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Scientific Article

Early Clinical Outcomes and Local Control Following Spine Stereotactic Proton Ablative Radiation Therapy

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Purpose: To evaluate the local control (LC) outcomes and safety profile of stereotactic proton ablative radiation therapy (SPAR) for spine metastases in a highly selected patient population, with emphasis on reirradiation cases.

Methods and Materials: We retrospectively reviewed all patients who received SPAR between June 2015 and October 2019. Treatments were delivered in 1 to 5 fractions with a median of 3 fractions. The median prescription dose was 39 Gy (range, 20-60 Gy) to the high-dose clinical target volume (CTV) and 24 Gy (range, 16-50 Gy) to the low-dose CTV. All treatments were delivered using pencil-beam scanning proton therapy with single-field or multifield optimization. LC was assessed per spine response assessment in neuro-oncology (SPINO) criteria using follow-up imaging. Survival and recurrence outcomes were estimated by the Kaplan-Meier method. Acute and late adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

Results: Forty-two patients (47 lesions) were treated with SPAR, with 66% treated in the reirradiation setting. With a median imaging follow-up of 13 months, 1- and 2-year LC rates were both 74% (95% CI, 58%-91%). Ten lesions progressed locally (8 in-field, 2 marginal), most commonly within the vertebral body. No significant predictors of progression were identified aside from low-dose CTV and D95%. Acute AEs included 9 pain flares and one grade 3 dermatitis. Late AEs included 3 vertebral compression fractures and one grade 3 peripheral neuropathy. No cases of radiation myelopathy were observed.

Conclusions: SPAR provides durable LC with acceptable toxicity in a highly selected patient population. These findings support the feasibility of SPAR in complex or reirradiation cases, though broader applicability may be limited by access to high-precision proton therapy systems.

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

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Introduction

Improvements in local, systemic, and supportive therapies have led to prolonged survival in patients with metastatic cancer.[1] Among these patients, spinal metastases are common, affecting up to 30% over the disease course and often causing significant morbidity.[2,3] Spine stereotactic ablative radiation therapy (SABR) has become a standard approach for managing these lesions, delivering high-dose radiation to the tumor with sharp dose gradients to protect adjacent organs at risk (OARs) such as the spinal cord, esophagus, and bowel.[4-7] Across multiple studies, photon-based spine SABR has demonstrated local control (LC) rates of approximately 80% at 1 year in de novo cases and 70% to 90% in the reirradiation setting.[4,8]

Achieving durable local tumor control is critical in the modern metastatic setting, particularly for patients receiving systemic therapy or those with oligometastatic disease. Early-phase trials have demonstrated the clinical benefit of ablative local therapies in these populations,[9-13] and ongoing studies continue to investigate their role in both oligometastatic and polymetastatic settings.[14]

Intensity modulated proton therapy (IMPT) offers highly conformal dose delivery with rapid fall-off via the Bragg peak. This enables effective tumor targeting with reduced dose to surrounding normal tissue. Although proton therapy has been widely studied in the treatment of chordoma, chondrosarcoma, and other spine tumors,[15-19] data on ultrahypofractionated proton therapy for metastatic spine disease are limited, having been evaluated in prostate cancer,[20] early-stage breast cancer,[21] early-state lung,[22,23] and renal cell carcinoma.[24] Spine stereotactic proton ablative radiation therapy (SPAR) may provide a treatment option for anatomically complex or previously irradiated cases while maintaining highly conformal dose distributions. In this study, we report our institutional experience evaluating clinical outcomes and LC following SPAR.

Methods and Materials

Patient population

Following institutional review board approval, we retrospectively reviewed consecutive adult patients (age ≥18) with metastatic lesions of the spine who were treated with SABR using pencil-beam scanning technology between June 2015 and October 2019. We included patients with either single-level or multilevel spine disease. Patients who received treatment for multiple spine levels in one contiguous volume were counted as a single lesion. Likewise, lesions in which treatment volumes were separate were counted as separate lesions.

Patients were selected for SPAR at the discretion of the treating physicians, in consultation with a multidisciplinary team, based on clinical and dosimetric considerations. Proton therapy was preferentially offered in cases with prior radiation exposure to the spinal cord or adjacent neural structures, when gross tumor volume was near critical structures, or when maximal OAR sparing was required. Patients were selected for SPAR based on the following institutional criteria: (1) prior radiation exposure to the spinal cord or neural structures with concerning cumulative doses; (2) gross tumor volume in dose proximity to critical structures requiring sharp dose gradients; (3) need for sparing of anterior organs (esophagus, heart, bowel) particularly in reirradiation settings; and (4) young patients where long-term toxicity reduction was prioritized. Approximately 5 to 8 spine lesions annually meet these criteria at our institution, with the remainder receiving photon SBRT. These criteria differ from standard photon SBRT indications in that they specifically leverage the physical dose distribution properties of protons, namely, the finite range and absence of exit dose, to reduce integral dose to healthy tissues beyond the target. Although photon SBRT achieves adequate target conformality and cord sparing for most spine metastases, SPAR was considered when the clinical scenario required minimization of dose to organs anterior or lateral to the vertebral body (eg, esophagus, bowel, heart, kidneys), particularly in the reirradiation setting where cumulative doses to these structures were of concern. For reirradiation cases, treatment decisions were individualized based on the time interval from prior radiation therapy (RT), prior dose and fractionation, volume and location of field overlap, and the patient's clinical status and prognosis. Comparative photon plans were not generated, as the clinical decision for proton therapy was made prospectively per our institutional patient-selection protocol based on healthy tissue sparing considerations.

