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Scientific Article

Clinical Outcomes Among Patients Treated With Stereotactic Body Radiation Therapy to Femur Metastases for Oligometastatic Disease Control or Reirradiation: Results From a Large Single-Institution Experience

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Purpose: There are limited data regarding outcomes after stereotactic body radiation therapy (SBRT) for femur metastases, which was an exclusion criteria for the Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers (SABR-COMET) trial. We aimed to characterize clinical outcomes from a large single institution experience.

Methods and Materials: Forty-eight patients with 53 lesions were consecutively treated with femur SBRT from May 2017 to June 2022. The Kaplan-Meier method and Cox proportional hazard models were used to characterize time-to-event endpoints and associations between baseline factors and clinical outcomes, respectively. Local control and locoregional control were defined as the absence of tumor progression within the radiation treatment field or within the treated femur, respectively.

Results: Most patients had Eastern Cooperative Oncology Group performance status 0 to 1 (90%), prostate (52%) or breast/lung (17%) cancer, and 1 to 3 lesions (100%), including 29 proximal and 5 distal. Fifty-seven percent of the lesions were treated with concurrent systemic therapy. Median planning target volume was 49.1 cc (range, 6.6-387 cc). Planning target volume V100 (%) was 99% (range, 90-100). Fractionation included 18 to 20 Gy/1F, 27 to 30 Gy/3F, and 28.5-40 Gy/5F. Forty-two percent had Mirels score ≥7 and most (94%) did not have extraosseous extension. Acute toxicities included grade 1 fatigue (15%), pain flare (7.5%), nausea (3.8%), and decreased blood counts (1.9%). Late toxicities included fracture (1.9%) at 1.5 years and osteonecrosis (4%) from dose of 40 Gy in 5F and 30 Gy in 5F (after prior 30 Gy/10F). One patient (2%) required fixation postradiation for progressive pain. With median follow-up 19.4 months, 1- and 2-year rates of local control were 94% and 89%, locoregional control was 83% and 67%, progression-free survival were 56% and 25%, and overall survival were 91% and 73%. Fifty percent of local regional recurrence events occurred within 5 cm of gross tumor volume.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: Femur SBRT for oligometastatic disease control in well-selected patients was associated with good outcomes with minimal rates of acute and late toxicity. Patterns of local regional recurrence warrant consideration of larger elective volume coverage. Additional prospective study is needed.

Introduction

Bone metastases impact up to 20% of patients with advanced cancer.[1] Skeletal-related events can impair quality of life and increase the risk of death.[2,3] The proximal femur is the most common site of pathologic involvement in the appendicular skeleton and at particular risk of fracture due to its role in weight-bearing.[3]

Palliative radiation has commonly been used to alleviate painful femur metastases and reduce fracture risk.[4] Patients who may benefit from prophylactic fixation may be identified using the Mirels criteria, which combines radiographic and clinical factors to identify long bones at high risk of fracture after irradiation.[5] Systemic treatment, and pain or bone-modifying agents, or radiopharmaceuticals, also play important roles for femur management, which frequently involves a multimodal approach.

Stereotactic body radiation therapy (SBRT) enables the delivery of ablative doses of radiation and has become increasingly adopted to address oligometastatic bone disease, in the setting of radioresistant histologies, reirradiation, and for potential benefits in pain control.[6-9] However, there remains limited data regarding the safety or efficacy of femur SBRT.[10] The SABR-COMET[11-13] trial demonstrated survival benefits of comprehensive SBRT for patients with oligometastatic disease and a controlled primary tumor but excluded patients with femur metastases. A randomized clinical trial comparing single-fraction SBRT to conventional palliative radiation therapy (RT) for nonspine bone metastases included only 18% of patients with extremity lesions.[9] A recent retrospective multicenter pooled analysis of SBRT for long bones included 84 patients with femur metastases and reported a 6% rate of femur fracture (n = 5) and identified a significant association of extraosseus extension with fracture and local failure risk across all long bone sites.[8] It remains less clear whether the potential benefits of SBRT in local control outweigh the potential risks of toxicity for this weight-bearing location. Spinal SBRT-induced vertebral compression fracture has been associated with dose per fraction or underlying instability as per the Spinal Instability Neoplastic Scoring system but less is known of predictive factors for fracture after nonspine bone SBRT.[14-18]

