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Scientific Article

A Prospective Study Assessing the Efficacy and Toxicity of Stereotactic Body Radiation Therapy for Oligometastatic Bone Metastases

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Purpose: Stereotactic body radiation therapy (SBRT) is a promising treatment for oligometastatic disease in bone because of its delivery of high dose to target tissue and minimal dose to surrounding tissue. The purpose of this study is to assess the efficacy and toxicity of this treatment in patients with previously unirradiated oligometastatic bony disease.

Methods and Materials: In this prospective phase II trial, patients with oligometastatic bone disease, defined as ≤3 active sites of disease, were treated with SBRT at Brigham and Women's Hospital/Dana Farber Cancer Center and Beth Israel Deaconess Medical Center between December 2016 and May 2019. SBRT dose and fractionation regimen were not protocol mandated. Local progression-free survival, progression-free survival, prostatic specific antigen progression, and overall survival were reported. Treatment-related toxicity was also reported.

Results: A total of 98 patients and 126 lesions arising from various tumor histologies were included in this study. The median age of patients enrolled was 72.8 years (80.6% male, 19.4% female). Median follow-up was 26.7 months. The most common histology was prostate cancer (68.4%, 67/98). The most common dose prescriptions were 27/30 Gy in 3 fractions (27.0%, 34/126), 30 Gy in 5 fractions (16.7%, 21/126), or 30/35 Gy in 5 fractions (16.7%, 21/126). Multiple doses per treatment regimen reflect dose painting employing the lower dose to the clinical target volume and higher dose to the gross tumor volume. Four patients (4.1%, 4/98) experienced local progression at 1 site for each patient (3.2%, 4/126). Among the entire cohort, 2-year local progression-free survival (including death without local progression) was 84.8%, 2-year progression-free survival (including deaths as well as local, distant, and prostatic specific antigen progression) was 47.5%, and 2-year overall survival was 87.3%. Twenty-six patients (26.5%, 26/98) developed treatment-related toxicities.

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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: Our study supports existing literature in showing that SBRT is effective and tolerable in patients with oligometastatic bone disease. Larger phase III trials are necessary and reasonable to determine long-term efficacy and toxicities.

Introduction

Bone metastases are among the most common sites of metastatic disease and one of the most common reasons for referral to radiation oncology.[1,2] Radiation therapy (RT) local therapy options for bone metastases have historically relied on 2- and 3-dimensional external beam RT. However, the RT technique options for management of patients with metastatic disease has changed substantially in the past several decades. Specifically, stereotactic body RT (SBRT) has become increasingly used for the treatment of bone metastases.[3,4] Multiple phase I/II trials in the past decade have examined the use of SBRT for oligometastatic disease (bone and nonbone) in non-small cell lung cancer,[5-7] prostate cancer,[8,9] and patient populations with multiple histologies, with improvements reported in progression-free survival and overall survival. Furthermore, results from randomized trials (including recent data from the SC24 trial for painful spine metastases) now support use of SBRT for spine[10-12] and nonspine metastases,[13] contributing to its increased adoption in clinical practice in both oligometastatic and more widely metastatic disease.

Given the established use of SBRT for treatment of bone metastases, there is a need for prospective data on patients with bone metastases treated with SBRT. Patients with bone-only metastases generally may have more favorable outcomes compared with bone and visceral or central nervous system metastases.[14] However, bony metastatic disease remains a heterogeneous entity, and disease outcomes vary based on histology,[15-17] spine versus nonspine bone site, radiation dose, category of oligometastatic disease if relevant,[18] and systemic therapy regimens. Despite the increased use of SBRT for both spine and nonspine bone metastases, long-term prospective data from patients treated with SBRT for nonspine bone metastases are limited, with few prospective clinical studies reported.[13,19] There additionally remains the need for long-term outcomes of patients treated with spine SBRT due to known risks of post-SBRT vertebral compression fracture.[20,21] Thus, given the common use and guideline recommendations supporting use of SBRT for spine and nonspine metastatic disease,[22,23] additional prospective data are needed to better address long-term disease control outcomes and toxicities of bone SBRT and to provide specific outcomes based on relevant disease characteristics and treatment details. In this study, we report our results from a phase II prospective trial of oligometastatic patients with spine and nonspine bone metastases treated with SBRT.

Methods and Materials

This prospective, phase II trial enrolled patients age ≥18 and Eastern Cooperative Oncology Group performance status ≤2 with oligometastatic bone disease, defined as ≤3 active sites of disease including the primary disease site. Patients were also required to have a life expectancy of >3 months as defined by agreement of both the Chow et al[24] and TEACHH[25] prognostication models. Oligometastatic lesions were required to be ≤6 cm in maximum dimension and evaluable on either a computed tomograpy (CT) or magnetic resonance imaging (MRI) scan spanning ≤3 contiguous vertebral bodies if located in the spine. Metastatic disease was required to be biopsy-proven, although each metastatic lesion was not required to be biopsied. Patients who had prior irradiation to oligometastatic lesions were excluded from this study. Patients were treated at Brigham and Women's Hospital/Dana Farber Cancer Center and Beth Israel Deaconess Medical Center between December 2016 and May 2019. This investigation was approved by the Brigham and Women's Hospital/Dana Farber Cancer Center and Beth Israel Deaconess Medical Center institutional review board, and informed consent was obtained from all patients.

The gross tumor volume (GTV) was defined as all known disease determined by the planning CT and any other diagnostic imaging. For spine lesions, the clinical target volume (CTV) was defined per international consensus guidelines.[26] For nonspine bone lesions, the CTV was defined as the GTV plus areas considered to contain microscopic disease, determined by the treating radiation oncologist and typically ranging from 5 to 20 mm. The planning target volume (PTV) was defined as a 0 to 2-mm margin around the CTV for spine lesions to compensate for the variability of treatment setup and internal organ motion. In nonspine bone lesions, the PTV ranged from 2 to 5 mm based on institutional practice.[27-29] Dose prescription was determined by the treating physician and ranged from 16 Gy in 1 fraction to 30 to 35 Gy in 5 fractions. There were no protocol-mandated dose/fractionation regimens. Dose was normalized such that at least 95% of the PTV received the prescription dose. The minimum allowable dose within the PTV was >80% of the prescribed dose to a volume that was at least 1 cc. Oligometastatic bone lesions were treated with either a single dose to the entire target region or with dose painting, which incorporates a lower dose to the CTV and a higher dose to the GTV. Doses for both the CTV and GTV are reported when dose painting was employed. For example,

18 Gy to the CTV and 20 Gy to the GTV in a single fraction is reported as 18/20 Gy in 1 fraction. Biologically equivalent dose (BED) was calculated using the formula $\mathrm{BED} = nd\left(1+\frac{d}{\frac{\alpha}{\beta}}\right)$, where n is the number of fractions, d is the dose per fraction, and α/β is 10 in this study for all tumor histologies.