Computed tomography simulation technique

Immobilization for computed tomography (CT) simulation was selected by the treating physician. Typically, patients with cervical or upper thoracic lesions were immobilized with a custom head- and shoulder-rest using Klarity mold (Klarity Medical) and a 5-point Aquaplast

mask (Orfit Industries) with or without a mouthpiece. To help with shoulder immobilization, some physicians used indexable hand grips. For lower thoracic, lumbar, and sacral lesions, patients were typically immobilized over memory foam and an indexable knee cushion (CIVCO) with either arms up with upper Vac-Lok or arms down with hand grips. Careful attention was necessary to avoid skin folds in the neck or back, which impacts range uncertainty. CT simulation was routinely obtained at 1 mm increments to encompass the clinical target and appropriate OARs. Magnetic resonance imaging (MRI) in the treatment position was performed for target and OAR delineation. CT myelograms were also obtained for OAR delineation for patients with surgical hardware that would cause MRI artifacts. Extended Hounsfield Unit (HU) CT reconstruction was used in patients with spinal hardware, and a medical physics consult was requested to verify hardware material identification and Hounsfield number assignment accuracy.

Treatment planning techniques

Clinical target volume (CTV), OARs delineation, prescription dose, and fractionation were determined by the treating physician. Our institutional practice for photon- and proton-based spine SBRT often uses a 2 CTV delineation technique with a low-risk CTV (ctv_low) and simultaneous integrated boost (SIB) to gross tumor volume (GTV) + 0 to 2 mm margin (ctv_high) as previously described.[4] The CTV closely resembles the Radiation Therapy Oncology Group guidelines.[5]

Depending on the proximity of the CTVsto the OAR structures, IMPT plans were generated using either the single-field optimization or the multifield optimization techniques in the Eclipse Treatment Planning system v15.1 (Varian). Doses were prescribed using a relative biological effectiveness (RBE) estimate of 1.1 Gy. The dose calculation grid size was $2.5 \times 2.5 \times 2.5$ mm^3. Generally, 2 to 3 treatment beams were used per plan per isocenter. Hitachi ProBeat-V synchrotron proton therapy system, with 97 discrete proton energy levels, was modeled in the treatment planning software. This model uses a spot library with proton energy from 71.3 MeV to 228.8 MeV, corresponding to a clinical treatment range of 3.9 g/cm^2 to 32.35 g/cm^2. The spot size at the isocenter, defined by spot sigma in air, was measured as 5.7 mm at the lowest energy (71.3 MeV) and 2.5 mm at the highest energy (228.8 MeV). Range shifters of 25 mm and 45 mm water equivalent thickness were used in treatment planning and delivery to ensure dose coverage to superficial CTVs. Instead of additional margin expansion from the CTV, range and setup errors were explicitly considered as part of the optimization problem to ensure robust CTV coverage. Robust IMPT plans were created with the Eclipse Nonlinear Universal Proton Optimizer (NUPO) robust optimization algorithm. A setup uncertainty of 3 mm and a range uncertainty of 3% were chosen as the robust optimization parameters to account for patient daily setup errors and proton range uncertainties. The robustness of each IMPT plan with respect to the setup and range uncertainties using the worst-case analysis method was evaluated in Eclipse.

As part of the routine plan check and quality assurance process, every proton plan was recalculated using an in-house Graphics Processing Unit (GPU)-accelerated Monte Carlo (MC) second check dose engine. The biological dose distribution for each IMPT plan was estimated using a simple linear relationship between the dose-averaged linear energy transfer and the MC-calculated physical dose distribution.[25,26] Both the biological dose and the physical dose were reviewed during the plan evaluation process to ensure no hot spots inside the OARs.

Dose fractionation schemes were selected based on reirradiation cord tolerance as published by Sahgal et al[27] and our central nervous system (CNS) disease group consensus. Three-fraction regimes (39 Gy in 3 fractions to the high-dose CTV structure) were preferred for most cases, with single-fraction or 5-fraction schedules selected based on tumor size and histology, prior radiation, and proximity to critical structures.

The OARs were given priority 1 for treatment optimization and met TG101 constraints.[28] A planning risk volume expansion of 1.5 to 2 mm was applied to the spinal cord and cauda equina for both robust optimization and plan evaluation purposes. The target coverage goal for ctv_low and ctv_high was D90% $\geq$100% (priority 2) and D0.03 cm^3 $\leq$120% (priority 2). As part of routine treatment plan evaluation, treatment plans were evaluated for CTV coverage and increased RBE dose within OARs, such as the cord, cauda equina, sacral plexus, esophagus, heart, peripheral nerves, bowel, and rectum, and modified as necessary to limit biologic hot spots in these structures. A sample SPAR plan is shown in Fig. 1.

Follow-up imaging was obtained at 3- to 6-month intervals or sooner if clinically indicated. Imaging modality (MRI, CT, or positron emission tomography) was selected based on the clinical scenario.

