Spine stereotactic radiosurgery for metastatic sarcoma: patterns of failure and radiation treatment volume considerations

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OBJECTIVE Given the relatively lower radiosensitivity of sarcomas and the locally infiltrative patterns of spread, the authors sought to investigate spine stereotactic radiosurgery (SSRS) outcomes for metastatic sarcomas and to analyze patterns of failure.

METHODS The records of 48 patients with 66 sarcoma spinal metastases consecutively treated with SSRS between 2002 and 2013 were reviewed. The Kaplan-Meier method was used to estimate rates of overall survival (OS) and local control (LC). Local recurrences were categorized as occurring infield (within the 95% isodose line [IDL]), marginally (between the 20% and 95% IDLs), or out of field.

RESULTS Median follow-up time was 19 months (range 1–121 months), and median age was 53 years (range 17–85 years). The most commonly treated histology was leiomyosarcoma (42%). Approximately two-thirds of the patients were treated with definitive SSRS (44 [67%]) versus postoperatively (22 [33%]). The actuarial 1-year OS and LC rates were 67% and 81%, respectively. Eighteen patients had a local relapse, which was more significantly associated with postoperative SSRS ($p = 0.04$). On multivariate modeling, receipt of postoperative SSRS neared significance for poorer LC ($p = 0.06$, subhazard ratio [SHR] 2.33), while only 2 covariates emerged as significantly correlated with LC: 1) biological equivalent dose (BED) > 48 Gy (vs BED ≤ 48 Gy, $p = 0.006$, SHR 0.21) and 2) single vertebral body involvement (vs multiple bodies, $p = 0.03$, SHR 0.27). Of the 18 local recurrences, 14 (78%) occurred at the margin, and while the majority of these cases relapsed within the epidural space, 4 relapsed within the paraspinal soft tissue. In addition, 1 relapse occurred out of field. Finally, the most common acute toxicity was fatigue (15 cases), with few late toxicities (4 insufficiency fractures, 3 neuropathies).

CONCLUSIONS For metastatic sarcomas, SSRS provides durable tumor control with minimal toxicity. High-dose single-fraction regimens offer optimal LC, and given the infiltrative nature of sarcomas, when paraspinal soft tissues are involved, larger treatment volumes may be warranted.

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KEY WORDS spine metastasis; sarcoma; stereotactic body radiation therapy; spine stereotactic radiosurgery; SSRS; oncology

ABBREVIATIONS BED = biological equivalent dose; CTCAE = Common Terminology Criteria for Adverse Events; CTV = clinical target volume; GTV = gross tumor volume; LC = local control; OS = overall survival; PFS = progression-free survival; PTV = planning treatment volume; RT = radiation therapy; SHR = subhazard ratio; SSRS = spine stereotactic radiosurgery.

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SARCOMAS have a high propensity for distant metastasis. Approximately 30% of patients presenting with localized sarcomas will eventually develop distant disease, and about 10% of patients have metastases at the time of presentation.^{7,30} The most common site for metastasis is the lung parenchyma, with spinal disease developing in a smaller proportion of patients. However, sarcoma spinal metastases represent a dominant source of morbidity and negatively impact quality of life as a result of cancer-related, neuropathic, or mechanical pain; pathological fracture; and spinal cord compression.⁸ Therefore, aggressive local therapy with either radiation therapy (RT) or surgical intervention is often needed to control symptoms, preserve function, and enhance local tumor control.

Spine stereotactic radiosurgery (SSRS) has become a widely adopted conformal method of delivering high, ablative doses of RT for metastatic spinal disease. Among all cancer types, SSRS offers a favorable risk-benefit profile while providing 1-year local control (LC) rates generally above 85%.^{1,3,5,13,14,23,25,29} However, there are limited data on the efficacy of SSRS for the treatment of metastatic sarcoma. Among the few published reports are inconsistent tumor control rates ranging between 51% and 88% at 1 year.^{6,10,18,19} Notably, the lower tumor control rates in this range are not dissimilar to the rates expected from conventional fractionation.^{2,10,14,16,22} Therefore, if these outcomes truly reflect the course of sarcoma spinal metastases following SSRS, why is tumor control poorer for this histological entity?