Patients were simulated with stereotactic setup per institutional protocols. Participants were positioned on a flat tabletop with customized immobilization. For rib lesions which may move with respiratory motion, a 4-dimensional CT or inspiration/expiration breath hold was used for target delineation. Treatment planning was performed with a high-resolution CT scan at minimum, with MRI fusion and positron emission tomography/CT fusion scans when available to define GTV. CT myelogram was also performed in certain clinically relevant cases at the discretion of the treating radiation oncologist. All cases were planned with either volumetric modulated arc therapy or CyberKnife. Patients completed SBRT with 1 of 3 treating radiation oncologists at Brigham and Women's Hospital/Dana Farber Cancer Center and 1 of 3 radiation oncologists at Beth Israel Deaconess Medical Center, and physician-graded toxicity was reported at the indicated time points. Systemic therapy (including androgen deprivation therapy [ADT], targeted therapy, immunotherapy, and chemotherapy) was prescribed at the discretion of the treating medical oncologist. Intrafraction motion tolerance was 1 mm/1 degree (spine) or 2 mm/2 degree (nonspine bone) and was tracked with CT, ExacTrac, or orthogonal kV imaging. Each lesion was treated as a single isocenter unless lesions were close enough in proximity to be included in a 1-isocenter multiple-metastasis plan. SBRT treatments with >1 fraction were delivered with 1 to 3 days between each fraction. For patients with multiple lesions receiving SBRT, no more than 2 sites were treated with SBRT on the same day.

Follow-up intervals were specified per protocol. Patients were first evaluated with imaging (CT or MRI as per the treating physician) at 3 months posttreatment. Patients were then imaged every 6 months thereafter through 2 years posttreatment with imaging modalities determined by the treating physicians. Patients were then imaged annually through 3 to 5 years posttreatment. The imaging modality used for follow-ups was not required to be the same imaging modality as the baseline imaging, but the same diagnostic modality of each time point was used during follow-up.

Local failure was defined as radiographic progression at treated sites. Primary endpoints were local progression-free survival (LPFS), including death without local progression, and progression-free survival (PFS), including deaths as well as local, distant, and prostatic specific antigen (PSA) progression. Secondary endpoints included PSA PFS and overall survival (OS). PSA progression was defined as nadir plus 2 ng/mL per Prostate Cancer Clinical Trials Working Group 3 guidelines,[30]

Table 1 Baseline demographics of patients (N = 98 patients* with 126 lesions) enrolled on protocol

Variable	N (%)
Sex (N = 98)	
Male	79 (80.6%)
Female	19 (19.4%)
Age (N = 98)	
Mean (SD)	72.0 (10.4)
Median (range)	72.8 (25.0 − 93.4)
Ethnicity (N = 98)	
Caucasian	87 (88.8%)
Black	2 (2.0%)
Hispanic/Latino	3 (3.1%)
Unknown	6 (6.1%)
Marital status (N = 98)	
Single, never married	10 (10.2%)
Married or domestic partnership	82 (83.7%)
Widowed	2 (2.0%)
Divorced	2 (2.0%)
Separated	1 (1.0%)
Unknown	1 (1.0%)
Number of metastatic bone sites treated with SBRT (N = 98)	
1	72 (73.4%)
2	18 (18.4%)
3	6 (6.1%)
Withdrawn	2 (2.0%)
ECOG (N = 98)	
0	65 (66.3%)
1	31 (31.6%)
2	2 (2.1%)
Diagnosis (N = 98)	
Breast cancer	6 (6.2%)
Lung cancer	7 (7.1%)
Prostate cancer	67 (68.4%)
Kidney cancer	7 (7.1%)
Melanoma	2 (2.0%)
Sarcoma	1 (1.0%)
Other	8 (8.2%)
ESTRO/EORTC classification (N = 98)	
Synchronous oligometastatic disease	22 (22.4%)
Metachronous oligoprogression	11 (11.2%)
Metachronous oligorecurrence	46 (46.9%)
Induced oligoprogression	3 (3.1%)

(*continued on next page*)

Table 1 (*Continued*)

Variable	N (%)
Induced oligorecurrence	6 (6.1%)
Induced oligopersistence	2 (2.0%)
Repeat oligoprogression	4 (4.1%)
Repeat oligorecurrence	1 (1.0%)
Repeat oligopersistence	1 (1.0%)
NA*	2 (2.0%)
Bone Sites Treated (N = 126)	
C-spine	5 (4.0%)
T-spine	34 (27.0%)
L-spine	19 (15.1%)
Sacrum	8 (6.3%)
Hip/lower limb	37 (29.4%)
Pelvis	1 (0.8%)
Rib	10 (7.9%)
Shoulder/upper limb	4 (3.2%)
Skull	2 (1.6%)
Sternum	5 (4.0%)
Clavicle	1 (0.8%)
Symptomatic lesion (N = 126)	
Yes	46 (36.5%)
No	80 (63.5%)
Soft tissue/paraspinal extension (N = 126)	
Yes	16 (12.6%)
No	110 (87.3%)
Epidural disease (N = 126)	
Yes	10 (7.9%)
No	116 (92.1%)
Baseline evaluation imaging (N = 126)†	
CT	57 (45.2%)
MRI	70 (55.6%)
PET/CT	2 (1.6%)
PSMA PET	1 (0.8%)
Dose (BED10 Gy) (N = 126)	
1 fraction	
16 (41.6)	1 (0.8%)
16/18 (41.6/50.4)	3 (2.4%)
18 (50.4)	5 (4.0%)
18/20 (50.4/60.0)	19 (15.1%)
20 (60.0)	2 (1.6%)
3 fractions	
27 (51.3)	12 (9.5%)
27/30 (51.3/60.0)	34 (27.0%)
30 (60.0)	2 (1.6%)
5 fractions	
22.5/30 (32.6/48.0)	2 (1.6%)
25/28.5 (37.5/44.8)	1 (0.8%)
25/30 (37.5/48.0)	2 (1.6%)
30 (48.0)	21 (16.7%)
30/33 (48.0/54.8)	1 (0.8%)
30/35 (48.0/59.5)	21 (16.7%)

Abbreviations: BED = biologically effective dose; C-spine = cervical spine; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; ESTRO = European Society for Radiation Therapy and Oncology; L-spine = lumbar spine; MRI = magnetic resonance imaging; NA = not applicable; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; T-spine = thoracic spine.

*Includes 2 patients who withdrew from study and were not treated on protocol.

†Note that some patients had multiple baseline evaluation imaging studies.

where the nadir was the lowest recorded PSA following SBRT treatment completion.[31] Multiple lesions are possible for a single patient. If multiple progressions occurred, the earliest progression was taken for a single patient. Univariate and multivariable analyses was performed using Cox regression analysis.

Results

A total of 98 patients (80.6% male, 19.4% female) with 126 lesions were enrolled in the study, for whom demographic data are summarized in Table 1. Of the 126 lesions, 65 were spine sites, and 61 were nonspine sites. Two patients withdrew shortly following enrollment because of disease progression before initiation of planned

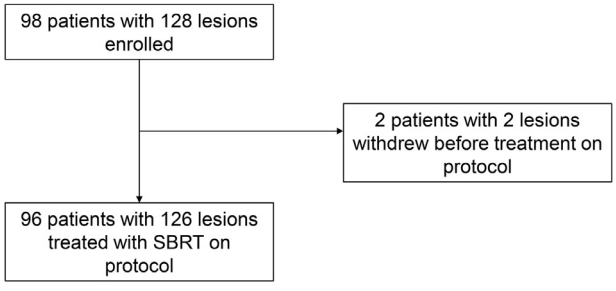


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. *Abbreviation:* SBRT = stereotactic body radiation therapy.