Treatment delivery and verification

Daily image guidance involved stereoscopic oblique kilovoltage imaging and 6 degree of freedom matching to the spine for each treatment field. Spine matching tolerance was 2 mm. CT-on-rails was used for treatment localization and dose robustness evaluation. During the proton beam delivery, the patients were closely monitored by a surface-guided imaging system to assess intrafraction patient motion. Patient position was reverified at each gantry and couch angle with 2-dimensional/3-dimensional kV imaging.

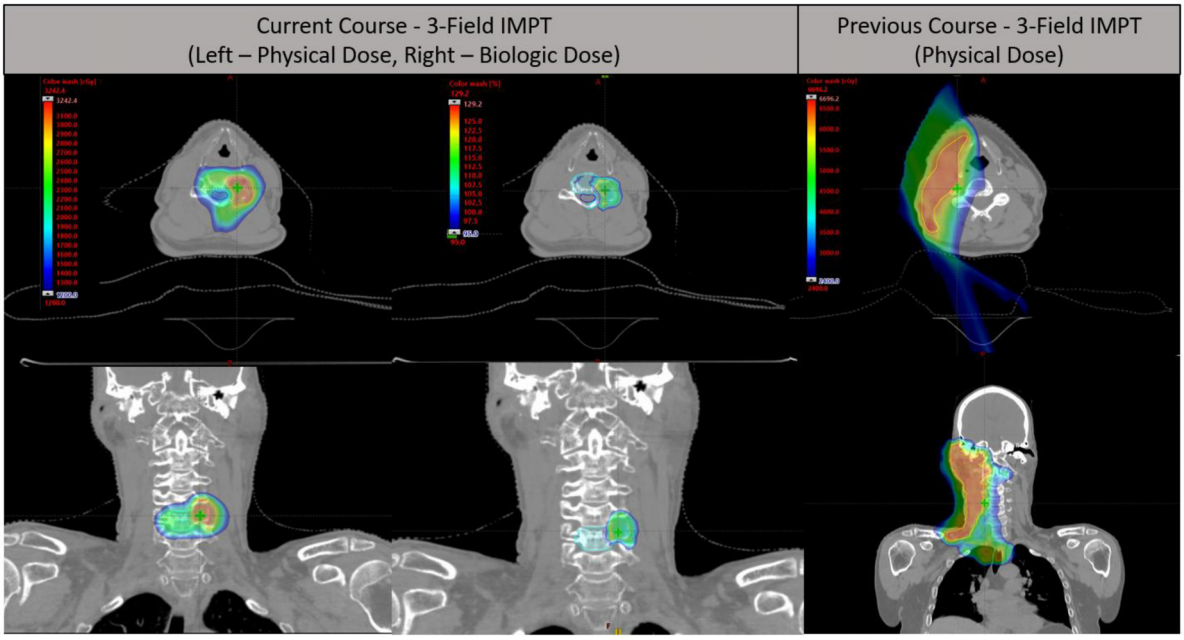

Figure 1 A selected patient received a 3-field multifield optimized stereotactic proton ablative radiation therapy for the C5 vertebral body. Radiation therapy dose was 30 Gy (relative biological effectiveness = 1.1) to ctv_high and 24 Gy to ctv_low in 3 fractions. The patient had received prior adjuvant chemoradiation therapy with intensity modulated proton therapy (IMPT), 60 Gy in 30 fractions.

Patients completed at least one verification CT scan (typically treatment day 1) to assess target volume coverage, dose to OARs, and the need for adaptive replanning. Replanning was performed per the physician's discretion and typically was undertaken to reduce inhomogeneity, improve CTV coverage, and/or decrease dose to OARs.

Outcomes

Patient, tumor, and treatment characteristics and oncologic outcomes were collected retrospectively. Tumor characteristics, including location, spinal canal encroachment, radiologic appearance, and vertebral body integrity, were based on diagnostic images obtained before SPAR. Local tumor control was based on the SPINO response assessment consensus criteria.[29] Local recurrence was defined as evidence of disease progression at the site of SPAR seen on positron emission tomography, magnetic resonance, or single-photon emission planar bone scans. Pre- and post-SPAR spine procedures, including cryoablation, radiofrequency ablation, or vertebral cement augmentation, were documented based on review of procedural reports. Pre-SPAR interventions were considered part of prior treatment history. Post-SPAR procedures were not classified as evidence of disease progression unless supported by imaging findings.

Spine stability and epidural disease burden were evaluated using validated clinical scoring systems. The spinal instability neoplastic score (SINS) was used to assess vertebral stability. Epidural spinal cord compression was graded according to the Bilsky classification on MRI.

Acute and late RT adverse events (AEs) were collected per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Acute AEs were defined as within 30 days of the start of SPAR, whereas late AEs were those greater than 30 days after completion of SPAR. Because of different dose fractionation schemes, the biologic effective dose and equivalent dose in 2 Gy fractions (EQD2) were calculated for the target ($\alpha/\beta = 10$) and cord ($\alpha/\beta = 2$) structures.

Statistical analysis

LC was defined as the absence of radiographic progression within the treatment target volume on follow-up imaging. LC and overall survival (OS) were estimated using the Kaplan-Meier method. Survival, recurrences, follow-up, and AEs were measured from the day of SPAR completion. Patients without local recurrence were considered censored for local recurrence, and patients who were alive at last follow-up were considered censored for OS. A univariable Cox model was used to assess the association of baseline variables with the risk of local recurrence.