Perhaps the explanation is related to the biology of sarcomas, or perhaps it is related to treatment delivery. There is an interesting philosophical and arguably incongruent difference in the therapeutic approach between highly conformal SSRS and the wide-margin, large-volume conventional fractions used for primary sarcomas.^{9,15,27} Given the propensity of primary sarcomas to recur in the soft tissue when inadequate radiation field margins are used, it may be necessary to modify SSRS treatment fields for this histology in the metastatic setting. To better understand the efficacy of SSRS for metastatic sarcomas, we reviewed our experience to investigate tumor control outcomes and better characterize patterns of failure to aid in strategies for improved LC.

Methods

Patients

We identified 48 consecutive patients with 66 sarcoma spinal metastases treated with SSRS at the University of Texas MD Anderson Cancer Center during the period between 2002 and 2013. Thirty-five of the lesions (53%) had been treated in 3 institutional Phase I/II trials evaluating single- and multifraction SSRS for spinal metastases.^{5,11,12} After obtaining approval from the institutional review board, we extracted patient, tumor, and outcome characteristics from the medical records for the entire group.

Treatment

All patients were treated using CT-guided intensity-modulated SSRS using the CT-on-rails EXaCT targeting system or Trilogy treatment delivery system with on-board

cone-beam CT (Varian Medical Systems), as previously described.^{4,21} After patients were immobilized in an Elekta BodyFix stereotactic body frame (Elekta) and aligned using a CT-on-rails (GE Healthcare) or cone-beam CT, treatments were delivered typically using a 9-field step-and-shoot intensity-modulated radiation treatment plan. Each procedure was monitored by the treating radiation oncologist and a dedicated radiation physicist to verify target positioning and quality assurance.

Metastatic spinal tumors were treated with various doses and fractionations. Given that the first institutional protocols established safety and efficacy, the regimens investigated were more conservative. However, more contemporary patients were treated with standardized regimens based on tumor radiosensitivity and previous RT. Contouring of the gross tumor volume (GTV) and clinical target volume (CTV) was consistent with recent consensus guidelines for SSRS (not specific to histology).⁹ The GTV was defined as visible tumor on an MR image fused with the planning CT scan, and the CTV, which contains the GTV, was defined as at-risk contiguous bone marrow or soft-tissue margin in cases with paraspinal extension of disease. The planning treatment volume (PTV) was defined with no margin to the CTV. The dose was commonly normalized between the 80% and 90% isodose line,²¹ so that the prescription line enclosed the PTV, except near the spinal cord as necessary. Postoperative SSRS target delineation began with fusion of the preoperative MR image to the planning CT scan. The GTV was defined as any residual disease and/or the postoperative bed. The CTV was defined as the GTV with contiguous bone marrow space and any additional postoperative bed at risk for harboring microscopic disease. Additional radiation details and outcomes of postoperative SSRS were recently published by Tao and colleagues.²⁶ To account for the various fractionation schemes, a biological equivalent dose (BED) was calculated for the prescription based on the α/β value of 10 Gy for tumor effect.

Follow-Up and Relapses

The median follow-up for the entire cohort was 19 months (range 1–121 months) and for all living patients 31 months (range 10–121 months). Acute (defined as less than 3 months) and long-term toxicities were prospectively recorded for patients treated on protocol (53%); otherwise, toxicities were retrospectively graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Patients were seen every 3 months for physical examination and MRI of the spine to assess for radiological tumor recurrence. Local recurrences were defined as radiological evidence of progression as identified by the reading radiologist. After confirmation by the radiation oncologist, local recurrences were subclassified based on anatomical location of the tumor recurrence (epidural space vs paraspinal) and its proximity to isodose lines. In-field relapses were defined as being entirely encompassed within the 95% isodose line, whereas marginal relapses occurred partially or fully in the penumbra commonly between the 20% and 95% prescription isodose lines.