Table 2 Summary of patients who developed local progression following stereotactic body radiation therapy

Variable	Patient A*	Patient B	Patient C	Patient D †
Primary cancer diagnosis	Non-small cell lung cancer	Renal cell carcinoma	Prostate	Prostate
Site treated on protocol	L5	L1	Left coracoid	Right acetabulum
Dose fractionation	30 Gy in 5 fractions	30 Gy in 5 fractions	30 Gy in 5 fractions	30/35 Gy in 5 fractions
Planned target volume (cm^3)	152.3	43.4	29.0	93.3/14.8
Time to local progression (mo)	20.5	7.6	30.9	30.3

*This patient was also treated to the left ilium and left acetabulum on this protocol.
†This patient was also treated to a sacral lesion on this protocol.

SBRT (Fig. 1). The median disease-free interval (defined as time from primary diagnosis to diagnosis of oligometastatic diseases) was 35.8 (range, 0-352.3 months). Most patients treated with SBRT (72/96, 75.0%) did not have prior systemic therapy before SBRT; 18.8% (18/96) had 1 previous line of systemic therapy, 5.2% (5/96) had 2 previous lines of systemic therapy, and 1.0% (1/96) had 4 previous lines of systemic therapy. Concurrent therapy was administered with SBRT in 66/96 patients (68.8%), all of which were hormonal therapy treatments except for 1 patient treated with pembrolizumab and 1 patient treated with crizotinib.

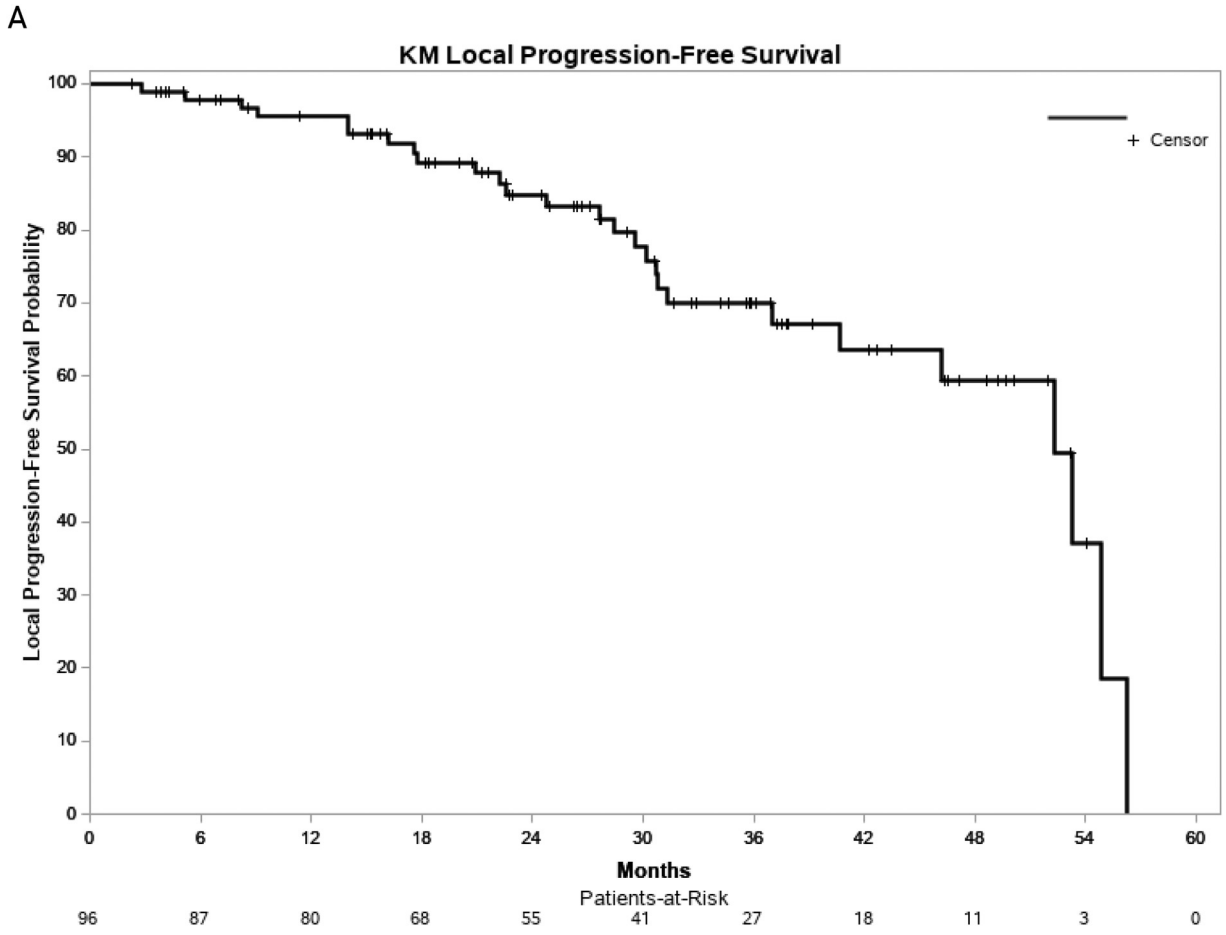
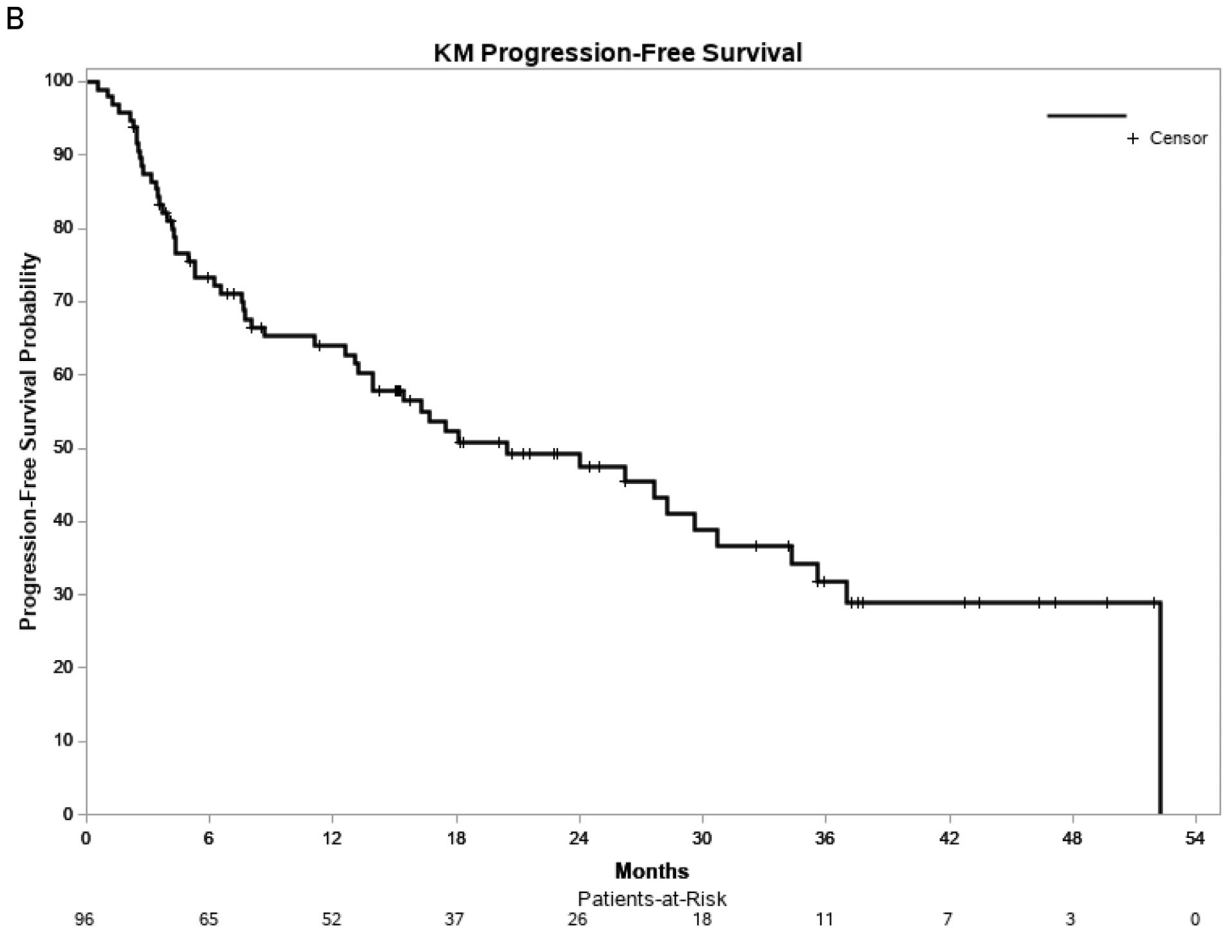