Results

Study cohort and treatment characteristics

Patient characteristics are shown in Table 1. The median patient age was 66 years (range, 27-81 years). A

Table 1 Pre-RT patient and spinal lesion characteristics

Variable Number or median (range)	
Number of patients	42
Number of spinal lesions	47
Age (y)	66 (27-81)
Sex: male/female	29/13
Primary tumor site	
Prostate	25
Bone/Sarcoma	4
Colorectal	4
Breast	3
Uterine	2
Lung	2
Kidney	2
Skin/melanoma	2
Head/neck	2
Endocrine	1
Spine segment	
Cervical	2
Thoracic	11
Lumbar	21
Sacrum	13
Prior local intervention	
Surgery	4
Ablation	2
Prior RT	31
Overlapping RT	16
Palliative RT	10
SABR	5
Spine disease characteristics	
SINS score	
Stable (0-6)	27
Potential unstable (7-12)	20
Bilsky grade	
0	38
1	6
2	3
Vertebral body involvement	37
Soft tissue extension	7
Posterior element involvement	
Unilateral	12
Bilateral	8
Number of levels treated	
1	31
2	9
3	5
4	1
7	1

(*continued on next column*)

Table 1 (*Continued*)

Abbreviations: RT = radiation therapy; SINS = spinal instability neoplastic score.

total of 47 metastatic lesions in 42 patients (29 male and 13 female) received spine SPAR. The most common primary histology was prostate adenocarcinoma (53%), followed by bone/soft tissue sarcoma (9%) and colorectal (9%). Most lesions were located in the thoracic (23%) or lumbar (44%) spine.

Spine stability and epidural involvement were evaluated using the SINS and Bilsky scoring systems, respectively. Most lesions (57%) were classified as stable by SINS (score, 0-6), whereas the remaining 43% were deemed potentially unstable (score, 7-12). By Bilsky grade, 81% of lesions were grade 0 (no epidural involvement), 13% were grade 1, and 6% were grade 2.

Treatment characteristics prior to SPAR are found in Table 1. Thirty-one (66%) lesions were treated in the setting of prior RT, either overlapping RT fields (16, 38%) or spine retreatment (15, 36%). Three (5.9%) lesions received combined modality ablation (2 cryotherapy and 1 radiofrequency). Two lesions underwent prophylactic kyphoplasty, and 3 lesions underwent therapeutic kyphoplasty following SPAR.

Target radiation dose and dosimetric details are found in Table 2. One, 3, or 5 fractions were used in 4 (8%), 38 (81%), and 5 (11%), respectively. Of the treated lesions, 91% used SIB technique to boost the ctv_high. The median prescription doses for ctv_high and ctv_low were 39 Gy (range, 20-60 Gy) and 24 Gy (range, 16-50 Gy), respectively.

LC and outcomes

Forty-two (89%) lesions had imaging follow-up. The median follow-up for LC was 13 months (range, 1.5-36 months). LC at 1 and 2 years was 74% (CI, 58%-91%) and 74% (CI, 58%-91%). Ten patients experienced local disease progression: 8 in-field and 2 marginal. The location of the disease progression was the vertebral body (7), posterior elements (2), and epidural (1). Individual patient-specific information on the 10 patients/sites with disease

Table 2 Univariate models of dosimetric factors for local control at 1 and 2 years

Parameter	Median (IQR)	HR (95% CI)	P value	Median BED (IQR)*	HR (95% CI)	P value
GTV						
Volume (cc)	13.0 (5.35-40.9)	0.95 (0.77-1.2)	0.68			
High-dose CTV						
Volume (cm3)	18.0 (5.18-33.6)	0.96 (0.8-1.1)	0.59	89.7 Gy (60-89.7 Gy)	1.00 (0.97-1.03)	0.79
Prescription (GyE)	39 GyE (30-39 GyE)	1.02 (0.96-1.09)	0.52	102 Gy (77.6-111 Gy)	1.00 (0.98-1.03)	0.71
Dmax	111% (108%-115%)	1.02 (0.96-1.09)	0.47	41.8 Gy (28.1-54.7 Gy)	1.01 (0.9-1.03)	0.5
Dmin	60.7% (47.5%-90.0%)	1.05 (0.8-1.4)	0.71	66.6 Gy (55.3-84.9 Gy)	0.99 (0.97-1.02)	0.68
D95%	90.8% (79.5%-100%)	0.87 (0.6-1.2)	0.41	74.6 Gy (59.9-90.8 Gy)	0.99 (0.96-1.02)	0.65
D90%	98.1% (86.0%-101%)	0.85 (0.6-1.2)	0.37	90.4 Gy (66.9-95.4 Gy)	1.00 (0.97-1.03)	0.98
Dmean	102% (98.8%-104%)	0.75 (0.4-1.7)	0.48			
Low-dose CTV						
Volume (cm3)	65.3 (36.0-87.5)	1.01 (1.001-1.01)	**0.02**	43.2 Gy (43.2-60 Gy)	1.00 (1.00-1.009)	0.058
Prescription (GyE)	24 GyE (24-30 GyE)	1.02 (0.95-1.10)	0.6	100 Gy (75.0-110 Gy)	1.01 (0.98-1.03)	0.71
Dmax	148% (139%-177%)	1.03 (0.96-1.09)	0.39	22.6 Gy (18.0-30.3 Gy)	0.97 (0.9-1.03)	0.37
Dmin	60.3% (44.5%-74.1%)	0.87 (0.6-1.2)	0.37	45.4 Gy (41.6-51.6 Gy)	0.94 (0.9-0.995)	**0.048**
D95%	100% (90.5%-105%)	0.73 (0.5-1.01)	0.58	49.4 Gy (44.3-56.5 Gy)	0.96 (0.9-1.02)	0.21
D90%	103% (97.9%-109%)	0.76 (0.5-1.1)	0.17	69.2 Gy (57.5-79.6 Gy)	0.99 (0.95-1.03)	0.57
Dmean	122% (114%-128%)	0.86 (0.5-1.4)	0.54			