There is also limited evidence to guide appropriate gross tumor volume (GTV) and clinical target volume (CTV) delineation.[19] Increasing the CTV to encompass surrounding areas of micrometastatic disease within the femur may also proportionally increase the risk of bone marrow suppression, fracture, or osteonecrosis. American Association of Physicists in Medicine (AAPM-Task Group 101) femoral head constraints based on the experience at UT Southwestern and University of Virginia limited the femur volume able to receive 30 Gy or higher in 5 fraction SBRT to less than 10 cc (V30 Gy $\leq$10 cc), although the report acknowledges at best this only approximates normal tissue tolerance.[20]

We aimed to characterize the safety and efficacy of femur SBRT using a large single institution retrospective analysis of all patients treated with femur SBRT and to characterize the patient or treatment factors associated with clinical outcomes.

Methods and Materials

With institutional review board approval (Partners IRB 2020P002190) and from a data repository of 600 patients treated with SBRT for nonspine bone metastases, we retrospectively reviewed 48 patients with 53 femur lesions of any primary cancer treated with SBRT between May 2017 to June 2022.

All patients were immobilized in a custom Vac-Lok bag with thermoplastic masks to immobilize the legs or an extremity board. The GTV was defined based on computed tomography (CT) and magnetic resonance imaging (MRI), whole-body prostate-specific membrane antigen, or fluorodeoxyglucose positron emission tomography at clinician discretion. The CTV was limited to surrounding bone with additional expansions, typically 1 to 2 cm inclusive of the circumference of bone, with an additional 3 mm margin into soft tissue in cases of extraosseous tumor extension. Planning target volume margins were 2 to 5 mm. A simultaneous integrated boost approach was applied to escalate dose to the GTV with a lower dose prescribed to the CTV at physician discretion. Treatment was delivered with 6 MeV-photon volumetric modulated arc therapy (2-3 arcs) or intensity modulated radiation therapy using 2 to 3 hemi-arcs. Due to the conformality of treatment plans, there were no additional requirements to spare a strip of skin beyond a "soft" femur metric to limit the V30 Gy, V21.9, or V14 for 5, 3, or 1 fraction treatments to <10 cc unless necessary for target coverage.

Patients were followed per standard of care with bone imaging (bone scan, CT, or whole-body positron emission tomography) typically every 3 months. Metachronous oligometastatic disease was defined as presentation with up

to 5 metastases at an interval greater than 6 months from time of initial cancer diagnosis. The Mirels score was calculated for all femur lesions based on site (lower limb + 2, trochanteric region + 3), size (<1/3 of bone diameter + 1, 1/3-2/3 of bone diameter +2, >2/3 of bone diameter +3), nature (blastic +1, mixed +2, lytic +3), and pain (mild +1, moderate +2, functional +3).[5] Lesion size and nature was characterized using CT instead of roentgenograms as originally described by Mirels.

Local recurrence (LR) was defined based on new/growing lesions within the SBRT field captured within follow-up imaging. Local regional recurrence (LRR) was defined as new/growing lesions within the treated femur. Distant progression was defined as progression outside the treated femur. Overall survival (OS) was defined as the time interval between the start date of SBRT to the most recent follow-up or death from any cause. Toxicity was graded using Common Terminology Criteria for Adverse Events, version 5.0. Acute toxicities and late toxicities were defined as less or more than 6 months post radiation treatment, respectively.

The biologic effective dose (BED) was calculated as follows: BED = D*(1+[d/(α/β)]) where D is total dose in Gray (Gy), d is dose per fraction, and α/β, dose at which linear and quadratic components of cell killing are equal for a given tissue, was estimated to be 10 Gy for bone metastases.

Descriptive statistics were used to report patient and treatment characteristics. The Kaplan-Meier method was used to characterize time-to-event endpoints and Cox proportional hazards models were performed to evaluate the association between baseline factors and clinical outcomes.[21,22] Statistical analyses were performed using SAS software version 9.4.

Table 1 Baseline characteristics (patient level)

	N (%)
All	48 (100)
Age at RT start, y	
Median	67.5
Range	11-87
Sex	
Female	12 (25.0)
Male	36 (75.0)
Race	
White	42 (87.5)
Asian	2 (4.2)
Other/unknown	4 (8.3)
ECOG PS	
0	18 (37.5)
1	25 (52.1)
2	4 (8.3)
3	1 (2.1)
Histology	
Prostate	25 (52.1)
Breast and lung	8 (16.7)
Other	15 (31.3)
Indication*	
Metachronous	33 (68.8)
Synchronous	15 (31.3)

*Primary indication for stereotactic body radiation therapy was categorized as metachronous or synchronous oligometastatic disease.
Abbreviations: ECOG PS = Eastern Cooperative Group Performance Status; RT = radiation therapy.

