Original Article

A Multi-Institutional Phase 2 Trial of Stereotactic Body Radiotherapy in the Treatment of Bone Metastases in Pediatric and Young Adult Patients With Sarcoma

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BACKGROUND: Metastasectomy is standard of care for pediatric patients with metastatic sarcoma with limited disease. For patients with unresectable disease, stereotactic body radiotherapy (SBRT) may serve as an alternative. Herein, the authors report the results of a prospective, multi-institutional phase 2 trial of SBRT in children and young adults with metastatic sarcoma. **METHODS:** Patients aged >3 years and ≤40 years with unresected, osseous metastatic nonrhabdomyosarcoma sarcomas of soft tissue and bone were eligible. Patients received SBRT to a dose of 40 Gray (Gy) in 5 fractions. Local control (LC), progression-free survival (PFS), and overall survival (OS) were calculated using the Kaplan-Meier method. **RESULTS:** Fourteen patients with a median age of 17 years (range, 4-25 years) were treated to 37 distinct metastatic lesions. With a median follow-up of 6.8 months (30.5 months in surviving patients), the Kaplan-Meier patient-specific and lesion-specific LC rates at 6 months were 89% and 95%, respectively. The median PFS was 6 months and the median OS was 24 months. In a post hoc analysis, PFS (median, 9.3 months vs 3.7 months; log-rank $P = .03$) and OS (median not reached vs 12.7 months; log-rank $P = .02$) were improved when all known sites of metastatic disease were consolidated with SBRT compared with partial consolidation. SBRT was well tolerated, with 2 patients experiencing grade 3 toxicities. **CONCLUSIONS:** SBRT achieved high rates of LC in pediatric patients with inoperable metastatic nonrhabdomyosarcoma sarcomas of soft tissue and bone. These results suggest that the ability to achieve total consolidation of metastatic disease with SBRT is associated with improved PFS and OS. ***Cancer* 2020;0:1-9**. © *2020 American Cancer Society*.

KEYWORDS: neoplasm metastasis, pediatrics, radiotherapy, sarcoma.

INTRODUCTION

Approximately 20% of solid malignancies in children are sarcomas.[1] Malignant bone tumors including Ewing sarcoma and osteosarcoma account for approximately 40% of pediatric sarcomas, with soft-tissue sarcomas comprising the remaining 60%.[2,3] Improvements in systemic therapy, radiotherapy (RT), and surgical techniques have improved survival in patients with localized disease,[4-7] but the prognosis remains poor for patients with metastatic disease and more effective therapies are needed.[6,8-13]

Although multiagent systemic therapy is the mainstay of treatment for patients with metastatic pediatric sarcoma, it is unfortunately not curative and may cause significant toxicities when used for an extended duration. As such, patients with limited metastatic disease often are treated with surgical metastasectomy combined with systemic therapy to improve survival and provide an opportunity for cure.[10,14-31] However, many patients are not eligible for surgical resection and conventionally fractionated RT is unlikely to provide durable local control for radioresistant histologies.[31-35] In addition, conventionally fractionated RT requires prolonged breaks from full-dose systemic therapy.

As an alternative, stereotactic body RT (SBRT) allows for the delivery of ablative doses to small volumes with a steep dose gradient to spare surrounding normal structures. Although SBRT is increasingly used in adult patients for the treatment of oligometastatic disease,[36-44] to our knowledge there are limited data regarding its safety and efficacy in a pediatric population.[45,46] There is a particularly strong rationale for SBRT in this population as a strategy to reduce dose to nontarget tissues and potentially reduce the late effects of RT. In addition, the noninvasive nature and convenient fractionation schedule of SBRT allows for minimal treatment breaks from systemic therapy. Finally, SBRT allows for biological dose escalation that

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may improve local control in patients with sarcoma, which is considered to be a radioresistant histology.[34,36]

In the current study, we report the results of a prospective, multi-institutional, phase 2 trial designed to examine the efficacy and toxicity of SBRT in a pediatric and young adult population with nonrhabdomyosarcoma (NRMS) sarcomas of soft tissue and bone metastatic to bone.