Figure 2 Kaplan-Meier (KM) curves for (A) local progression-free survival (LPFS), (B) progression-free survival (PFS), and (C) overall survival for the whole cohort, followed by KM curves for (D) LPFS, (E) PFS, and (F) overall survival separated by patients with prostate cancer or nonprostate cancer. Progression is defined in this curve as radiographic progression. LPFS includes death without local progression. PFS is defined as local, distant, and prostatic specific antigen progression as well as death.



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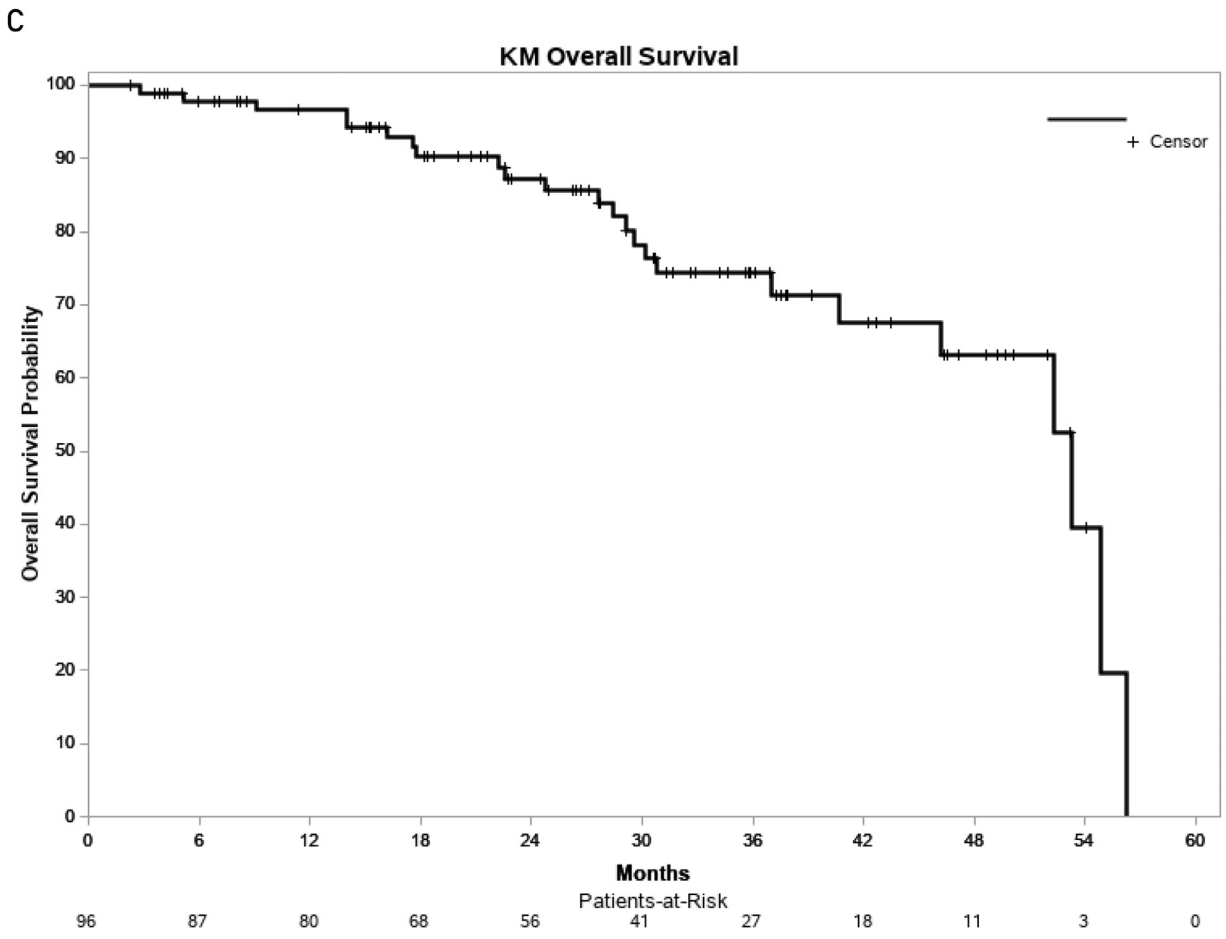
Most patients (75.0%; 72/96) had a single metastatic bone site treated with SBRT, and 25.0% (24/96) had 2 to 3 lesions treated (Table 1). The most common primary histology (Table 1) treated was prostate (69.8%; 67/96). The majority (89.6%; 60/67) of patients with prostate cancer received ADT with their SBRT (defined as within 90 days of SBRT). The most common dose prescriptions (Table 1) were 27/30 Gy in 3 fractions (27.0%, 34/126), 30 Gy in 5 fractions (16.7%, 21/126), or 30/35 Gy in 5 fractions (16.7%, 21/126). The mean BED delivered was 55.8 Gy_{10} to the GTV and 49.4 Gy_{10} to the CTV. The mean and median GTV volumes for all lesions were 13.6 cc and 6.5 cc, respectively (range, 0.2-120.3 cc). The mean and median PTV volumes were 61.2 cc and 49.6 cc, respectively (range, 4.1-338.6 cc). For cases in which patients were treated with a dose painted approach, a second PTV (PTV2) treated to a higher dose was also used. Among these lesions, median and mean PTV2 volumes were 18.2 cc and 10.6 cc, respectively (range, 0.3-174.7 cc). Among spine-only lesions, the mean and median GTV volumes were 12.9 cc and 6.3 cc (range, 0.2-116.3 cc), respectively, mean and median PTV volumes were 56.5 cc and 49.7 cc (range, 6-189.7 cc), respectively, and mean and median PTV2 volumes were 13.8 cc and 8.7 cc (range, 0.3-55.2 cc), respectively. Median follow-up was 26.9 months.