Results

Baseline characteristics

Between May 2017 and June 2022, 48 patients with 53 femur metastases were treated with SBRT (Table 1). The median age was 67.5 years and patients were predominantly men (75%), White (88%), and with Eastern Cooperative Oncology Group performance status ≤1 (90%). The most common histology was prostate (52%) or breast/lung (17%), and the most common indication for SBRT was metachronous oligometastatic disease (69%; Table 1).

Among 53 lesions, 29 were proximal and 5 distal. Most patients did not have extraosseous bone extension (94%), and 42% had a Mirels score[5] ≥7 (Table 2). Fifty-seven percent of patients received concurrent systemic therapy with SBRT, including androgen deprivation therapy (n = 18) or immunotherapy (n = 5). Planning MRI was performed for 93% of metastases. Sixty-nine percent were treated with a simultaneous integrated boost. The median planning target volume (PTV) was 49.1 cc (range, 6.6-387). The median PTV covered by 100% of prescription dose or higher (PTV V100) was 99% (range, 90-100) and by 90% of prescription dose or higher (PTV V90) was 100% (range, 97.4-100). Ninety-eight percent of lesions had PTV V90 = 100%, and 57% had PTV V100 ≥99%. Fifty-seven percent of lesions were prescribed a BED_{10}>50 range (37.5-60). Eighty-five percent had femur V30 Gy equivalent ≥10 cc (Table 2).

Local control, locoregional control, progression-free survival, and overall survival

The median follow-up was 19.4 months. The 1- and 2-year rates of local control (LC) were 94% and 89%,

Table 2 Baseline characteristics of tumor and treatment factors of the study population at the lesion level

	N (%)
All	53 (100)
Bone Mets SBRT indication	
Oligometastasis	47* (88.7)
Reirradiation	2 (3.8)
Radioresistant histology	5* (9.4)
Extraosseous extension	
No	50 (94.3)
Yes	3 (5.7)
Femur metastasis localization	
Proximal epiphysis	29 (54.7)
Metaphysis	13 (24.5)
Diaphysis	5 (9.4)
Distal epiphysis	4 (7.5)
Diaphysis, distal	1 (1.9)
Metaphysis, diaphysis	1 (1.9)
Mirels score	
<7	31(58.5)
≥7	22 (41.5)
Concurrent systemic treatment	
No	23 (43.4)
Yes	30 (56.6)
Androgen deprivation therapy	18
Immunotherapy	5
Chemotherapy	4
Targeted therapy	2
Hormonal therapy	1
PTV volume (cc)	
Median	49.1
Range	6.6-387.0
PTV V100 (%)	
Median	99
Range	90-100
PTV V100 (%)	
<99	23 (43.4)
≥99	30 (56.6)
PTV V90 (%)	
Median	100
Range	97.4-100
PTV V90 (%)	
<100	1 (1.9)
100	52 (98.1)
BED	
≤50	23 (43.4)
>50	30 (56.6)
Femur V30 equivalent,† cc	
<10	8 (15.1)
≥10	45 (84.9)
Fractionation	
One fraction	
18 Gy × 1	1 (1.9)
20 Gy × 1	1 (1.9)
Femur V14 (cc)	
Median	19.1
Range	12.5-25.6
Three fractions	
9 Gy × 3	4 (7.5)
10 Gy × 3	3 (5.7)
Femur V21.9 (cc)	
Median	34
Range	6-58.1
Five fractions	
5.7 Gy × 5	1 (1.9)
6 Gy × 5	22 (41.5)
7 Gy × 5	19 (35.8)
8 Gy × 5	2 (3.8)
Femur V30 (cc)	
Median	31.8
Range	0.01-266

(*continued on next column*)

Table 2 (*Continued*)

Abbreviations: BED = biologically effective dose; PTV = planning target volume; SBRT = stereotactic body radiation therapy.
*Three lesions were both oligometastasis and radioresistant histology; 2 lesions were not categorized into any of these 3 types.
†V30 Gy for 5 fractions, V21.9 Gy for 3 fractions, and V14 Gy for 1 fraction, where V is the volume of femur receiving dose (Gy) or higher in cubic centimeters (cc).

locoregional control were 83% and 67%, PFS were 56% and 25%, and OS were 91% and 73%, respectively (Fig. 1, Table E1).