MATERIALS AND METHODS

Study Design and Patients

The current study was a prospective, multi-institutional, single-arm, phase 2 study of SBRT for the treatment of bone metastases in patients with pediatric sarcomas. The protocol was opened at 4 institutions and patients were enrolled from 3 institutions from August 2014 through September 2018. Eligible patients were aged >3 years and ≤40 years with NRMS sarcomas of soft tissue and bone of any primary site and were treated according to a pediatric paradigm. Patients were required to have histologically or cytologically confirmed metastatic disease with measurable osseous metastases, defined as at least 1 lesion that could be accurately measured in at least 1 dimension as ≥20 mm using conventional techniques (eg, plain films or bone scan) or as ≥10 mm using spiral computed tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks of the initiation of SBRT. Included tumors in all sites had a maximal axial dimension (MAD) of ≤5 cm or <250 cm^3 (volumetric). Patients were required to have surgically unresectable disease, which was defined as surgical or medical inoperability as determined by a multidisciplinary tumor board or surgeon. Patients who refused surgical resection also were eligible. Patients were required to have a life expectancy of ≥9 months (based on the opinion of the treatment team) and a Lansky performance status ≥50. Physicians were permitted to treat up to 5 distinct lesions per patient.

Patients were excluded if they: 1) had received prior chemotherapy or RT within 2 weeks prior to the initiation of RT; 2) had received any prior RT to the treatment site; 3) were pregnant or were females of childbearing potential who refused a pregnancy test; or (4) had rhabdomyosarcoma (RMS) histology due to the radiosensitive nature of their disease. Patients were not allowed to participate in concurrent clinical trials, but all patients were eligible to receive systemic therapy at the time of clinical or radiographic disease progression or at 2 weeks after the completion of SBRT.

The institutional review board or ethics committee at each participating institution approved the protocol and all amendments.

RT Specifications and SBRT Technique

Prior to treatment initiation, all patients were required to have dedicated diagnostic imaging of the lesion. This could be a CT, MRI (required for spine sites), or positron emission tomography (PET) scan. Prior to treatment, a CT simulation using 1-mm to 3-mm slice thickness was performed using custom-made, rigid immobilization appropriate for stereotactic treatment. All organs at risk 5 to 10 cm superior and inferior to the target were contoured for dose volume histogram analysis. If the target lesion was located in an area subject to motion during treatment, techniques to image and treat moving targets were permitted.

SBRT was planned to a dose of 40 Gray (Gy) in 5 daily fractions (8 Gy per fraction). Patients ideally were treated on 5 consecutive days but were allowed a 14-day treatment interval to account for unforeseen circumstances or missed days. An attending radiation oncologist delineated the macroscopic (gross) tumor target volume (GTV). For bone sites aside from the spine, the GTV was isometrically expanded by 2 mm to create the planning target volume (PTV). For nonspinal sites, >90% of the PTV was required to receive 40 Gy. For patients with spinal metastases who were undergoing treatment on protocol, the vertebral body was contoured as a separate clinical target volume and the clinical target volume was isometrically expanded by 2 mm to create the PTV. The GTV was treated to 40 Gy and the PTV to 30 Gy. The spinal cord dose constraints were 20.2 Gy to a volume of <0.25 cm^3, 12.1 Gy to a volume of <1.2 cm^3, or a maximum point dose of 27 Gy in 5 fractions. The cauda equina dose constraints were 27 Gy to a volume of <5 cm^3 or a maximum point dose of 28.8 Gy in 5 fractions. Other protocol dose constraints for organs at risk are provided (see Supporting Table 1). Dose constraints were based on the American Association of Physicists in Medicine (AAPM) Task Group 101 report.[47] Protocol dose constraints were reduced by 10% based on the assumption that patients on protocol have received prior systemic therapy that could increase sensitization of normal tissues to RT. Daily image guidance with cone beam CT was required.

Follow-Up and Endpoints

Patients were seen in follow-up at 1 month, every 3 months for 3 to 12 months, and every 6 months from 12 to 36 months after receipt of SBRT. Patients remained on protocol until there was evidence of local or distant disease progression. At the time of disease progression,

patients were removed from the study and followed for survival only.