Abbreviations: BED = biologic effective dose (α/β = 10); CTV = clinical target volume; D(x)% = dose to x% of volume; Dmax = maximum dose; Dmean = mean dose; Dmin = minimum dose; GTV = gross tumor volume; HR = hazard ratio. Boldface values: statistically significant.

progression is found in Table 3. Of 10 local progressed cases, 7 occurred in the vertebral body, 2 in posterior elements, and only 1 in the epidural space (Table 3). Notably, only 1 of 10 local failures occurred in the epidural space. However, this cohort was predominantly Bilsky 0 to 1 (94%), where epidural recurrences would not be highly anticipated regardless of treatment modality. Salvage treatments included systemic therapy (n = 6), reirradiation (n = 2), and surgical intervention (n = 1). One patient received best supportive care.

Predictors of local disease progression

Multiple patient-specific, dosimetric, and radiographic factors were considered as univariate variables for predicting disease progression (Tables 2, 4, and 5). D95% for ctv_low (HR, 0.94; CI, 0.9-0.995; P = .048) and volume of ctv_low (HR, 1.01; CI, 1.001-1.01; P = .02) were predictive of local disease progression. Biological sex, age ≥60 years, prostate histology, number of treated vertebral body levels, ctv_high dose, ctv_low dose, gtv, and other dosimetric factors were not predictive of local disease progression (Table 2). Reirradiation cases did not show significantly higher local progression rates (P = .33, Table 4).

Secondary outcomes

Median follow-up for OS was 14 months (range, 1.8-36 months). OS at 1 and 2 years were 75% (95% CI, 62%-92%) and 68% (CI, 51%-90%), respectively. Acute and late AEs were collected for the patient cohort. There were no grade 4 or 5 AEs. There were 10 patients with 16 acute AEs. There were 9 (18%) pain flares (5 grade 1 and 4 grade 2), 3 (6%) grade 1 transient peripheral neuropathies, 1 (2%) grade 3 radiation dermatitis, 1 (2%) grade 1 radiation dermatitis, 1 (2%) grade 1 esophagitis, and 1 (2%) grade 2 fatigue. For late AEs, there was 1 grade 3 peripheral neuropathy (unilateral) secondary to cement extravasation following kyphoplasty. There were 3 (9%) vertebral compression fractures (VCFs), with 2 of 29 (7%) with de novo VCF at 11 and 17 months and 1 of 5 (20%) with progression of an existing VCF at 17 months. There were no cases of myelopathy.

Discussion

We evaluated our institutional experience with ablative proton therapy for metastatic lesions of the spine. Here,

Table 3 Description of patterns of local failure with patient-specific and treatment variables

Patient	Bone location of failure	Dosimetric location of failure	Time to failure (mo)	Histology	Prior RT	ctv_high dose (GyE)	ctv_low dose (GyE)	Fractions	Additional local therapy
Patient 1	VB	Low dose	4.6	Endometrial carcinoma (grade 2)	SABR	30	24	3	Pre-RT surgery
Patient 2	VB	High dose	6.8	Prostate adenocarcinoma (5 + 4)	None	39	24	3	-
Patient 3	VB	High dose	6.7	Prostate adenocarcinoma (4 + 3)	Overlapping RT	39	24	3	-
Patient 4	VB	Low dose	27	Prostate adenocarcinoma (5 + 4)	None	39	24	3	-
Patient 5	VB	High dose	7.5	Prostate adenocarcinoma (4 + 3)	Palliative RT	39	24	3	-
Patient 6	VB	High dose	7.0	Prostate adenocarcinoma (4 + 5)	Palliative RT	39	24	3	-
Patient 7	VB	Marginal	26	Breast, IDC, ER+/PR+, grade 3	None	60	50	5	-
Patient 8	Epidural	Low dose	9.0	Melanoma	None	27	21	3	-
Patient 9	PE	Marginal	6.7	Prostate adenocarcinoma (5 + 4)	SABR	36	none	3	-
Patient 10	PE	High dose	6.3	Prostate adenocarcinoma (4 + 4)	Overlapping RT	39	27	3	-

Abbreviations: ctv = clinical target volume; ER+ = estrogen receptor−positive; IDC = invasive ductal carcinoma; PE = posterior element; PR+ = progesterone receptor−positive; RT = radiation therapy; VB = vertebral body.

we report our initial LC and toxicity outcomes using spine SPAR. From a cohort enriched for reirradiation cases (66%), we included patients who received spine SPAR in the de novo, reirradiation, and postoperative settings with multiple single-fraction and multifraction regimens. Our results indicate that spine SPAR can provide acceptable local tumor control and has a low risk of AEs. These findings build upon a growing body of photon-based spine SBRT studies from our institution, which have demonstrated high LC rates, low toxicity, and validated predictors for vertebral fracture and myelopathy.[30-33] In contrast to more mature photon studies, SPAR introduces proton-specific dosimetric characteristics, such as sharper distal fall-off, RBE-informed dose modeling, and the potential for reduced OAR exposure, particularly in complex or reirradiation settings. Multiple prospective and retrospective studies have shown spine SABR to have excellent local tumor control of 70% to 90% in the de novo, reirradiation, and postoperative setting with photon-based techniques.[4,8] With a median follow-up of 13 months, the 1- and 2-year local tumor control was 74% in this cohort. Notably, we did not identify dose, SINS score, Bilsky grade, single versus multifraction, and GTV as significant predictors of local disease progression.