TABLE 1. Patient and disease characteristics

Variable	No. (%)			p Value
	All Tumors	Recurrence	No Recurrence	
No.	66	18	48	
Time from CA Dx to spine met in mos				
Median	36	26	42	0.78
Range	0–264	0–101	0–264	
Age at time of SSRS in yrs				
Median	53	51	56	0.78
Range	17–85	17–79	17–85	
Sex				
Male	31 (47)	8 (26)	23 (74)	1.0
Female	35 (53)	10 (28)	25 (71)	
Tumor type				
Leiomyosarcoma	28 (42)	9 (32)	19 (68)	NA
Epithelioid	9 (14)	1 (11)	8 (89)	
MFH/UPS	8 (12)	1 (12)	7 (88)	
Chondrosarcoma	6 (9)	3 (50)	3 (50)	
Solitary fibrous tumor	5 (8)	0 (0)	5 (100)	
Myxoid liposarcoma	5 (8)	1 (20)	4 (80)	
Osteosarcoma	3 (4)	1 (33)	2 (67)	
Dediff liposarcoma	1 (2)	0 (0)	1 (100)	
Ewing's	1 (2)	1 (100)	0 (0)	
Spine section affected				
Cervical	10 (15)	3 (30)	7 (70)	0.79
Thoracic	40 (61)	10 (25)	30 (75)	
Lumbosacral	16 (24)	5 (31)	11 (69)	
Bilsky grade at time of SSRS				
0	23	4	19	0.67
1a	19	6	13	
1b	15	6	9	
1c	4	1	3	
2	4	1	3	
3	1	0	1	
Previous RT				
Yes	11 (17)	2 (18)	9 (82)	0.71
No	55 (83)	16 (29)	39 (71)	
Vertebral body count				
Single	48 (73)	10 (21)	38 (79)	0.07
Multiple	18 (27)	8 (44)	10 (56)	
Treatment type				
Definitive	44 (67)	8 (18)	36 (82)	0.04
Postop	22 (33)	10 (45)	12 (54)	

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TABLE 1. Patient and disease characteristics

Variable	No. (%)			p Value
	All Tumors	Recurrence	No Recurrence	
Fractionation				
Single fraction	31 (47)	5 (16)	26 (84)	0.10
Multifraction	35 (53)	13 (37)	22 (63)	
BED in Gy				
<50	11 (17)	5 (45)	6 (54)	0.19
50–59	40 (61)	11 (28)	29 (72)	
≥60	15 (23)	2 (13)	13 (87)	
Vital status at last FU				
Alive	9 (14)	2 (22)	7 (78)	1.0
Dead	57 (86)	16 (28)	41 (72)	

CA = cancer; Dediff = dedifferentiated; Dx = diagnosis; FU = follow-up; met = metastasis; MFH/UPS = malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; NA = not applicable.

Statistical Analysis

Descriptive statistics were used to evaluate baseline characteristics, and categorical data were analyzed using Fisher's exact test and chi-square analyses. Survival times were calculated from the start date of SSRS to the first occurrence of the considered event. The Kaplan-Meier method was used to estimate rates of overall survival (OS) and LC. Log-rank tests were applied to assess for equality across groups.

The Cox proportional-hazards model was used for univariate and multivariate analyses of OS. Multivariate assessment was done by backward elimination, with all factors with a $p \leq 0.25$ on univariate analysis included in the assessment. Estimated hazard ratios were reported when significant ($p \leq 0.05$). For LC and progression-free survival (PFS), a competing risk analysis was performed using the Fine and Gray method; death was treated as a competing risk. Estimated subhazard ratios (SHRs) were reported when significant ($p \leq 0.05$). A 2-sided 5% significance level was used for analysis. StataCorp statistical software version 13.1 was used for data analysis.

Results

Cohort Characteristics

Patient, tumor, and treatment characteristics are summarized in Table 1. The overall median age was 53 years (range 17–85 years), and 53% of the patients were female. The most commonly treated sarcoma histology was leiomyosarcoma (28 [42%]), followed by epithelioid sarcoma (9 [14%]) and malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma (8 [13%]).

At presentation, the majority of tumors were Bilsky Grade 0–1b (42 [64%]).² However, patients with higher degrees of cord compression (Bilsky Grades 1c–3) at presentation were more likely to undergo surgery ($p < 0.001$) than the patients with lower Bilsky grades. Therefore, at

the time of SSRS treatments, most tumors were Bilsky Grades 0–1b (57 [86%]), whereas 4 patients (6%) each had scores of 1c and 2.

The majority of lesions occurred within the thoracic vertebral bodies (40 [61%]) and only required treatment to a single vertebral body (48 [73%]). Most lesions were treated with definitive SSRS alone (44 [67%]) as opposed to SSRS postoperatively (22 [33%]), with a fairly equal distribution between single-fraction and multifraction regimens (31 [47%] vs 35 [53%], respectively).