The primary endpoint was lesion-specific local control at 6 months after SBRT. Of note, bone healing and remodeling may lead to persistent imaging abnormalities after RT to bone sites, even in the absence of residual disease. Given the inherent difficulties in using Response Evaluation Criteria in Solid Tumors (RECIST) in defining response in osseous lesions after RT, local control was defined as the absence of local disease progression. Local disease progression was defined as: 1) the development of a new soft-tissue mass ≥1 cm in MAD at a site without a soft-tissue component or with a soft-tissue component measuring <1 cm in MAD at baseline; 2) an increase in the MAD of the soft-tissue component by >20% in lesions with a soft-tissue component measuring ≥1 cm in MAD at baseline; and 3) a previous bone metastasis that was found to be avid on [^{18}F]fludeoxyglucose–PET, became nonavid after SBRT, and then became avid again. In the last instance, either a contrast-enhanced MRI or a biopsy was required to confirm disease progression.

Secondary endpoints were progression-free survival (PFS; defined as the time from the initiation of SBRT to first documented disease progression at any location or death due to any cause, whichever occurred first), overall survival (OS; defined as the time from the initiation of SBRT until death due to any cause), toxicity, and pain response. Patients without documented death or disease progression at the end of protocol follow-up or at the time of analysis were censored at the date of last follow-up. Toxicity was described using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[48] Pain response was evaluated using the Brief Pain Inventory (BPI) at each designated follow-up evaluation.

Statistical Analysis

Kaplan-Meier estimates were provided for: 1) lesion-specific local control, measured separately for each lesion treated within a patient; and 2) patient-specific local control, PFS, and OS. A post hoc analysis was performed for hypothesis generation. For this analysis, patient charts were reviewed retrospectively to determine whether patients had all known sites of metastatic disease treated with SBRT (total consolidation) or only some sites treated with SBRT (partial consolidation). The log-rank test was used to compare PFS and OS among patients treated with total consolidation compared with those treated with partial consolidation. Univariable and multivariable Cox regression analyses were performed to evaluate the influence of covariates on PFS and OS. Paired-sample Wilcoxon signed-rank tests were performed to assess changes in pain scores on the BPI. Results with a P <.05 were considered to be statistically significant. Toxicity was assessed using descriptive analyses.

Statistical analyses were performed using Stata statistical software (version 16.0; StataCorp LLC, College Station, Texas). This study is registered with ClinicalTrials.gov (ClinicalTrials.gov identifier NCT01763970).

RESULTS

Patient and Treatment Characteristics

From August 2014 to September 2018, a total of 14 patients were enrolled; the patients had a median age of 17 years (range, 4-25 years) and 37 distinct sites of osseous metastatic disease were treated. Nine of the 14 patients (64%) were aged <18 years. The majority of patients (64%) were male and White (64%), with a median baseline Lansky performance status of 90 (range, 70-100). Seven patients had Ewing sarcoma, 3 patients had osteosarcoma, and 4 patients had high-grade soft-tissue sarcomas. Patients were treated to a median of 3 lesions (range, 1-5 lesions). All patients received systemic therapy prior to RT. Eight patients (57%) had all known sites of metastatic disease treated with SBRT (total consolidation) whereas 6 patients had only a portion of the known sites of metastatic disease treated with SBRT (partial consolidation). Six patients (43%) reported pain at baseline whereas 8 patients (57%) reported no pain. Patient characteristics are summarized in Table 1.

All patients were treated with SBRT to a total dose of 40 Gy in 5 fractions of 8 Gy per fraction. The median treatment duration was 7 days (range, 5-15 days), including patients with multiple sites of disease (isocenters) who did not initiate treatment concurrently. Treatment sites included the skull (1 lesion), pelvis (6 lesions), extremities (9 lesions), and spine (21 lesions). Baseline measurements of the longest tumor dimension were recorded for 32 lesions, and the median dimension was 2.0 cm (range, 0.7-3.3 cm).