There were 10 LRR among 53 treated femur lesions (Table 3, Fig. 1C). There were no significant associations identified between the risk of LRR and lesion characteristics, including histology or type of oligometastatic presentation, extraosseous extension, PTV, or BED prescribed (Table 3).

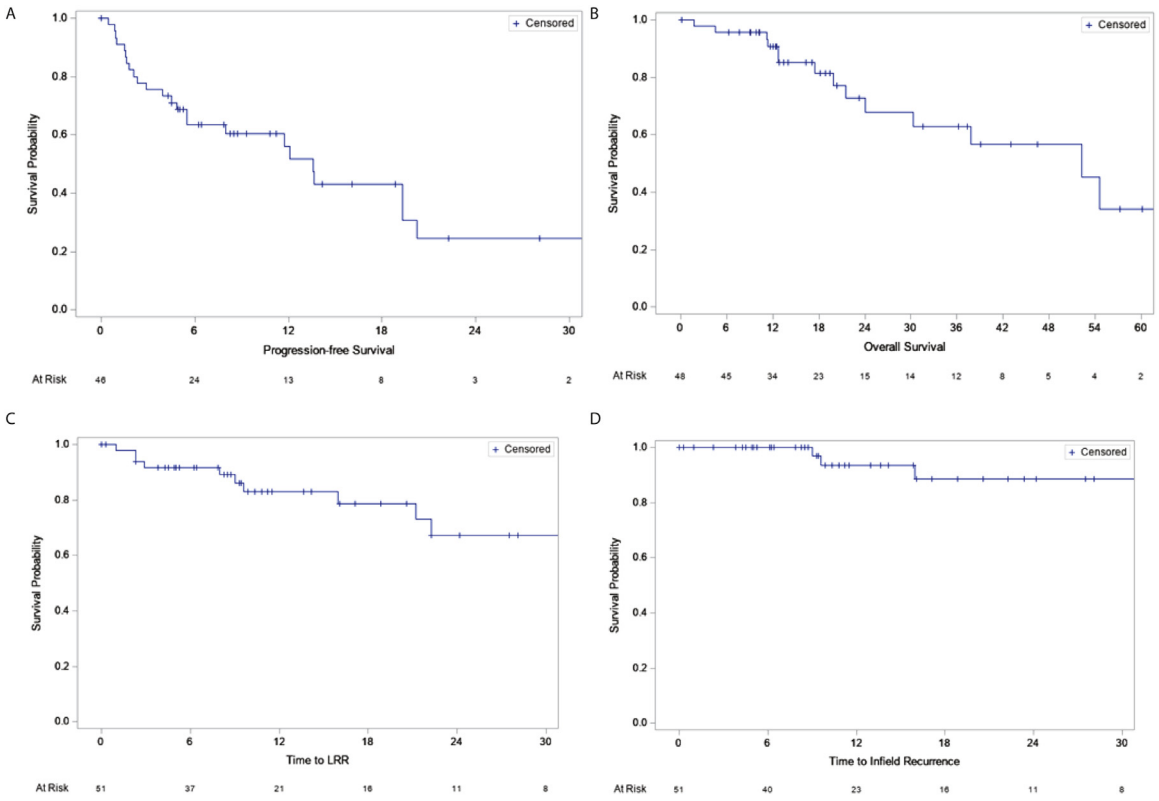

Figure 1 Progression-free survival, overall survival, time to local regional recurrence, and in-field recurrence after femur stereotactic body radiation therapy.