A higher proportion of patients who had been treated with postoperative SSRS experienced local recurrence compared with those who had received definitive SSRS (45% vs 18%, $p = 0.04$). There were no other significant differences between patients with local relapse and those without, including Bilsky grade at the time of SSRS ($p = 0.67$; Table 1).

Patterns of Disease Recurrence

Nineteen patients (29%) developed local or adjacent vertebral body relapse—local only, 8 patients; in both locations, 10; and in the adjacent vertebral body alone, 1. The median time to any treatment failure was 8 months (range 1–71 months).

Actuarial 1- and 3-year LC rates were 81% and 61%, respectively (Fig. 1). Eighteen patients (27%) had local disease recurrence with a median time of 8 months to

failure (range 1–71 months). On multivariate modeling, with death as a competing risk factor, the 2 covariates independently associated with higher LC rates were single vertebral body involvement (vs multiple vertebral bodies, $p = 0.03$, SHR 0.27, 95% CI 0.08–0.85) and BED > 48 Gy (vs BED ≤ 48 Gy, $p = 0.006$, SHR 0.21, 95% CI 0.07–0.64; Table 2).

To better define patterns of failure, we evaluated local recurrences as infield (3 [17%]), at the margin within the isodose penumbra (14 [78%]), or out of field (1 [6%]; Table 3). Among the 3 cases of infield failures, 2 (67%) had leiomyosarcoma histology. Among the 14 cases of marginal local recurrences, 10 (71%) occurred within the epidural space; the other 4 cases had marginal recurrences within the paraspinal musculature. Retrospective review of these latter cases—3 leiomyosarcoma, 1 alveolar soft part sarcoma—revealed that the CTVs were probably too conservative. For the 1 out-of-field recurrence, retrospective review of pretreatment imaging revealed that the tumor outside the delineated target might have been present prior to treatment.

Overall Survival

Actuarial 1- and 3-year OS rates were 67% and 26% (Fig. 1), respectively, with a median OS of 17 months (range 1–121 months). When variables were assessed using a backward elimination technique, 3 covariates emerged

FIG. 1. Outcomes for patients with metastatic sarcoma treated with SSRS: OS (A) and LC (B). Patients with single vertebral body (SVB) involvement had better LC ($p = 0.01$, C), and those with definitive treatment had nearly significantly better LC than those who had postoperative SSRS ($p = 0.1$, D). MVB = multiple vertebral body.

TABLE 2. Actuarial 1- and 3-year LC rates and competing risk analysis of factors associated with LC

Parameter	1-Yr LC%	3-Yr LC%	Univariate Competing Risk	
			p Value	SHR (95% CI)
RT yr, continuous	—	—	0.15	0.90 (0.78–1.04)
Age at SSRS treatment, continuous	—	—	0.41	0.99 (0.95–1.02)
Sex				
Female	79	62		Reference
Male	84	59	0.94	0.97 (0.39–2.39)
Tumor type				
Leiomyosarcoma	82	80		Reference
Other	58	64	0.9	0.94 (0.38–2.36)
Spine section				
Cervical	80	80		Reference
Thoracic	80	61	0.81	1.17 (0.33–4.10)
Lumbosacral	82	56	0.75	1.26 (0.31–5.13)
Vertebral body count				
Multiple	50	50		Reference
Single	93	64	0.06	0.39 (0.14–1.06)
Previous RT				
No	79	59		Reference
Yes	90	0	0.51	0.62 (0.15–2.59)
Treatment type				
Definitive	87	70		Reference
Postop	71	44	0.07	2.31 (0.92–5.80)
Fractionation				
Multifraction	79	52		Reference
Single fraction	84	73	0.21	0.52 (0.19–1.44)
BED				
≤48 Gy	80	20		Reference
>48 Gy	81	66	0.04	0.33 (0.12–0.94)

as independent predictors of survival outcomes: 1) Karnofsky Performance Status (continuous, $p = 0.008$, HR 0.94, 95% CI 0.90–0.98), 2) local recurrence ($p = 0.001$, HR 0.18, 95% CI 0.07–0.51), and 3) time to local failure ($p < 0.001$, HR 1.00, 95% CI 1.00–1.00).