Disease Control and Survival

The median follow-up was 6.8 months (range, 1.1-36.2 months) in all patients and 30.5 months (range, 1.4-36.2 months) in the 6 patients who were still alive at the time of last follow-up. Patient-specific local

TABLE 1. Demographic Characteristics of Patients at Baseline

Characteristic	Patients N = 14
Age, y	
Median	17
Range	4-25
Sex	
Male	9
Female	5
Race	
White	9
Non-White	5
Lansky performance status	
Median	90
100	3
80-90	10
70	1
Histology	
Ewing sarcoma	7
Osteosarcoma	3
Soft-tissue sarcoma	4
No. of sites treated	
Median	3
1	4
2	1
3	6
	2
5	1
Consolidation of metastatic disease	
Total	8
Partial	6
Prior systemic therapy	
Yes	14
Pain at baseline	
Yes	6
No	8

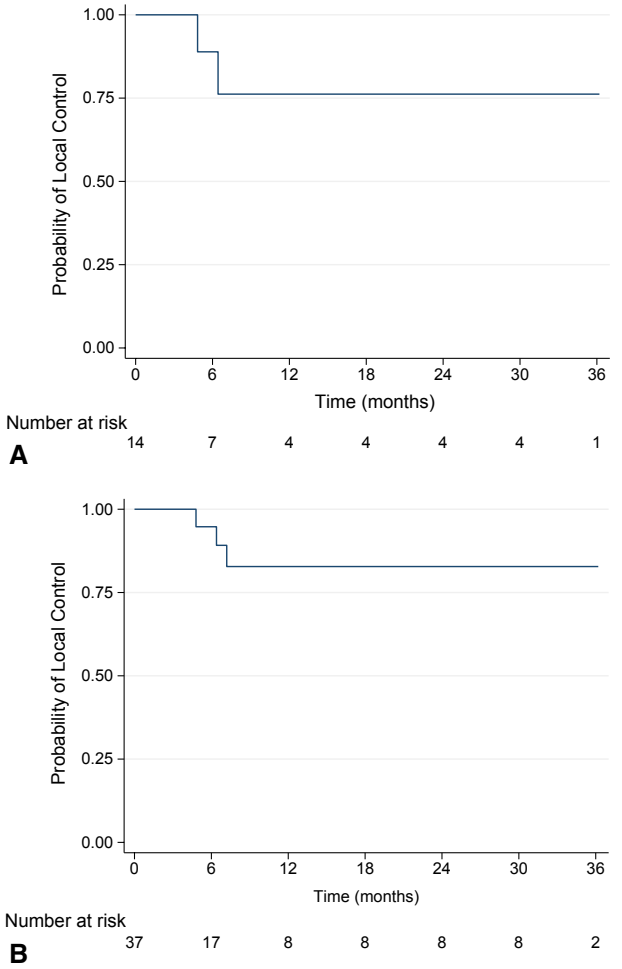

Figure 1. (A) Patient-specific (14 patients) and (B) lesion-specific (37 lesions) Kaplan-Meier plot from time of initiation of stereotactic body radiotherapy (SBRT) until local failure.

tumor control at 6 months was 89% (95% confidence interval [95% CI], 43%-98%) (Fig. 1A), and lesion-specific local control at 6 months was 95% (Fig. 1B). The median PFS was 6 months, and the 6-month and 12-month PFS rates were 50% (95% CI, 47%-93%) and 29% (95% CI, 9%-52%), respectively (Fig. 2A). The median OS was 24 months, and the 6-month, 12-month, and 24-month OS rates were 100%, 84% (95% CI, 49%-96%), and 50% (95% CI, 21%-74%), respectively (Fig. 2B). Among patients with Ewing sarcoma, there was no difference noted with regard to lesion-specific local control (log-rank $P = .77$), patient-specific local control (log-rank $P = .98$), PFS (log-rank $P = .37$), or OS (log-rank $P = .22$) when compared with patients with osteosarcoma and other soft-tissue sarcoma histologies.

A post hoc analysis was performed to determine the effect of total consolidation versus partial consolidation on PFS and OS. Eight patients had all known sites of metastatic disease treated with SBRT and 6 patients received treatment to a portion of the known metastatic sites. For patients treated with total consolidation, the mean number of sites of metastatic disease at the time of SBRT was 2.3 (SD, 1.2 sites) compared with a mean of 8.7 sites (SD, 5.4 sites) in patients treated with partial consolidation ($P = .03$). For patients with all lesions consolidated by SBRT, the median PFS was 9.3 months, which was significantly longer than that of patients who received partial consolidation (median PFS, 3.7 months; log-rank $P = .03$) (Fig. 3A). In patients who were totally consolidated, the median OS was not reached, as compared with a median OS of 12.7 months in patients who were partially consolidated (log-rank $P = .02$) (Fig. 3B). On univariable analysis, patients aged >17 years had inferior PFS compared with patients aged ≤17 years (hazard ratio [HR], 4.88; 95% CI, 1.11-21.46 [$P = .04$]), and patients treated with total consolidation had improved PFS compared with those who received partial consolidation (HR, 0.24; 95% CI, 0.06-0.97