The clinical characteristics of the 8 patients with 10 LRR events are summarized in Table 4. Diverse histologies were represented, including 1 patient with renal cell cancer (20%) and 1 patient with prostate cancer (20%) who both experienced LRR after SBRT to 2 discrete femur lesions. Metastases were predominantly in the proximal femur (70%). The most common fractionation regimen was 30 Gy/5F (40%) and 35 Gy/5F (40%) with a median femur V30 of 31.8 cc (range, 0.01-266; Table 2). All patients were planned with MRI and a CTV margin (range, 1-3 cm) applied to the GTV. Among patients with LRR, the median GTV was 16.55 cc (range, 2.05-50.4). The median interval to recurrence was 9.6 months (range, 1-22). Three recurrences were true LR within the prior treatment area. Five recurred in a discrete location within 5 cm of the GTV. One patient with oligorecurrent prostate cancer had a proximal femur lesion (lesion 44) treated to 35 Gy/5F to avoid need for ADT and had recurrence within the distal femur (>20 cm from GTV) detected on follow-up MRI 2 months later. The distal lesion (lesion 45) was treated with SBRT (35 Gy/5F), and subsequent follow-up MRI revealed at least 5 new subcentimeter T2 hyperintense enhancing foci within the femoral head and neck, concerning for metastatic foci (>20 cm from GTV) and out-of-field of the prior proximal femur SBRT. The patient began treatment with enzalutamide and had no further progression as of last follow-up 19 months after his second course of femur SBRT (Table 4).

Toxicities

Common acute toxicities were grade 1 fatigue (14.3%) and pain flare (7%). Other reported acute toxicities included grade 1 nausea (4%) and decreased blood counts (2%).

Three patients required fixation after completion of femur radiation, all unrelated to progression (Table 5). One underwent fixation due to progression of pain, and 2 experienced radiation-induced necrosis. The median time from RT to surgery was 32 months (range, 5-57). Post-RT fixation was not associated with femur V30 $\geq$10 cc (Table E2).

Patient 46 was a 67-year-old man with oligometastatic prostate cancer (Table 5). He had a 3.8 cm lytic lesion in the left proximal epiphysis with no extraosseous disease extension and Mirels score 9. He was seen by a surgeon who recommended radiation treatment and weight bearing as tolerated. He was treated to a dose of 30 Gy/5F. The GTV and PTV were 22 cm^3 and 97 cm^3, respectively. He underwent fixation 4.9 months post SBRT for persistent pain requiring crutches despite initial improvement in pain after radiation. Pathology from surgery showed no residual cancer (Table 5).

Table 3 Associations between time to LRR* and covariates (lesion level)

			UVA	
Covariate	**N**	**No. of event**	**HR† (95% CI)**	***P* value**
All	53	10	-	-
Histology				.08
Prostate	26	2	Ref	
Other	27	8	3.97 (0.83, 18.89)	
Indication				.60
Synchronous	17	2	0.66 (0.14, 3.16)	
Metachronous	36	8	Ref	
Extraosseous extension				.73
No	50	9	Ref	
Yes	3	1	1.45 (0.18, 11.87)	
PTV volume (cc)				.96
<55	29	5	Ref	
≥55	24	5	0.97 (0.26, 3.61)	
PTV V100 (%)				.22
<99	23	3	Ref	
≥99	30	7	2.38 (0.59, 9.55)	
BED				.43
≤50	23	4	Ref	
>50	30	6	1.70 (0.46, 6.25)	
V30 equivalent,‡ cc				.17§
<10	8	0	Ref	
≥10	45	10	NA‖	

Abbreviations: BED = biologically effective dose with an alpha/beta = 10; HR = hazard ratio; LRR = locoregional recurrence; PTV = planning target volume covered by 90% or 100% prescription dose (V90, V100); UVA = univariate analysis; V30 equivalent = volume of femur receiving 30 Gy (5 fraction), 21.9 Gy (3 fraction), or 14 Gy (1 fraction) or higher in cubic centimeters (cc).

*Time to LRR was defined as the time from RT start date to locoregional recurrence. Lesions without locoregional recurrence were censored at the date of last disease assessment.

†As the risk of failures was changed due to the administration of systemic treatment during the follow-up period, a Cox proportional hazards regression model with systemic treatment as a time-dependent covariate was used to evaluate the associations between covariates and time to LRR.

‡V30 Gy for 5 fractions, V21.9 Gy for 3 fractions, and V14 Gy for 1 fraction.

§*P* value by log-rank test.

‖HR cannot be estimated as no local regional recurrence was observed in the V30 <10 category.