No significant clinical or dosimetric predictors of failure were identified, though lower D95% to the ctv_low and smaller target volumes were associated with local progression. The locations of local disease progression were notable. There was only one case of epidural disease progression. It is important to note that our cohort was predominantly Bilsky 0 to 1 (94%), where epidural failures would not be anticipated. Additionally, modern photon SBRT practices employ more relaxed spinal cord constraints than the early phase 1/2 trial by Chang et al,[34] which used a spinal cord Dmax of 9 to 10 Gy. As such, the low epidural failure rate in our cohort likely reflects the low burden of epidural disease rather than a treatment modality−specific effect. In our cohort, 7 of the 10 cases of disease progression occurred in the vertebral body, with 7 in either the high or low-dose CTV. The higher risk of disease progression could be because of factors including prior radiation, aggressive histologic behavior, or reduced radiosensitivity in certain lesions, though classic radioresistant histologies were not predominant in this cohort (Table 3). Additionally, MC-based proton dose calculation in high-density bone has been shown to produce a lower absorbed dose than analytical algorithms, because of more accurate modeling of mass density and secondary particle production.[35,36] Some radiation oncologists, therefore, increased dose prescription to overcome this potential dose reduction with proton treatment, eg, an increase from 36 to 39 Gy in 3 fractions. Current institutional efforts are underway to examine biological modeling for the possible association of local disease progression with ablative proton RT.

Table 4 Univariate models of pre-RT characteristics for local control at 1 and 2 years

Variable (n)	Local control at 1 year (95% CI)	Local control at 2 years (95% CI)	HR (95% CI)	*P* value
Overall (42)	74 (59-91)	74 (55-91)		
Sex				
Male (28)	67 (49-91)	67 (44-91)	1.0 (Ref)	.67
Female (14)	92 (72-100)	92 (65-100)	0.71 (0.15-3.42)	
Other histology (16)	79 (52-100)	79 (41-100)	1.0 (Ref)	.61
Prostate/breast histology (26)	71 (54-94)	71 (50-94)	1.52 (0.31-7.54)	
Age (y)				
< 60 (12)	75 (47-100)	75 (39-100)	1.0 (Ref)	.59
≥ 60 (30)	73 (56-94)	73 (51-94)	0.68 (0.169-2.73)	
Bilsky grade				
= 0 (39)	72 (56-92)	72 (52-92)	1.0 (Ref)	.82
> 0 (8)	83 (50-100)	83 (50-100)	0.79 (0.10-6.42)	
Vertebral body involvement				.40
Yes (34)	70 (52-91)	70 (48-91)	1.0 (Ref)	
No (8)	85 (62-100)	86 (54-100)	2.44 (0.31-19.27)	
Soft tissue involvement				
Yes (7)	83 (45-100)	83 (45-100)	1.12 (0.136-9.18)	.92
No (35)	74 (58-92)	74 (54-93)	1.0 (Ref)	
Posterior element involvement				
None (22)	61(40-91)	61 (37-91)	1.0 (Ref)	.29
Unilateral (10)	100	100	0.31 (0.04-2.64)	.71
Bilateral (7)	80 (49-100)	80 (40-100)	0.66 (0.08-5.65)	
SINS score				
Per 1 point			1.25 (0.92-1.70)	.16
Stable (0-6) (32)	78 (63-97)	78 (58-97)	1.0 (Ref)	
Potential unstable [7-12] (7)	60 (22-100)	60 (22-100)	2.75 (0.53-14.27)	.23
Number of levels treated				
= 1 (27)	70 (52-93)	70 (48-93)	1.0 (Ref)	
> 1 (14)	80 (56-100)	80 (47-100)	1.03 (0.27-4.01)	.96
RT fractions				
= 1 (2)	100	100	1.0 (Ref)	.79
> 1 (40)	73 (58-91)	73 (54-91)	0.66 (0.03-13.61)	
Any prior overlapping RT				
No (13)	79 (63-100)	79 (59-100)	1.0 (Ref)	.33
Yes (29)	64 (37-100)	64 (37-100)	1.99 (0.49-7.97)	

Abbreviations: HR = hazard ratio; RT = radiation therapy; SINS = spinal instability neoplastic score.