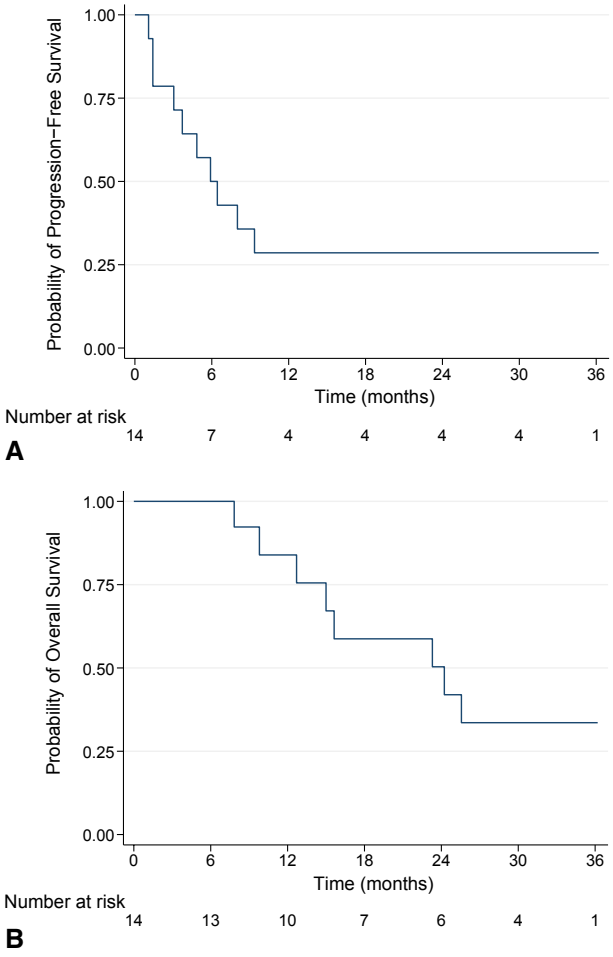

Figure 2. Kaplan-Meier plot of (A) progression-free survival from time of initiation of stereotactic body radiotherapy (SBRT) until any disease progression or death and (B) overall survival from time of initiation of SBRT until death.

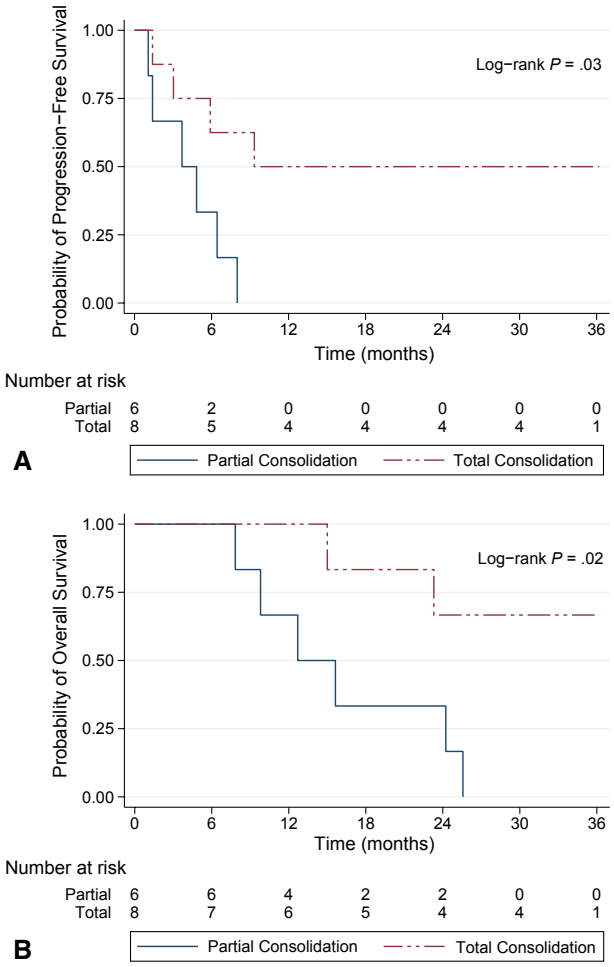

Figure 3. Kaplan-Meier plot of (A) progression-free survival and (B) overall survival in patients who received stereotactic body radiotherapy as total consolidative therapy or partial consolidative therapy.