Patient 19 was a 16-year-old woman with Ewing's sarcoma and had a 5.1 cm blastic lesion in the proximal femur with no extraosseous disease extension and Mirels score 6. She received 40 Gy/5F and vincristine/doxorubicin/cyclophosphamide/ifosfamide-etoposide (VDC/IE) plus ganitumab on a clinical trial. The GTV and PTV were 17 cm^3 and 164 cm^3, respectively. Four and a half years later, she developed right hip pain impacting her gait. MRI and CT scans showed abnormal architecture of the proximal femur consistent with treatment-related osteonecrosis. Pathology from surgery 59 months post-RT was consistent with bone necrosis (Table 5).

Patient 36 was a 52-year-old woman with metastatic non-small cell lung cancer and Mirels score 9 and underwent SBRT reirradiation (30 Gy/5F) to a 5.2 cm mixed lytic/sclerotic lesion of the metaphysis 2.5 years after prior palliative RT (30 Gy/10F). The GTV and PTV were 50 cm^3 and 241 cm^3, respectively. Forty-four months post SBRT, pathology from surgical fixation reported osteonecrosis (Table 5).

Discussion

To our knowledge, this study is one of the largest reports of outcomes after femur SBRT with patients treated primarily for the purpose of oligometastatic disease control using commonly used bone SBRT regimens.

Table 4 Locoregional recurrence lesion characteristics

No.	Histology	MRI for planning?	Orig. dose (Gy/F)	Met. vertical location	GTV (cm^3)	CTV (cm)	PTV (mm)	Date of SBRT completion	Date of recurrence	Time to recurrence (mo)	Recurrence location	Recurrence location (cm) from GTV	Distant metastasis
9	Renal	Yes	30/5	Proximal	50.5	1	2	11/19/2018	3/13/2020	16	Proximal, mid shaft	Inclusive of previous lesion and more	Yes: SC and RP lymph nodes
10	Renal	Yes	35/5	Distal	5.4	1.5	2	8/28/2020	6/1/2022	21	Proximal, mid shaft	4.8	Yes: liver, pancreas
20	Cholangiocarcinoma	Yes	30/3	Proximal	7.6	1	2	5/18/2020	11/15/2020	6	Proximal	1.6	Yes: liver and bone†
21	Breast	Yes	30/5	Proximal	14.3	1	2	7/1/2020	5/4/2022	22	Proximal	4	Yes: T7-T9, L3
27	Ewings Sarcoma	Yes	40/5	Proximal	7.1	1	2	3/30/2021	11/22/2021	8	Proximal	3	Yes: right ilium
32	Melanoma	Yes	35/5	Proximal	3.7	1.5	2	10/1/2021	10/28/2021	1	Proximal (intertrochanteric)	3	Yes: lungs, lymph nodes, liver, Intramuscular, bone
39	Non-small cell lung cancer	Yes	30/5	Distal	49.6	3	2	10/20/2020	7/16/2021	9	Distal	Increased size of lesion	Yes: left infrahilar
42	Cholangiocarcinoma	Yes	30/5	Proximal	18.8	1.5	2	9/9/2021	6/21/2022	9	Proximal	Increased size of lesion	Yes: T11
44	Prostate	Yes	35/5	Proximal	6.4	1	2	4/19/2021	6/22/2021	2	Distal	>20	No
45	Prostate	Yes	35/5	Distal	2.1	1	2	8/4/2021	10/6/2021	2	Proximal	>20	No

Abbreviations: CTV = clinical tumor volume; GTV = gross tumor volume; Gy/F = Gray per fraction; MRI = magnetic resonance imaging; No. = lesion number; PTV = planning target volume; RP = retroperitoneal; SBRT = stereotactic body radiation therapy; SC = supraclavicular.
†Left sacral, right S1, R posterior ilium.

Table 5 Surgical fixations post SBRT

No.	Age, y	Primary tumor	Type	Vertical location	Dm	Mirels score	Extraosseous disease	Re-RT (Y/N), prior dose (Gy/F)	GTV (cm^3)	PTV (cm^3)	Dose (Gy/F)	PTV BED_{10}	Time to surgery (mo)	Pathology
19	16F	Ewing's sarcoma	Blastic	Proximal	>2/3	6	No	No	17	164	40/5	60	59	Osteonecrosis
36	52F	NSCLC	Mixed	Metaphysis	>2/3	9	No	Yes/ (30/10)	50	241	30/5	45	44	Osteonecrosis
46	67M	Prostate	Lytic	Proximal epiphysis	<1/3	9	No	No	22	97	30/5	45	5	No evidence of malignancy

Abbreviations: BED_{10} = biologically equivalent dose using an alpha/beta of 10; Dm = diameter; F = female; GTV = gross tumor volume; Gy/F = Gray per fraction; M = male; N = no; No. = number; NSCLC = non-small cell lung cancer; PTV = planning target volume; RT = radiation therapy; Y = yes.