Toxicity

Based on the CTCAE version 4.3, there were 35 treatment-related acute toxicities (53%), all of which were either Grade 1 or 2 (no Grade 3 or 4; Table 4). The most common acute toxicity was fatigue (15 cases [23%] of Grade 1, 5 cases [8%] of Grade 2). Gastrointestinal toxicities were also relatively common (15 [23%]). There were 6 (9%) treatment-related instances of nausea, and the mid-spine (T5–L2) was the SSRS target in all of these cases. Additionally, there were 6 (9%) episodes of dysphagia (4 cases of Grade 2); 5 of those cases had received SSRS to the cervical spine. Pain flares were uncommon but occurred in 3 patients (4%) after SSRS, with 2 cases occurring in patients who had received single-fraction SSRS ($p = 0.48$).

TABLE 3. Characteristics of 18 local failures

Variable	No. (%)
Time to LR in mos	
Median	8
Range	1–71
Local failure type	
Infield	3 (17)
Marginal	14 (78)
Out of field	1 (6)
Marginal failure location	
Epidural	10 (71)
Paraspinal	4 (28)
Failure in adjacent vertebral bodies	
No	8
Yes	10
Explanation for LR	
Underdosed	15
Due to spinal cord	10
Due to RT vol	5
Uncertain/biology	3
Salvage for LR	
Supportive care	7
Surgery	5
RT	4
Surgery + RT	1
Systemic therapy	1

LR = local recurrence.

Late toxicities were less common. There were 4 insufficiency fractures (6%) occurring at a median time of 13 months post-SSRS (range 6–23 months), and they were not associated with single- versus multifraction SSRS regimens ($p = 0.36$). While 3 of the insufficiency fractures were relatively asymptomatic, 1 case was particularly concerning, causing severe spinal stenosis and associated myelomalacia, though notably without neuropathies. There were

TABLE 4. Acute and chronic treatment-related toxicities

Toxicity	Total No.	CTCAE Toxicity Score			
		1	2	3	4
Acute					
Fatigue	15	10	5		
Esophagitis	6	2	4		
Nausea	6	4	2		
Pain flare	3	1	2		
Diarrhea	3	2	1		
Dermatitis	2	2			
Chronic					
Insufficiency fracture	4	3		1	
Sensory neuropathy	2	1	1		
Motor neuropathy	1	1			

no cases of Grade 3 or 4 late neurological toxicities, but there were 2 patients (3%) with post-SSRS neuropathies, probably associated with treatment and not disease progression. One patient with a documented history of scleroderma developed both a Grade 1 motor neuropathy (right foot drop and decreased rectal tone) and a Grade 1 sensory neuropathy (bilateral lower-extremity numbness), approximately 13 months after definitive SSRS had been delivered. A separate patient developed neuritis, which caused lower-extremity hyperesthesias and paresthesias, also approximately 13 months following postoperative SSRS.

Discussion

Local management of sarcoma spinal metastases is challenging given the limited definitive surgical options, the radioresistant nature of this tumor, and the difficulty in delivering meaningful ablative doses using conventional RT. Therefore, the use of highly conformal high-dose SSRS may offer a way to improve outcomes for patients with metastatic sarcoma to the spine. In the current series, we observed favorable local tumor control using SSRS. However, patients who received SSRS after surgery had a higher rate of local recurrence, and a low BED was associated with poorer tumor control. According to our analysis of failure patterns, the majority of local failures were marginal recurrences, commonly occurring in the epidural space (Fig. 2). Importantly, however, several marginal recurrences probably happened because of insufficient treatment volume, particularly when there was soft-tissue extension. Despite relatively high rates of LC and a favorable toxicity profile associated with SSRS, OS remains poor given the limited systemic options for treating metastatic sarcomas.

With the wide adoption of SSRS,²⁰ multiple studies have reported high LC rates above 85% among all disease histologies.^{3,5,13,14,23,25,29} Among the few investigators specifically treating sarcomas, however, the LC rates are not as consistent.^{6,10,19} In the present study, we observed a favorable 1-year LC rate of 81%, which is lower than the rate for other histologies but consistent with the rates in 2 recent series reporting 1-year control rates of 88% and 78%.^{6,10} However, authors from the Cleveland Clinic observed a notably lower radiographic control rate (51% at 12 months).¹⁹ While this series by Miller and colleagues is a bit of an outlier, it does highlight the difficulty in treating these spine lesions.