[P = .046]). However, on multivariable analysis with both covariates included, there was no statistically significant difference noted with regard to the risk of disease progression by age or consolidation status. Similarly, on univariable analysis for OS, patients with a Lansky performance status of 70 to 80 had an increased risk of death compared with patients with a score of 90 to 100 (HR, 6.97; 95% CI, 1.12-43.38 [P = .04]), whereas patients who received total consolidation had a decreased risk of death compared with those who received partial consolidation (HR, 0.17; 95% CI, 0.03-0.88 [P = .035]). However, on multivariable analysis with both covariates included, neither variable had a statistically significant effect on the risk of death (Table 2). At the time of the analysis, there were 4 patients (29%) with both local and distant disease control. All 4 patients had been treated with total consolidation and had no evidence of active disease.

Toxicity

Toxicity is summarized in Table 3. Nine patients experienced a total of 16 reported toxicities that were potentially related to SBRT. The majority of recorded toxicities were grade 1 (12 of 16 toxicities; 75%). Two patients experienced grade 3 toxicities. One 20-year-old patient treated to T9 developed grade 3 esophagitis while receiving treatment and was unable to tolerate solid foods for several days. The patient was managed medically with enteral nutritional support (supplemental shakes) and opiate analgesics and was tolerating a full diet by the next follow-up 1 month later. This patient did not require tube feeds or hospitalization due to dysphagia. The patient received

TABLE 2. Univariable and Multivariable Cox Regression Analysis

Characteristic	Progression-Free Survival				Overall Survival			
	Univariable Analysis HR (95% CI)	*P*	Multivariable Analysis[a] HR (95% CI)	*P*	Univariable Analysis HR (95% CI)	*P*	Multivariable Analysis[a] HR (95% CI)	*P*
Age (>17 y vs ≤17 y)	4.88 (1.11-21.46)	.04[b]	2.57 (0.36-18.37)	.35	2.35 (0.58-9.48)	.23		
Race (non-White vs White)	1.76 (0.48-6.41)	.39			1.51 (0.36-6.36)	.58		
Sex (female vs male)	0.36 (0.08-1.73)	.20			0.37 (0.07-1.84)	.22		
Histology (other vs Ewing sarcoma)	1.67 (0.47-6.00)	.43			1.37 (0.34-5.53)	.65		
LPS (70-80 vs 90-100)	2.63 (0.65-10.61)	.17			6.97 (1.12-43.38)	.04[b]	3.1 (0.43-22.16)	.26
Consolidation (total vs partial)	0.24 (0.06-0.97)	.046[b]	0.42 (0.06-2.89)	.38	0.17 (0.03-0.88)	.04[b]	0.24 (0.04-1.47)	.12

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LPS, Lansky performance status.
[a]Includes covariates found to have a significant association on univariable analysis.
[b]Indicates statistical significance at $P < .05$.

TABLE 3. Treatment Toxicities Potentially Attributable to SBRT

Age of Patient, Years	Site(s) Treated	Toxicity Reported	CTCAE (Version 4.0) Grade	Time of Toxicity[a]
17	Humeral head, pterygoid process of the sphenoid	Alopecia	1	1 mo
		Nasal congestion	1	1 mo
20	Humeral head, T9, L3	Esophagitis	3	On treatment
19	C6, T12, L2, L4	Fatigue	1	On treatment
25	T12, L2, L4	Lower lumbar/sacral back pain	1	1 mo
		Lower extremity weakness	1	1 mo
		Lower lumbar/sacral back pain	2	3 mo
16	Distal radius	Wrist pain	1	12 mo
		Soft-tissue necrosis (osteonecrosis) wrist	3	22 mo
		Fracture	3	35 mo
4	Ilium and ischium	Skin hyperpigmentation	1	9 mo
17	L3	Fatigue	1	1 mo
		Back pain	1	1 mo
5	T1	Compression fracture	1	6 mo
17	Ischium, pubic ramus, femur	Paresthesia of the lower extremity	1	3, 6, 12 mo
		Back pain	1	12 mo

Abbreviations: CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SBRT, stereotactic body radiotherapy.
[a]Time of toxicity was defined as the elapsed time from the initiation of SBRT to documented toxicity. Each row represents 1 individual patient.

