vertebral fractures.^{7,42}

Characterizing the natural history of myeloma fractures is challenging, as many patients present with fractures of varying severity and undergo radiation treatment to fracture sites.^{21,27} In the present cohort, 63% of patients had preexisting in-field vertebral compression fractures at the time of SRS, highlighting the osteolytic disease process of myeloma. Following SRS, 12 vertebral fractures occurred (21%), of which nearly all (n = 10) were progressed fractures. This suggests that SRS rarely (4%) induces de novo fractures in this population at this prescription dose, with preexisting fractures representing an obvious risk factor. Our fracture rate is lower than reports in several studies, and is likely due to a lower median prescription dose (14 Gy) used in treating myeloma patients at our institution.³⁷ In a large multiinstitutional investigation of 410 spinal segments treated with SRS, the incidence of vertebral fracture was 14% (7% de novo).³⁷ The authors observed a significantly increased rate of fracture with single-fraction doses above 20 Gy, as well as with lytic lesions, prior vertebral fracture, and spinal deformity. In a separate single-institution investigation including 167 fractionated SRS treatments, the incidence of fracture was 11% (7% de novo).¹² Given the excellent local control and modest treatment-related toxicity observed, the benefit of fractionated SRS would likely be marginal for improving safety. However, we would encourage limiting the prescription dose to 14–16 Gy given the radiosensitive nature of this disease.

There are limited comparative data to support the efficacy of prophylactic vertebral augmentation in combination with SRS, particularly for symptomatic end points. In this investigation, 21% of treatment sites underwent verte-

bral augmentation prior to SRS, and the incidence of SRS-related fracture was relatively low; accordingly, routine prophylactic vertebral augmentation may offer marginal benefit. Because the majority of observed fractures were progressive (83%), vertebral augmentation may potentially be considered in a subset of patients with preexisting fractures (35 sites, 63% of cohort). However, among these 35 sites, only 10 (29%) progressed after SRS. Accordingly, the number needed to treat to prevent 1 radiographic progressed fracture is approximately 3. Further, as many post-SRS fractures are asymptomatic, the perioperative morbidity and cost effectiveness of routine prophylactic vertebral augmentation requires evaluation in a larger study. Notably, concurrent steroid utilization at the time of SRS did not increase the risk for post-SRS fracture.

While fracture is the chief late toxicity following spine SRS, pain flare represents a common acute toxicity. In this series, only 2 treatments (4%) resulted in the development of pain flare, which resolved rapidly with steroids. Prospective data suggest that the incidence of pain flare is approximately 10%–20% following spine SRS.²⁹ Randomized trials have identified the utility of prophylactic steroids against pain flare following irradiation of bone metastases.⁹ Accordingly, the incidence of pain flare in this study may be low secondary to the use of dexamethasone in myeloma chemotherapeutic regimens. Indeed, 61% of patients received steroids at the time of SRS.

Multivariate modeling revealed several variables that were associated with pain relief. Of note, use of bisphosphonates augmented pain relief (HR 2.02, $p < 0.01$), further highlighting their efficacy in control of skeletal-related events and pain.²⁴ Indeed, prior investigations have suggested a survival benefit with the use of these agents in multiple myeloma.⁶ In addition, those with spinal cord compression experienced more rapid adjusted pain relief (HR 2.23, $p < 0.01$). Accordingly, patients with epidural disease and cord compression may expect rapid decompression with SRS (Fig. 3), while those with chronic mechanical pain unrelated to cord compression may expect a smaller benefit. Although prescription dose had no impact

FIG. 3. Sagittal (*upper*) and axial (*lower*) images of a T7–9 SRS dose plan (A) demonstrating spinal cord planning risk volume (pink), clinical target volume (green), prescription isodose line (yellow line), 10-Gy isodose line (blue line), and 16-Gy isodose line (orange line). Sagittal T2-weighted (*upper*) and axial noncontrast T1-weighted (*lower*) MR images through the thoracic spine before SRS (B), 1 month after SRS (C), and 12 months after SRS (D), demonstrating resolution of the epidural disease with no associated significant vertebral body height loss in a previously untreated patient. Figure is available in color online only.

on pain response, multivariate analysis demonstrated that maximum target dose was associated with rapid time to pain relief (HR 1.29, $p < 0.01$), and did not significantly impact future fracture risk. This may suggest a role for relaxing homogeneity constraints.

There is a paucity of data reporting spine SRS outcomes in multiple myeloma. Jin et al. conducted a study of 31 myeloma epidural lesions (in 24 patients) compressing the spinal cord, treated using SRS.¹⁷ After a median follow-up of 11 months, overall pain control was 86%, complete symptom relief was achieved in 54%, and radiographic response was 81% at 3 months. The authors supported the use of SRS in myeloma-associated spinal cord compression, citing the impressive radiographic and clinical improvements after treatment, as well as the relative convenience over surgery or fractionated radiotherapy. In a smaller study conducted by Rock et al. that included 4 patients with myeloma treated with radiosurgery, the overall neurological deterioration after SRS was just 8%.³³ However, these studies were more limited in scope and did not use multivariate methods to identify predictors of treatment response.

There are a number of limitations that must be considered with the present study. As a retrospective investigation, these data are subject to greater measurement bias, selection bias, and confounding than prospective studies. However, no prospective investigations have been conducted investigating this technique in multiple myeloma, with RTOG study 0631 specifically excluding patients with myeloma.^{35,36} The size of this study was relatively small, limiting the generalizability and utility of multivariate regression. In particular, a limited number of patients presented

with a neurological deficit, limiting the capacity to draw conclusions regarding reversal of such deficits. However, with the exception of prescription dose and fractionation, all technique-related variables were consistent among treatments in an effort to minimize treatment variability. As with most palliative investigations, characterization of symptomatic response is challenging given the subjectivity and heterogeneity of patient perspectives. In an effort to combat this challenge, we used prospectively collected validated tools such as the BPI in an attempt to standardize monitoring during clinical follow-up.

The strengths of this study lie in the consistency of treatment delivered, the utilization of both primary and secondary outcome variables for monitoring objective (e.g., survival, fracture) and subjective (e.g., pain) end points, and the incorporation of multivariate modeling to identify variables associated with favorable and unfavorable outcome. Based upon these results, our study suggests that the utilization of spine SRS in the myeloma population is a safe and effective means for palliating pain and neurological deficits.

Conclusions

In this study we report a series of 56 myeloma lesions treated with spine SRS, with specific attention to pain relief. A rapid and durable symptomatic response was observed, with a median time to pain relief of 1.6 months. This response was durable in 85% of patients at 12 months following treatment, with 91% local control. Our study also demonstrates minimal toxicity in this population. The efficacy and minimal toxicity of spine SRS is likely related

to the delivery of ablative and conformal radiation doses to the target. As a radiosensitive disease, SRS should be considered with doses of 14–16 Gy in a single fraction for patients with multiple myeloma and limited spinal disease, in patients with myelosuppression requiring “marrow-sparing” radiation therapy, or in patients with recurrent disease after conventional radiotherapy.

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Disclosures

Dr. Suh has received travel and lodging expenses from Elekta.

Author Contributions

Conception and design: Angelov, Miller, Balagamwala. Acquisition of data: Miller, Balagamwala, Emch. Analysis and interpretation of data: Angelov, Miller. Drafting the article: Angelov, Miller. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Angelov. Study supervision: Angelov.

Supplemental Information

Previous Presentations

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