Sarcomas have historically been viewed as a relatively radioresistant histology, which underscores the importance of RT dose for local tumor control (Fig. 3). In a study by Kepka and colleagues, higher conventional RT doses were associated with improved LC of gross primary disease (< 63 Gy, 22% vs $\geq$ 63 Gy, 60%; $p = 0.02$).¹⁷ In our study, we observed that a BED > 48 Gy (Gy/fractions: 24/1, 27/3, 18/1) was significantly associated with improved LC on univariate analysis ($p = 0.04$, SHR 0.33). Chang and colleagues also reported that higher RT doses were associated with improved 2-year LC rates (> 22 Gy, $p = 0.03$).⁶ Perhaps lower RT doses (median 16 Gy in 1 fraction, range 10–16 Gy) explain the poorer LC rates observed by Miller and colleagues (51% at 1 year),¹⁹ compared with our typi-

FIG. 2. Illustrative example of an epidural marginal recurrence following SSRS treatment. The patient in this case had metastatic sarcoma with epidural extension (A) that was surgically decompressed (B). It was then treated with SSRS (C) to a dose of 24 Gy in a single fraction to the GTV and 16 Gy to the CTV. Unfortunately, about 10 months later, the patient had a relapse in the epidural space (red dashed line and arrow, D). Note that this area could not be covered by the prescription dose of 24 Gy because of spinal cord constraints. Figure is available in color online only.

cal dose of 24 Gy in 1 fraction or the median dose of 24 Gy reported by authors at Memorial Sloan Kettering Cancer Center (1-year LC 88%).¹⁰

One interesting observation from our study is the higher rate of local recurrence in patients treated with postoperative SSRS than in those definitively treated with SSRS alone (45% vs 18%, $p = 0.04$). This translated into a lower, though not statistically significant, 1-year LC rate among postoperative SSRS patients (71% vs 87% for definitive SSRS, $p = 0.07$, SHR 2.31), with the definitive SSRS patients attaining an LC rate similar to our recently published rate (88%) among 332 spinal lesions.³ The high rate of local relapse following postoperative SSRS for sarcomas was also recently observed by Tao and colleagues,²⁶ who reported a 1-year LC rate of 58% for sarcoma histologies compared with 88% for nonsarcomatous histologies ($p = 0.025$). Several factors may contribute to a higher relapse rate among postoperative SSRS patients including fractionation, radiation dose, risk of surgical seeding, or radiobiological principles such as devascularization of the tissues resulting in less oxygen delivery.

Fractionation has been associated with LC outcomes of SSRS according to a study by Folkert and colleagues, in which the authors found single-fraction SSRS to be the only factor associated with LC on multivariate analysis ($p = 0.03$, HR 0.35).¹⁰ In contrast, most of the patients in our study who received postoperative SSRS were treated with multifraction regimens (17 [77%] of 22), commonly 27 Gy

FIG. 3. Illustrative example of an in-field recurrence following SSRS treatment. The patient in this case had metastatic sarcoma (**A**) that was treated with SSRS (**B**) to a dose of 18 Gy in a single fraction to the GTV (red color wash and red dashed lines) and 16 Gy to the CTV (vertebral body). Not surprisingly, 18 Gy was not a high enough dose to provide durable LC for this sarcoma histology, and the patient had a relapse (red dashed lines with arrows, **C**) within the irradiated field. Figure is available in color online only.

in 3 fractions (13 [76%] of 17). Interestingly, the 27 Gy in 3 fractions that we deliver postoperatively has a BED of 51 Gy, which is lower than what would be prescribed in the postoperative primary sarcoma setting and is far below the threshold for controlling gross disease.¹⁷ Therefore, while fractionation and the delivered BED may contribute to a higher relapse rate among postoperative SSRS sarcoma patients, the benefits of escalating treatment must be weighed against the risks of injury.

Another complicating feature of sarcoma is its infiltrative, locally aggressive growth patterns. This has treatment implications given the highly conformal delivery of SSRS with no consensus recommendations for treating infiltrating paraspinal disease. Therefore, we performed an analysis of failure patterns to better understand the association between target volume and local recurrences. Of the 18 local recurrences, 14 were classified as marginal failures. Not surprisingly, many of these local failures occurred in the epidural space, which is consistent with previous reports showing that adequate coverage of tumors involving the epidural space close to the spinal cord (within 2–5 mm) is challenging.^{3,5,24}