This is also the first study to report LRR in a population where almost all patients were planned with MRI and to assess whether the Mirels score, a weighted scoring system for predicting fracture risk after conventional palliative radiation, has utility in predicting fracture risk among patients treated with femur SBRT. With a median follow-up of 19.4 months, we identified a 1-year LC rate of 94%, locoregional control rate of 83%, and 1-year rate of OS of 91%, with minimal rates of acute or late toxicity, including 1 fixation due to progression of pain (2%) and 2 instances of radiation-induced osteonecrosis requiring fixation (4%). Despite the high proportion of patients with Mirels score ≥7 (42%), our fracture rate is comparable with the 6% rate of fracture reported from a multi-institutional report of outcomes after long bone SBRT.[8] All patients who required surgical fixation post-SBRT had events unrelated to tumor progression.

The Mirels score was based on a retrospective analysis of 38 patients with 78 metastatic long bone lesions treated with irradiation in which 35% of lesions sampled fractured within a period of 6 months.[5] A score of 8 is suggestive (probability of fracture, 15%) of an impending fracture, and a score of 9 was associated with a 33% risk of fracture.[5] In our patient population, 57% had a Mirels score <7 and 43% had a score ≥7. Two patients with fracture had a Mirels score ≥8.

It is considered a standard of care to combine surgical stabilization of weight-bearing bone with postoperative radiation (commonly 30 Gy/10F) for an impending or confirmed pathologic fracture to reduce the risk of seeded LR.[23,24] Surgical fixation of the femur involves intraoperative reaming before placement of an intramedullary rod, which disseminates tumor both proximally and distally throughout the femur, and thus may require larger postoperative radiation treatment fields to encompass areas at microscopic risk of disease.[25,26] In addition to the increased challenge of target volume delineation postoperatively, the larger field of treatment also precludes the ability to deliver an ablative dose as it is not possible to treat the entire region at risk with 5 fraction SBRT without increased risk of osteonecrosis based on existing constraints.[20] As such, all patients treated at our institution with femur SBRT (defined as 5 fractions or fewer) were treated with radiation as an alternative to surgery after multidisciplinary discussion.

Many studies have found administration of zoledronic acid to prevent or delay skeletal-related events, as well as combining bisphosphonates with radiation therapy to increase bone density.[27-29] It is possible the addition of bone-modifying agents could have further reduced the risk of fracture.

Osteoradionecrosis (ORN) is caused by lack of blood supply to the bone, leading to ischemic cell death and the incidence of pelvic ORN has ranged from 2.1% to 34%, depending on radiation standards and the technology applied.[30-32] It has been reported that high doses of

radiation can increase the risk of ORN due to high calcium content of bone tissue, which absorbs 30% to 40% more radiation than the surrounding tissue and the sensitivity of bone to radiation therapy may also be increased in the context of chemotherapy.[32-34] Femur osteonecrosis is a rare but serious complication and has been associated with many risk factors, including mechanical stresses, genetic predisposition, corticosteroid use, alcohol intake, smoking, and other chronic diseases (renal disease, hematologic disease, inflammatory bowel disease, postorgan transplantation, hypertension, and gout).[30,35,36] In this study, the 2 patients who experienced ORN did not have any of these risk factors. However, tumor size (>2/3 of diameter of bone), high dose (40 Gy/5F), and reirradiation (30 Gy/10F) may have been factors that increased their risk. Exceeding the AAPM-TG 101 metric for femur necrosis V30 Gy <10 cc was not associated with increased risk of necrosis in our cohort; however, the median femur volume receiving 30 Gy or equivalent or higher was relatively low in this carefully selected group (31.8 cc for 5 fraction, 34 cc for 3 fraction, and 19.1 cc for 1 fraction treatments; Table 2).

We did not identify an association between patient, lesion, or treatment characteristics with the risk of toxicity. This likely reflects the heterogeneous clinical factors that impact a patient's risk of fracture as well as the low rate of events observed among our patient population. Future studies are indicated to determine the optimal sequence of SBRT and surgery for patients at risk of fracture and to establish whether there is a benefit of SBRT over conventional palliative radiation in the context of this weight-bearing bone. Multidisciplinary discussion for patients with higher Mirels score remains critical, as well as clinical follow-up, as patients are far more likely to experience fracture for reasons unrelated to tumor progression after femur SBRT.