24.7 Gy to a volume of 4.7 cm^3 and met the protocol volumetric dose constraint but the maximum point dose to the esophagus was 43.4 Gy, which exceeded the maximum point dose constraint of the protocol of 31.5 Gy. A second patient with severe treatment-related osteoporosis was treated to the distal radius. This patient developed necrosis of the distal radius requiring curettage and bone grafting approximately 22 months after the completion of SBRT. The patient subsequently developed a fracture requiring surgical repair at the bone graft site approximately 35 months after SBRT.

Pain Response

BPI forms were completed for 10 patients (71%) at baseline and at 1 month after SBRT. There was no statistically significant difference noted between baseline and 1 month post-SBRT scores for worst pain (baseline mean: 3.0 [SD, 3.7] vs 1-month mean: 2.5 [SD, 3.4]; $P = .06$), least pain (baseline mean: 1.2 [SD, 2.2] vs 1-month mean: 1.1 [SD, 1.7]; $P = 0.63$), average pain (baseline mean: 2.0 [SD, 2.4] vs 1-month mean: 2.1 [SD, 2.8]; $P = 0.63$), or current pain (baseline mean: 1.0 [SD, 2.1] vs 1-month mean: 1.3 [SD, 2.1]; $P = 1.0$). In addition, there were no differences in pain interference scores for each of the 7 items (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life).

DISCUSSION

To the best of our knowledge, the current study is the first multi-institutional prospective trial evaluating the role and outcomes of SBRT in pediatrics. Pediatric and young

adult patients with bone and soft-tissue sarcomas with limited metastatic disease are potentially curable with effective systemic therapy and local treatment. Although surgical resection of metastases and systemic therapy remain the standard of care, many patients cannot or will not undergo surgical resection due to anatomic factors, comorbidity, or patient preference. SBRT may provide an alternative that is convenient, noninvasive, and requires minimal disruption in systemic therapy, allowing a potential avenue for cure.

This phase 2 trial was conducted to examine the efficacy and toxicity of SBRT in patients with pediatric sarcoma with unresectable bone metastases. SBRT provided excellent 6-month local control (89% patient-specific control and 95% lesion-specific control) and was well tolerated with minimal, acceptable toxicity. Only 2 patients experienced grade 3 toxicities, and no grade 4 or 5 toxicities were observed. On post hoc analysis, total consolidation of metastatic disease with SBRT was associated with improved PFS and OS compared with partial consolidation.

These results are consistent with 2 retrospective studies that have examined the role of SBRT in patients with metastatic pediatric osteosarcoma or Ewing sarcoma. In 1 single-institution retrospective series, 14 patients treated with SBRT were reviewed.[46] Of 27 lesions, 14 were treated with definitive or curative intent and 13 with palliative intent. The authors reported an estimated 2-year local control rate of 85% among lesions treated with definitive intent. In this series, 1 patient experienced late grade 3 sacral plexopathy, and 2 patients experienced late grade 2 toxicities (myositis and avascular necrosis of the hip complicated by pathologic fracture).[46] In a second retrospective review, 7 patients were treated to 11 spinal lesions with SBRT to a median dose of 35 Gy in 5 fractions.[49] With a median follow-up of 11.1 months, the authors reported a local control rate of 73%. In this series, 1 patient developed late grade 3 radiation enteritis after undergoing reirradiation with SBRT as well as concurrent chemotherapy (ifosfamide, carboplatin, and etoposide) and adjuvant chemotherapy (gemcitabine and docetaxel).[49]