However, there were several local relapses that might have been avoided if larger treatment volumes had been used. We observed 4 marginal recurrences that all arose in the paraspinal soft tissue. At the time of treatment planning, there were probably inadequate CTV expansions applied to these cases to account for the microscopically invasive nature of sarcomas. Better definition of appropriate treatment volumes is particularly important given the high proportion of sarcoma patients who have paraspinal extension; in a report by Bilsky and colleagues, nearly 70% of the patients presenting with bone involvement also had soft-tissue extension.² Similarly, Miller and colleagues reported 60% of cases with paraspinal extension.¹⁹ They also found that involvement of the posterior elements was associated with radiographic failure ($p = 0.04$, HR 2.16), which may also be related to paraspinal extension. Given the relatively restrictive space for growth within the posterior elements, metastatic deposits tend to erode through the bony cortex and extend into the paraspinal space. If adequate CTV expansions are not applied, local tumor control is less likely.

Several years ago the International Spine Radiosurgery

Consortium published a recommendation for guidance on SSRS contouring.⁹ While it expressly recommended no extraosseous CTV expansion for bone-only disease, there were no specific guidelines for coverage of paraspinal extension of disease or paraspinal metastases. Alternatively, if we examine the guidelines for target delineation of extremity sarcomas, 2 consensus statements recommend a 3- to 4-cm longitudinal expansion of the GTV and a 1.5-cm radial expansion.^{15,27} These recommendations are based on historical pathological studies, including one showing that 60% of cases with satellite tumor cells outside the primary sarcoma tumor were within 1 cm, whereas 40% were within 1–4 cm.²⁸ Therefore, if we extrapolate from the available literature, for sarcomas metastatic to vertebral bodies that erode through the cortex into the paraspinal soft tissue, we recommend considering a larger radial CTV expansion (perhaps 1.5 cm) into soft tissue since this type of growth may be less longitudinally infiltrative along fascial planes. However, perhaps sarcomas metastatic directly to the paraspinal tissues warrant target delineation more similar to primary sarcomas with a generous longitudinal CTV expansion along the paraspinal musculature.

This study provides additional evidence of durable LC rates using SSRS for sarcoma metastases and, importantly, contributes a unique pattern-of-failure analysis to help reconcile the 2 vastly different RT paradigms. However, as with any retrospective analysis, there are inherent limitations when interpreting the results. First, while this study represents a relatively large series, considering the paucity of data for SSRS to sarcoma metastases, the number of patients and subsequent local recurrences are few, which limits the robustness of the analysis. Second, this study does incorporate patients enrolled in our early institutional trials, which may have treated patients more conservatively than is our current practice. Third, while about half of the patients in the current study were followed prospectively, some of the toxicity data were retrospectively extracted. The most commonly observed acute toxicity was fatigue (23%), and there were no Grade 3 toxicities; Folkert and colleagues reported similar acute toxicities.¹⁰ We also observed few late toxicities (4 compression fractures, 3 neuropathies), but we acknowledge the difficulty in retrospectively identifying treatment-related side effects.

Conclusions

Spine stereotactic radiosurgery for sarcoma metastases is a viable option for providing durable LC with minimal toxicity. According to our data and the available literature, doses ≥ 22 Gy in a single fraction provide optimal tumor control.^{6,10} Additionally, we observed a higher rate of local relapse in postoperative SSRS cases, which is also probably attributable to the RT dose and fractionation. In our analysis of patterns of failure, we found that the majority of relapses occurred within the epidural canal. However, in a small proportion of cases, more generous treatment volumes could minimize the risk of relapse. Specifically, in cases with paraspinal extension eroding through bone cortex, we recommend considering a larger CTV expansion (perhaps 1.5 cm) into the soft tissue, which is extrapolated from existing sarcoma consensus guidelines. For patients who have paraspinal metastases, more generous longitudinal expansions are probably warranted. In our continued pursuit of improved SSRS target delineation and conformity, we should remember the biological behavior of individual cancer types and the principles by which they shape our treatment volumes.

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Disclosures

Dr. Chang has received honoraria from Elekta and BrainLab for travel and speaking engagements. Dr. Rhines is a consultant for Stryker and Globus.

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Conception and design: Bishop, Tao, Ghia. Acquisition of data: Bishop, Tao. Analysis and interpretation of data: Bishop, Tao, Ghia. Drafting the article: Bishop, Tao, Guadagnolo, Ghia. 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: Bishop. Statistical analysis: Bishop, Allen.

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