Among the cohort of patients treated with SBRT on protocol, progression (including local progression, distant progression, or PSA progression) occurred in 49 patients. Of these patients, 4 experienced local failure (4.2%, 4/96) (Table 2). All patients who experienced local failure also experienced systemic failure. The 2-year LPFS (including death without local progression) was 84.8% (95% CI, 74.7%-91.1%), 2-year PFS (including deaths as well as local, distant, and PSA progression) was 47.5% (95% CI, 36.2%-57.9%), and 2-year OS was 87.3% (95% CI, 77.5%-93.0%). Among patients who progressed locally, the median time to local recurrence was 25.8 months (31.0 months among patients with prostate cancer, N = 2, and 14.5 months among patients with nonprostate cancer, N = 2) (Fig. 2). Median PFS (local and distant, including PSA progression) was reached at 20.4 months (95% CI, 13.2-30.7 months) among all patients, 29.6 months (95% CI, 15.9 to Not Reached [NA] months) among patients with prostate cancer (N = 67), and 3.7 months (95% CI, 2.6-26.2 months) among patients with nonprostate cancer (N = 29). Median OS was reached at 53.3 months (95%



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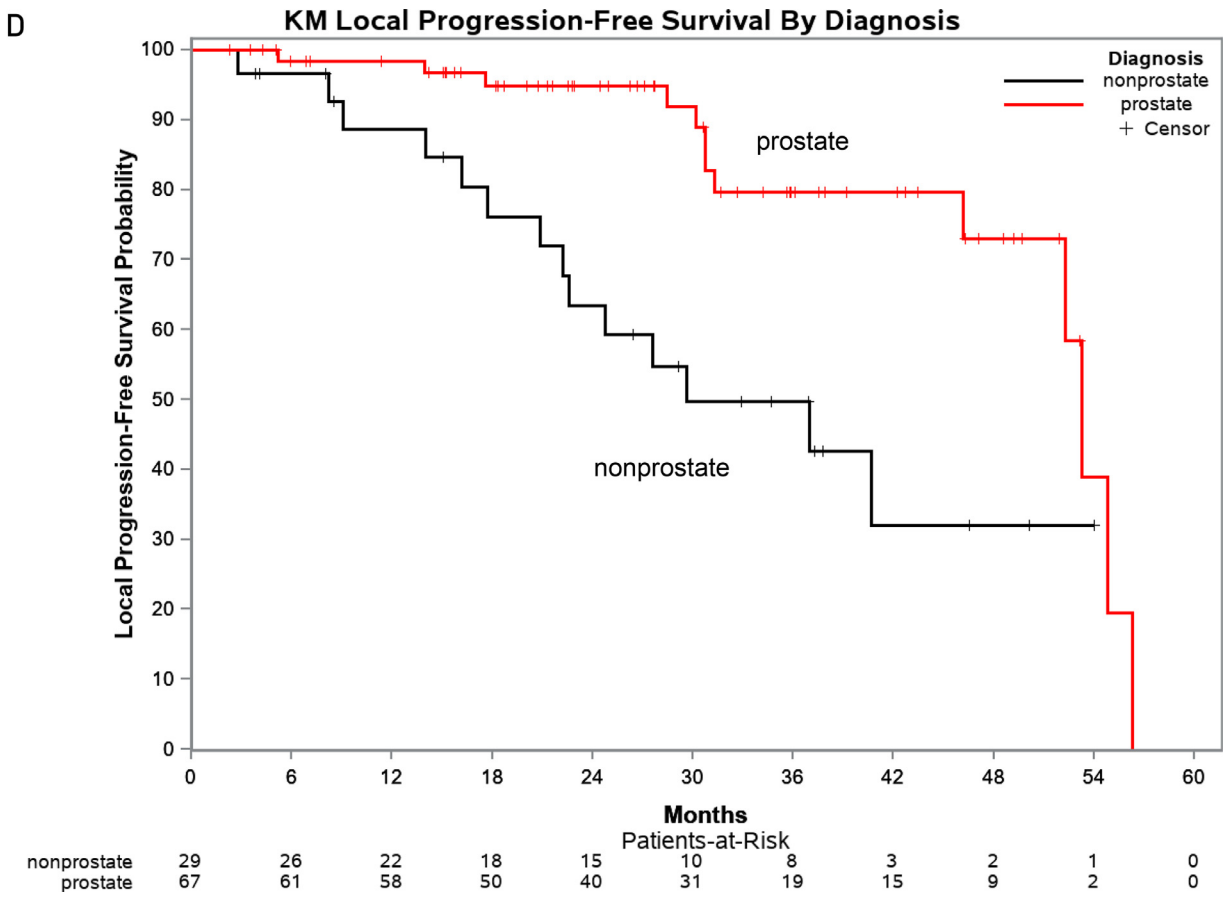
CI, 46.2 to NA months) among all patients, 53.3 months (95% CI, 52.3 to NA months) among patients with prostate cancer, and 37.0 months (95% CI, 22.6 to NA months) among patients with nonprostate cancer. Among patients with prostate cancer, median PSA PFS was 48.3 months (95% CI, 23.4 to NA months) (Fig. 3). Among those who experienced PSA progression (31.3% of 67 total patients with prostate cancer, N = 21), the median time to PSA progression was 11.1 months. The 2-year PSA progression-free rate was 65.0% (95% CI, 49.8%-76.6%).

The event rate in this study was too low to perform meaningful analyses on predictors of LPFS. Exploratory univariate and multivariable analyses among the entire cohort were performed using sex, diagnosis (prostate vs nonprostate), and location of SBRT (Table E1). Patients with prostate cancer were significantly less likely to experience systemic progression, local progression, or deaths upon univariate analyses (hazard ratio, 0.38; 95% CI, 0.22-0.65; $P < .01$). Patients with soft tissue/paraspinal extension or epidural disease were more likely to experience systemic progression, local progression, or deaths (hazard ratio, 3.19; 95% CI, 1.59-6.40; $P < .01$ and 6.02; 95% CI, 2.71-13.37; $P < .01$) upon univariate analysis.

Among the entire cohort, the most common treatment-related toxicities were fatigue (10/96; 10.4%), pain or soreness (7/96; 7.3%), and nausea (5/96; 5.2%) (Table 3). The highest-grade toxicity experienced was grade 3. Three patients experienced grade 3 vertebral fractures (all of which were managed with an interventional procedure). One additional patient experienced a grade 1 fracture for a total of 4 fractures in 66 spine sites (6.1%). Median time to fractures was 23.6 months (range, 13.7-39.2 months).