Our institutional practice employs a dual-CTV technique with SIB, allowing dose escalation to gross disease while respecting OAR constraints. These associations between ctv_low D95% metric and local progression suggest that maintaining adequate coverage of the low-dose coverage to a single CTV might improve LC, though this must be balanced against potential increased toxicity to adjacent OAR. For reirradiation cases, cumulative cord doses were carefully evaluated using MRI-based delineation. Although we followed TG-101 constraints for de

Table 5 Dose metrics to spinal neural structures and their association with local control

	Entire cohort		De novo/adjuvant SPAR		ReRT SPAR	
Parameter	**Median dose (GyE)**	**Median EQD2 (GyE)**	**Median dose (GyE)**	**Median EQD2 (GyE)**	**Median dose (GyE)**	**Median EQD2 (GyE)**
Cord	n = 23		n = 15		n = 8	
Dmax	19.8 (15.5-23.7)	43.2 (28.6-58.2)	18.9 (15.3-23.7)	39.1 (27.1-58.7)	20.1 (16.8-26.1)	43.8 (32.2-70.4)
D0.03cc	17.1 (13.9-22.1)	37 (23.1-50.2)	17.0 (13.9-22.1)	32.4 (23.1-51.6)	17.9 (15.1-21.9)	35.6 (26.7-50.8)
D0.1cc	16.2 (13.1-20.2)	35.4 (21.2-45.8)	16.2 (13.1-21.0)	30.0 (20.8-47.2)	17.0 (14.1-20.2)	32.8 (23.9-44.1)
D1cc	12.7 (9.27-16.5)	19.8 (12.4-30.0)	11.4 (9.1-16.5)	16.5 (11.5-30.8)	12.8 (9.5-16.5)	20.0 (12.4-31.0)
Cauda_equina	n = 17		n = 13		n = 4	
Dmax	25.9 (17.5-26.9)	68.9 (54.4-75.9)	25.9 (23.9-27.3)	68.7 (59.5-75.9)	20.4 (14.7-26.0)	47.5 (25.4-69.5)
D0.03cc	23.3 (16.1-24.1)	58.1 (45.8-61.3)	23.6 (22.4-24.3)	58.1 (53.1-61.3)	16.6 (12.2-22.3)	32.5 (18.6-52.8)
D0.1cc	22.6 (15.8-23.4)	54.0 (35.9-57.1)	22.7 (21.6-23.4)	54.5 (49.5-57.3)	14.7 (11.4-20.7)	26.3 (16.6-46.5)
D1cc	19.7 (12.7-21.5)	42.1 (23.3-49.2)	20.3 (14.7-21.5)	44.5 (25.3-49.2)	12.0 (8.8-17.8)	18.3 (10.9-36.3)
Sacral_plexus	n = 12		n = 9		n = 3	
Dmax	25.6 (22.3-32.8)	70.0 (61.5-77.2)	24.5 (21.8-28.0)	62.1 (45.6-79.1)	26.4 (25.3-41.2)	71.2 (66.0-162.0)
D0.03cc	23.2 (20.4-29.3)	56.6 (54.4-64.3)	23.2 (19.8-24.2)	52.8 (23.8-56.9)	23.2 (22.9-37.3)	56.4 (54.9-134.9)
D0.1cc	22.0 (20.8-25.0)	53.2 (50.3-60.5)	22.0 (18.2-23.4)	51.3 (42.4-57.2)	22.1 (21.7-35.2)	51.7 (50.0-120.6)
D1cc	19.4 (11.1-26.1)	41.0 (29.0-46.9)	19.0 (11.4-20.4)	39.6 (16.6-44.8)	19.7 (10.4-32.1)	42.4 (14.1-101.8)

Abbreviations: D(x)cc = dose to x volume in cc; Dmax = maximum dose; EQD2 = equivalent dose in 2 Gy per fraction; ReRT = reirradiation; SPAR = stereotactic proton ablative radiation therapy.
Cord and Cauda equina were delineated based on the magnetic resonance imaging T2 sequence. The sacral plexus was delineated based on the thecal sac.

novo treatments, reirradiation cases were individualized based on prior dose, time interval, and clinical necessity. The slightly higher cord doses observed in reirradiation cases reflect careful risk-benefit assessment in these complex scenarios, with no resulting myelopathy events observed. Although the association between ctv_low D95% and local progression suggests that dose escalation to the low-dose CTV might improve LC, this must be balanced against the risk of VCF. Proton therapy carries unique radiobiological considerations: the linear energy transfer and effective RBE increase at the distal edge of the Bragg peak, which may deposit within the vertebral body. Dose escalation could, therefore, theoretically increase VCF risk through enhanced biological effect in bone. This distal edge effect remains speculative and was not evaluated in the present study. Reassuringly, our observed VCF rate (9%) remains comparable to photon-based hypofractionated spine SBRT series, suggesting that at current dose levels, this effect is not clinically significant. Nonetheless, this consideration warrants attention in future dose escalation strategies.

In addition to acceptable LC, our analysis demonstrated that spine SPAR was safe to deliver. For acute AEs, there were 9 (18%) pain flares, which are comparable to photon-based spine SBRT,[37-39] and one grade 3 dermatitis event. For late AEs, there were 3 VCFs: 2 de novo VCFs (8%) and 1 progression of VCF (20%), and one grade 3 peripheral nerve dysfunction, which was secondary to a subsequent kyphoplasty procedure. Notably, there was no radiation-related myelopathy in the entire cohort, suggesting that our current immobilization, planning, optimization, modeling, and treatment delivery techniques for spine SPAR appear to be safe. These outcomes are broadly consistent with our institution's prior photon SBRT data.