We analyzed recurrence within the treated field and within the treated femur separately to characterize the pattern of failure post-SBRT (Table 4). The rate of LR was only 11% at 2 years. However, we observed a higher rate of LRR (17%), related to tumor progression within the femur yet outside the field of radiation treatment. Out of 7 out-of-field LRR, 5 occurred within 5 cm from GTV and 2 recurred within the femur, but more than 20 cm away from the GTV. All patients with LRR had MRI for treatment planning. One patient with oligorecurrent prostate cancer had LRR more than 20 cm from GTV detected on imaging follow-up on 2 separate occasions. This suggests that in most cases a CTV ranging from 1 to 3 cm as is practice at our institution is sufficient to capture areas at highest risk for micrometastatic disease. However, a 31% rate of LRR at 2 years within 5 cm of GTV warrants more consideration of larger elective volume coverage to a lower dose (eg, 25 Gy in 5 fractions). Of note, the phase 2 Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) and Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) trials for oligorecurrent prostate cancer did not require a CTV for bone metastases.[37,38] The optimal CTV for nonspine bone metastases and how patient or tumor characteristics should impact dose and fractionation remains an active area of investigation.[19] A larger or smaller CTV margin may be appropriate depending on tumor histology, the anticipated effectiveness of systemic therapy, the sensitivity of planning imaging, and weighed against the risks added by treating a larger volume. A recurrence 5 to 20 cm away from the initial treated site may be more akin to distant progression and not feasible to routinely encompass within a CTV. Our findings also have implications as far as follow-up for patients after SBRT as our LRR events were detected on MRI follow-up and the value of MRI in treatment planning of nonspine bone metastases also require further validation.[39]

The 2-year OS 73% likely reflects the diversity of histologies represented in our patient population where the competing risk of death remains high. Except for one patient with oligorecurrent prostate cancer who recurred within the same femur, all patients with LRR also experienced distant progression, which ultimately required a change in systemic therapy. Additional study is indicated to select for patients who benefit the most from this approach.

The strengths of this study include that it reflects a large population treated using common SBRT fractionation regimens with a uniform approach. We observed a limited rate of fracture or toxicity, and our results are consistent with outcomes reported from other studies.[8] Although the rate of toxicity is limited, the findings are of interest in illuminating other potential risk factors for fracture and osteonecrosis. Similarly, the pattern of failure also highlights the potential benefit of a CTV margin in the context of nonspine bone SBRT. This is the first study to assess the utility of the Mirels criteria (albeit with CT scans instead of radiographs) in predicting fracture risk among patients treated with SBRT.

Limitations include its retrospective nature and a sample size that would have limited its power to detect significant associations. Patients were predominantly White with oligometastatic prostate cancer and treated commonly with 30 to 35 Gy/5F to a small volume (median, PTV 54.7 cc) with limited femur receiving 30 Gy or higher (median, 31.8 cc) These results may not be generalizable for patients with larger metastases or more hypofractionated treatment, where a higher risk of toxicity would be anticipated.

Additional prospective studies are warranted to determine whether larger lesions can be safely treated with SBRT and to establish the role of SBRT in the pre- or postoperative setting. Our study provided a large experience using a standardized approach at a

high-volume center in which all patients had MRI imaging, standard follow-up, and many of the patients had oligometastatic prostate cancer, a common indication for SBRT.

Conclusion

High doses of radiation may be beneficial to help prevent cancer spread with a low risk of femur fracture. We did not identify an association between patient characteristics and survival outcomes or treatment characteristics and toxicity. Most targets included a CTV involving the circumference of bone and femur V30 Gy >10 cc was not associated with higher risk of fracture in a population with limited number of events. Osteonecrosis was observed for 1 of 2 patients who received 40 Gy in 5 fractions and 1 patient receiving SBRT reirradiation. In select patients, femur SBRT may be considered a safe and effective option for patients as part of an oligometastatic treatment paradigm. A significant rate of LRR at 2 years within 5 cm of GTV warrants consideration of elective radiation to a larger volume for patients with good prognosis and in whom a lower dose to larger volume can be safely delivered.

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Supplementary materials

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