Discussion

The emerging data on SBRT for spine and nonspine bone metastases has established its use in clinical practice, particularly for oligometastatic disease, where ablative local treatments may be performed with curative intent. Data on long-term toxicities (such as vertebral compression fracture following spine SBRT) are critical, as are outcomes from nonspine bone metastases treated with SBRT, of which there are few reported studies. In this study, we report the results of our institutional phase II



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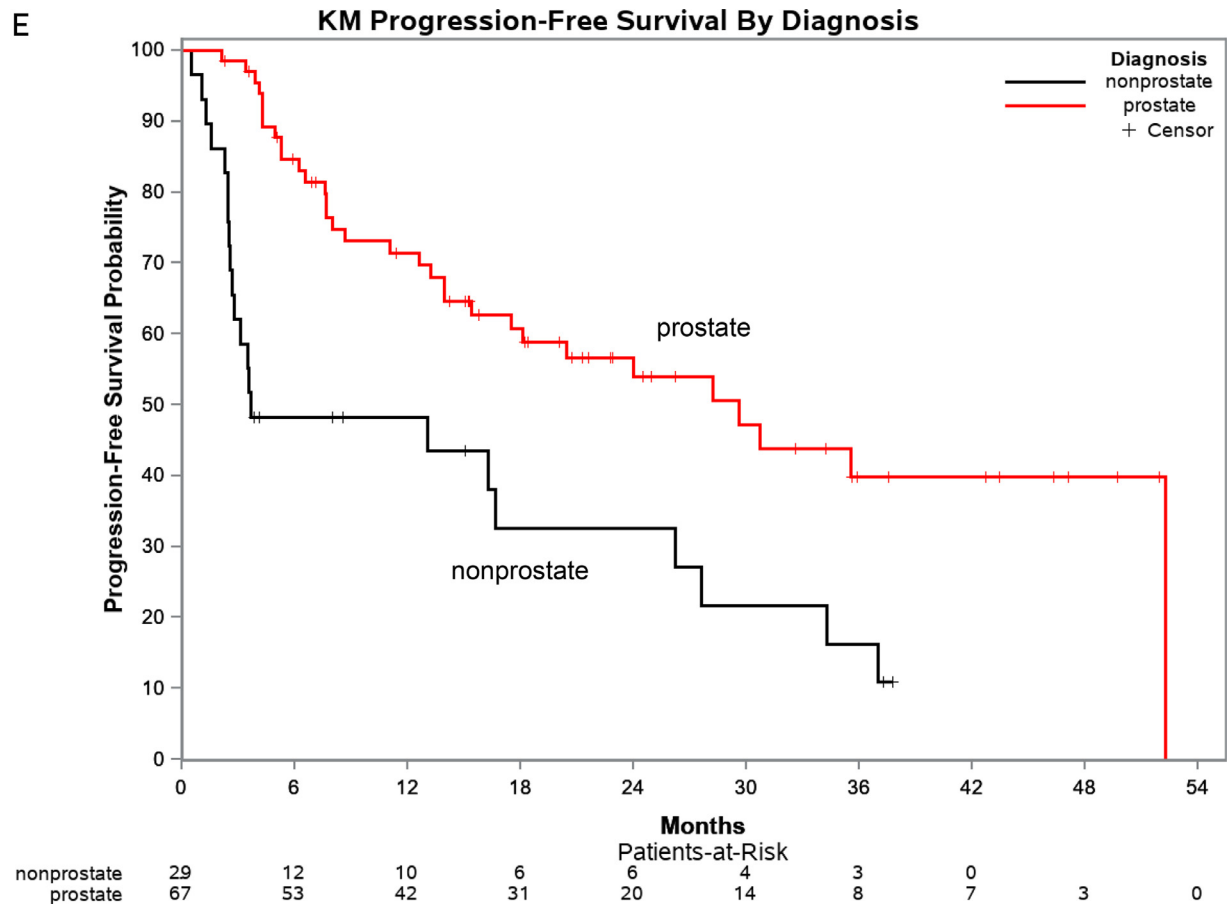
experience treating patients with 1 to 3 oligometastatic bone metastases with SBRT. We found overall high rates of local control at the sites receiving SBRT and acceptable toxicity profiles. Among 126 metastatic bone lesions treated with SBRT, only 4 sites locally progressed during the follow-up period of this study. PFS was also favorable in this study with a median of 20.4 months.

Our results contribute to the growing body of literature regarding disease outcomes following SBRT treatment for oligometastatic disease. Multiple prospective studies have assessed efficacy of treating oligometastatic (bone and nonbone) lesions with SBRT in a range of histologies.[4-6,15,17] While the SABR-COMET trial (which enrolled multiple histologies and included bone and none-bone lesions) was the first to show an OS benefit with addition of SBRT to oligometastatic lesions,[17] subsequent trials suggest that clinical benefit may vary based on clinical factors such as histology.[5,6,14-16] Given the number of clinical (histology, location, size) and treatment factors (dose/fractionation, coverage) that vary widely in the metastatic patient population, our study provides valuable disease outcome information on the more specific subset of patients with oligometastatic bone-only disease treated with SBRT. As SBRT continues to be incorporated into standard treatment options for patients with metastatic disease, additional prospective data on subpopulations of patients with metastatic disease will become increasingly important.

In this regard, there have been multiple studies that have demonstrated that SBRT to the spine is safe and effective,[10,28,32-34] although post-SBRT vertebral compression fracture is a known risk.[20,21,35] Approximately half of the lesions in our study were spine metastases, and the other half were nonspine bone metastases, the latter of which is represented by some retrospective studies[36,37] though relatively few prospective clinical studies in the literature.[13,38] A recent randomized phase II trial from MD Anderson enrolled patients with predominantly nonspine painful bone metastases and randomized to single-fraction SBRT versus conventional palliative RT,[13] which demonstrated a higher rate of pain response compared with multifraction conventional RT. However, direct comparisons of efficacy are not possible between this study and ours, given the significant differences in



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enrolled patient population in our study (≤3 active sites of disease, most of which were asymptomatic) and the primary endpoint of pain response in the MD Anderson study.