In addition, the findings of our post hoc analysis that suggest total consolidation of metastatic disease with SBRT is associated with improved PFS and OS are consistent with emerging studies that have shown similar benefits in adult patients with oligometastatic disease who are treated with local consolidation (surgery or RT)[37,38,41,50,51] as well as in patients with metastatic pediatric sarcoma.[10,16-18,24,29-31,52-54] A subset analysis of patients registered in the European Ewing Tumor Working Initiative of National Groups Ewing Tumour Studies 1999 (EURO-EWING 99) trial revealed that patients with de novo metastatic disease who received local therapy to primary and distant metastatic sites had improved 3-year event-free survival versus any local therapy to the primary site or distant metastatic sites or no local therapy at all (39% vs 17% vs 14%, respectively; $P < .001$).[52]

Despite these supportive data from the adult population, we acknowledge the possibility that the total consolidation group in the current study may have had longer OS than the partial consolidation cohort regardless of SBRT due to a lower burden of metastatic disease in the total consolidation group. It may be that the ability to achieve total consolidation due to limited disease, not the independent effect of consolidative SBRT, is associated with prolonged survival. With regard to differences in PFS by consolidation status, partially consolidated patients with untreated metastatic sites could be expected to progress at untreated sites sooner than a fully consolidated patient is able to develop new, measurable progression of disease. Because these possibilities cannot be excluded, we considered conclusions regarding our post hoc analysis to be exploratory, and future prospective investigation is needed to better characterize the impact of consolidation status. Regardless of the underlying mechanism, these data highlight the ability to achieve total consolidation as a meaningful prognostic variable.

The strength of the current study was the use of a prospective, multi-institutional design with a standardized dose to examine the use of SBRT in a previously unstudied patient population. Limitations included the small sample size and histological heterogeneity. Due to the rarity of pediatric sarcomas, all sarcoma histologies were included except RMS due to its marked radiosensitivity and durable response to conventionally fractionated RT. The heterogeneity of histologies limits the relevance of historical comparisons to homogenous patient populations. In addition, as patients progressed systemically, they were not required to undergo imaging to assess lesion-specific local control and thus, we were limited in our ability to report long-term local control rates for surviving patients. Finally, our evaluation of pain response after SBRT was limited due to the small number of patients reporting baseline pain. However, SBRT has been shown to be an effective treatment for the palliation of pain in adult patients with symptomatic bone metastases,[55] and further prospective studies are needed to determine the efficacy of SBRT for the

palliation of pain due to bone metastases in pediatric patients.

The results of the current study have demonstrated that SBRT can be used for the treatment of unresectable bone metastases in children and young adults with metastatic NRMS sarcomas of bone and soft tissue. Local control rates at 6 months are excellent and treatment appears to be well tolerated. Patients who have all sites of metastatic disease consolidated with SBRT may have improved PFS and OS, although further study to confirm this finding is needed. Given the limited treatment options in the metastatic setting in children and young adults with bone and soft-tissue sarcomas, SBRT to metastatic sites should be considered when feasible.

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CONFLICT OF INTEREST DISCLOSURES

Matthew M. Ladra has received honoraria for speaking engagements from ProKnow for work performed outside of the current study. Sara R. Alcorn is employed by the Johns Hopkins University School of Medicine; has received grants from Elekta, the National Institutes of Health (grant 5KL2TR001077), and the Radiation Oncology Institute (ROI2020-913); has received nonfinancial support from AngioDynamics; and has received personal fees from the Allegheny Health Network for work performed outside of the current study. Iris C. Gibbs has received honoraria and paid speaking fees from Accuray Inc for work performed outside of the current study. Stephanie A. Terezakis has received institutional research funding from ASELL LLC for work performed outside of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Christen R. Elledge: Data curation, formal analysis, methodology, visualization, and writing–original draft. **Matthew J. Krasin:** Conceptualization, investigation, methodology, writing–review and editing. **Matthew M. Ladra:** Investigation and writing–review and editing. **Sara R. Alcorn:** Formal analysis, validation, and writing–review and editing. **Peijin Han:** Formal analysis, validation, and writing–review and editing. **Iris C. Gibbs:** Conceptualization, methodology, and writing–review and editing. **Susan M. Hiniker:** Conceptualization, methodology, and writing–review and editing. **Nadia N. Laack:** Conceptualization, investigation, methodology, and writing–review and editing. **Stephanie A. Terezakis:** Conceptualization, investigation, methodology, supervision, visualization, and writing–review and editing.

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