Given that clinical outcomes vary significantly by primary histology, recently published trials have also explored histology-specific utility of SBRT in the oligometastatic setting. The most represented primary disease site in our study was prostate cancer, and the more favorable outcomes among these patients compared with patients with other histologies is in keeping with results from the growing literature of metastasis-directed therapy in patients with oligometastatic prostate cancer.[8,9,39,40] STOMP and ORIOLE are 2 large prospective phase II trials randomizing patients with prostate cancer with ≤3 metastatic sites to either surveillance or local ablative therapy.[8,9] In STOMP, the median ADT-free survival was 21 months (80% CI, 14-29 months) for patients who received surgery or SBRT, where indications for starting ADT were polymetastatic, local, or symptomatic progression. Although not a directly comparable endpoint, the median PFS was 29.6 months (95% CI, 15.9 to NA months) for patients with prostate cancer in this study. We note that time until PSA progression was 10 months (80% CI, 8-13 months) for patients who received either surgery or SBRT in STOMP, whereas the median time to PSA progression in our study was 48.3 months (95% CI, 23.4 to NA months). This discordance may reflect differences in patient population, sample size, definition of PSA failure, and baseline imaging studies. In this regard, most patients with prostate cancer in our study were not staged with next-generation imaging (only 1 patient received a baseline prostate-specific membrane antigen positron emission tomography/CT scan). Use of advanced prostate cancer–specific imaging may identify earlier (and potentially smaller) metastatic lesions,[41] and it will be important to monitor long-term disease control and toxicity outcomes among patients with metastatic prostate cancer in the pre- versus post-advanced imaging era. Lastly, most patients with prostate cancer (89.6%) in our study were prescribed ADT within 90 days of SBRT. We note that while it is difficult to conclude based solely on our study whether SBRT provides additional disease control benefit to ADT alone,

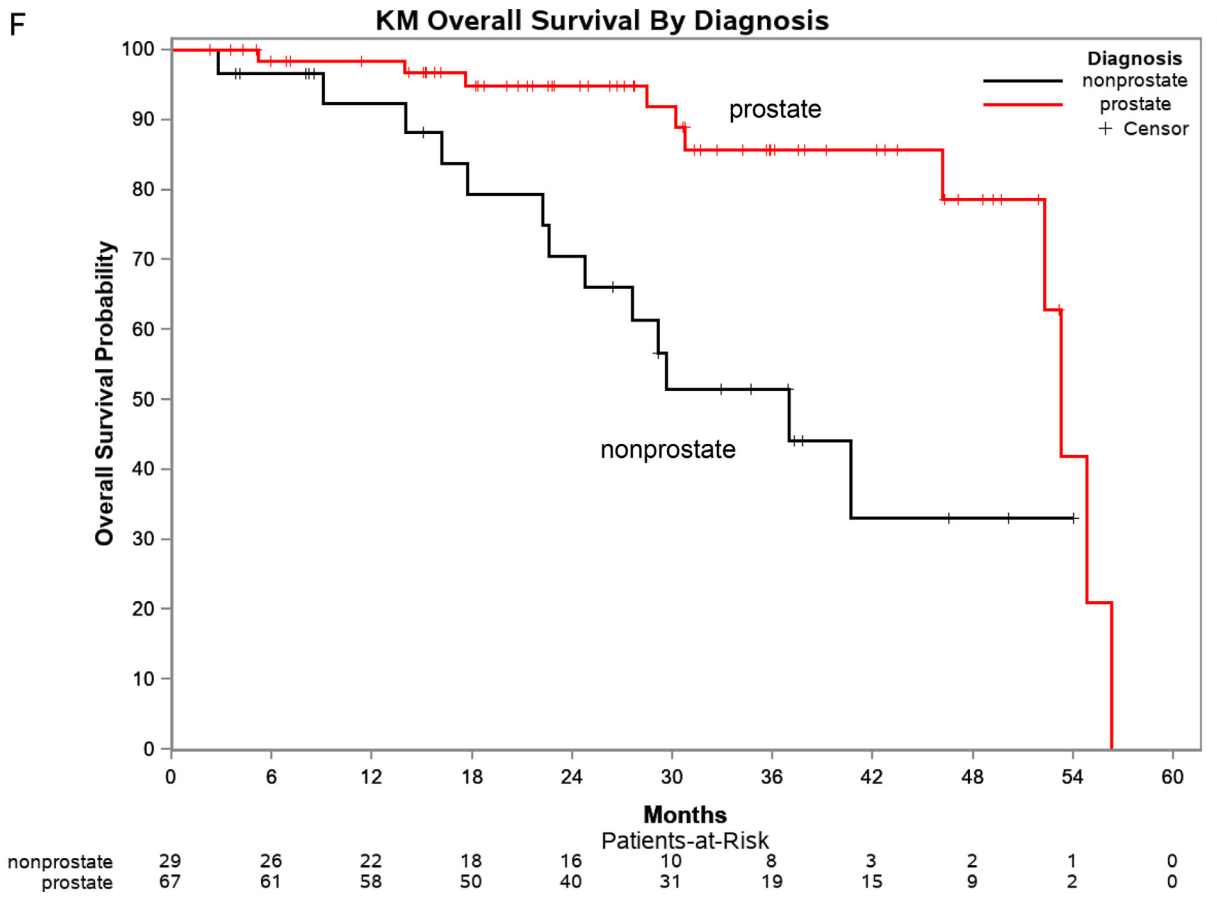

Figure 2 **Continued.**

the recent randomized phase II EXTEND trial demonstrated improvement in PFS with addition of metastasis-directed therapy to hormone therapy for oligometastatic prostate cancer.[40]

The treatment-related toxicity we observed in our study is comparable to that reported in prospective studies, as summarized in a recent large meta-analysis,[4] with grade ≥3 toxicities constituting <10% in most studies. We did observe 4 posttreatment fractures (6.1%) of the 66 spine sites treated in this cohort. This fracture rate is comparable to studies of fractures rates after spine SBRT studies: In a multi-institutional study of vertebral compression fracture following spine SBRT to 410 sites, the de novo fracture rate was 6.6%.[20] These findings emphasize that predictive scores such as the spinal instability in neoplasia score should be used to identify patients at risk for fracture after SBRT, and follow-up of spine SBRT patients should include ongoing assessment for fracture.[42]

Our results contribute to a growing body of literature characterizing long-term disease and toxicity outcomes among subsets of patients with metastatic disease treated with SBRT. However, we note several limitations of our study. While our inclusion of all histologies allows for more generalizable results, it limits the ability to report conclusively regarding disease-specific outcomes, especially among nonprostate histologies that were less represented in this group. In addition, the variation in histology also implies a range of systemic therapy regimens that were used in this study. Furthermore, systemic therapy regimens and timing of initiation of these regimens was determined independently by the patients' treating physicians and thus was not standardized. It is therefore difficult to distinguish the contribution of SBRT and choice of systemic therapy on progression and clinical outcomes. Similarly, a range of radiation doses was used in this study, and the choice of radiation dose was determined by the treating radiation oncologist. Lastly, we note that toxicities reported in this study were physician reported; patient-reported quality-of-life outcomes from this trial will be reported separately.

The above limitations of our study raise several active areas of study and debate in use of SBRT for management of metastatic disease. First, the optimal

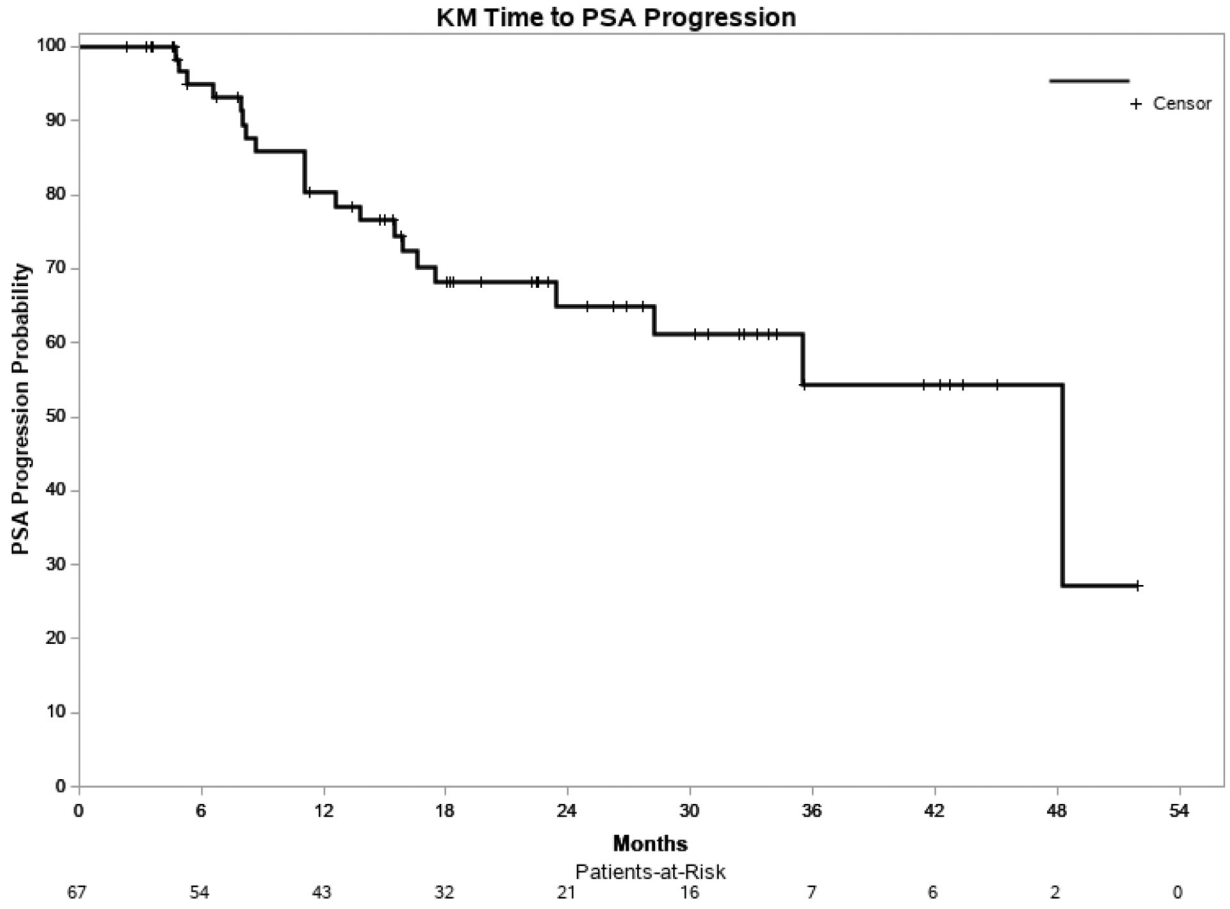

Figure 3 Kaplan-Meier (KM) curve for prostatic specific antigen (PSA) progression-free survival among patients with prostate cancer.

dose of radiation for SBRT for bone lesions is not well established. Choice of dose is often determined by institutional or historical precedent and further guided by size of the lesion, histology, and neighboring organs at risk. While these doses theoretically achieve high BED based on radiobiology models, the efficacy of varying dose regimens has not been compared and prospectively studied. In addition, conventions for prescribing dose vary widely based on trial and institution and make it challenging to interpret and apply a standard dose regimen.

Second, the range of systemic therapy regimens used in our study underscores the importance of effective systemic therapy in the management of oligometastatic disease. Given that oligometastatic treatment is generally given with curative intent, ablative local therapy to gross areas of disease may be most beneficial when combined with effective systemic therapy regimens that can successfully treat micrometastatic disease. Such benefit is suggested by recent data demonstrating benefit when tyrosine kinase inhibitor treatment is combined with SBRT in *EGFR*-mutated non-small cell lung cancer.[7]

Finally, we note that the definition of oligometastatic disease, and who may benefit from ablative local therapy, is an area of active investigation. Our study enrolled patients with ≤3 oligometastatic bone lesions, although the cutoff for number of metastatic sites that may still benefit from ablative treatment is unclear. These clinical decisions become more complicated as one considers size of lesions, rate of growth, time to development of metastases, and organ systems involved.[18] Other prospective trials using SBRT have used a wide range of definitions for oligometastatic disease,[9,36,43,44] underscoring the lack of consensus in definition. Phase III trials exploring the efficacy of SBRT for metastatic disease are ongoing that may help clarify the benefit of ablative therapy based on number of metastatic sites. SABR-COMET-3 is enrolling patients with 1 to 3 metastatic lesions, randomized to either standard of care or SBRT,[45] and SABR-COMET-10 is enrolling patients with 4 to 10 sites of metastatic disease, randomized to standard of care or SBRT.[46] Results from these trials may demonstrate benefit of SBRT for patients with as many as 10 metastatic sites and may further challenge current paradigms of who may benefit from ablative local therapy.

Table 3 Postbaseline treatment-related toxicities by grade, where 26 patients experienced treatment-related toxicities

Toxicity	Grade 1	Grade 2	Grade 3
Patients with only nonspine lesions			
Back pain	1 (1.0%)	-	-
Decreased appetite	1 (1.0%)	-	-
Dermatitis	1 (1.0%)	-	-
Diarrhea	1 (1.0%)	-	-
Fatigue	3 (3.1%)	-	-
Hip pain	1 (1.0%)	-	-
Hoarseness/hypophonia	1 (1.0%)	-	-
Nausea	1 (1.0%)	-	-
R sciatica pain	-	1 (1.0%)	-
Rib pain	-	1 (1.0%)	-
Patients with only spine lesions			
Abdominal bloating	1 (1.0%)	-	-
Back pain	2 (2.1%)	-	-
Diarrhea	1 (1.0%)	-	-
Dry mouth	1 (1.0%)	-	-
Dysphagia	1 (1.0%)	-	-
Esophagitis	2 (2.1%)	-	-
Fatigue	5 (5.2%)	-	-
Gastritis	-	1 (1.0%)	-
Nausea	3 (3.1%)	1 (1.0%)	-
Radiculitis	1 (1.0%)	-	-
Vertebral fracture	1 (1.0%)	-	3 (3.1%)
Vomiting	-	1 (1.0%)	-
Patients with both spine and nonspine lesions			
Back crepitus	1 (1.0%)	-	-
Fatigue	2 (2.1%)	-	-
L hip soreness	1 (1.0%)	-	-
Skin hyperpigmentation	1 (1.0%)	-	-
Skin induration	1 (1.0%)	-	-

Some patients experienced more than 1 toxicity. If a patient experienced the same toxicity more than once, the maximum-grade instance of the toxicity is recorded.

Conclusion

Taken together, the results from our prospective phase II trial provide additional data that support the use of SBRT for oligometastatic bone disease among patients with ≤3 lesions. Disease outcomes were favorable in our results, with low levels of physician-reported toxicity. Optimal dose, number of lesions treated, and predictors of local failure in this patient population merit further investigation.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101411.

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