There are warranted concerns for employing proton therapy for metastasis-directed therapy in patients with potentially short life expectancy, as proton therapy is a limited and more time-intensive resource associated with higher cost.[40] Proton SPAR should be used in highly select cases, such as reirradiation. At our institution, 5 to 8 spine lesions per year are currently treated with SPAR, and the remainder receive photon SABR. Further study of which patients will benefit most from proton therapy is required. Further, we have instituted a practice where patients with metastatic disease are evaluated by proton therapy center leaders to ensure appropriateness of treatment and of accommodation in the treatment schedule, considering other patient treatment needs, eg, pediatric cases.

Despite dose escalation, our LC rates (74% at 1-2 years) fall within the range reported in contemporary photon-based spine SABR literature, although they are on the lower end of recently reported benchmark outcomes. Several factors may explain this: (1) our cohort was enriched for reirradiation cases (66%); (2) MC calculations suggest a lower absorbed dose in bone than analytical algorithms predict; and (3) patient-selection bias toward more complex cases referred for proton therapy.

Although spinal cord constraints were respected during treatment planning, cumulative cord EQD2 was not used as the primary proton selection criterion. The primary rationale for SPAR at our institution is the reduction of integral dose to healthy tissues, particularly anterior OARs (esophagus, heart, bowel, and kidneys), where the finite range of protons eliminates exit dose. Because effective cord sparing can often be achieved with photon-based techniques, spinal cord dose reduction is not the primary indication for SPAR. Rather, the theoretical advantage lies in reducing dose to structures anterior to the vertebral body, particularly in the setting of reirradiation where cumulative doses to these organs may be clinically relevant. However, this potential advantage was not directly evaluated through comparative dosimetric analysis in the present study.

There are several limitations to our study. Our cohort was enriched for prostate histology (53%) and reirradiation cases (66%), which may limit generalizability to other histologies and de novo treatments. Prostate metastases may have more favorable LC compared to other histologies, potentially influencing our outcomes. The median follow-up of 13 months reflects the expected mortality in this patient cohort, which may limit our ability to detect late toxicities or long-term LC outcomes. Cumulative spinal cord EQD2 values were not systematically recorded during the study period and, therefore, could not be retrospectively reconstructed for all reirradiated patients. Proton therapy selection was primarily based on anticipated normal tissue sparing, including reduction of integral dose and sparing of adjacent OARs, rather than predefined cumulative spinal cord dose thresholds. This limitation precludes reporting cumulative cord EQD2 for the entire reirradiation cohort. Our study did not include comparative dosimetric analyses with photon SBRT plans, as the clinical decision for proton therapy was made prospectively per institutional protocol. Future comparative planning studies are needed to objectively quantify the dosimetric differences between SPAR and photon SBRT for spine metastases.

Future investigation of ablative RT continues in earnest with multiple phase 3 clinical trials evaluating metastasis-directed therapy in patients with oligometastatic and polymetastatic disease.[14] Additionally, there are multiple active and recruiting trials for spine SABR examining different dose and fractionation schemes and their impact on pain response, toxicity, and local tumor control. Significant interest has been placed in evaluating patients' immune system status and overall outcomes. Studies have demonstrated lymphocyte-sparing effects with proton therapy in esophageal cancer[41,42] and advanced lung cancer,[43] indicating blood pool and spleen sparing may be warranted and advantageous for SPAR in patients receiving systemic therapy.

This was a single-institution study, and our cohort was heterogeneous with regard to patient, patient selection, primary tumor site, treatment course, dose, fractionation, and follow-up time. Data were collected retrospectively, and the overall sample size was small and largely represented by prostate histology, which may have better LC and OS as compared to other histologies.[13,44] There are additional aspects of this study that affect generalizability and reproducibility, including that proton therapy is not widely available. It is important to note that the proton therapy system used in this study features a small spot size, which facilitates precise dose sculpting around critical structures such as the spinal cord. This technical advantage may not be available at all proton centers, particularly those with larger spot sizes. As such, our dosimetric results may not be fully generalizable to centers using different delivery systems. Moreover, in addition to standard Eclipse treatment planning system (TPS) proton optimization, we also evaluate and adjust plans with in-house MC calculations to assess for biological dose differences, which may affect implementation outside of our institution. Further study is needed to select optimal patients for SPAR and to improve treatment quality.

Our outcomes are generally consistent with previously reported photon and proton-based spine SABR experiences. In a prospective phase 1/2 study by Chang et al,[34] spine SBRT yielded a 1-year local tumor control rate of approximately 84% with minimal grade $\geq$3 toxicities. Although our cohort included a high proportion of reirradiation cases and used ultrahypofractionated proton therapy, we observed comparable 1- and 2-year local tumor control rates of 74% and similarly low toxicity rates, supporting the feasibility of SPAR in selected patients.

Recent dosimetric analyses by Shaaban et al[45] compared variable-RBE IMPT versus photon SBRT across a series of challenging spine metastasis cases. They reported enhanced target coverage with proton plans without increasing spinal cord exposure, thanks to robust sparing based on distal dose distributions. A separate 2024 review further underscores proton SBRT's promise in reducing exposure to anterior OARs while maintaining tumor coverage.[46] Although our study did not include a direct photon comparison, these prior dosimetric findings provide the rationale for our institutional proton patient-selection strategy. The present study contributes clinical outcome data demonstrating that ultrahypofractionated SPAR can achieve acceptable LC and low toxicity in selected patients, particularly in the reirradiation setting.

The recent joint European Society for Radiotherapy and Oncology and the International Stereotactic Radiosurgery Society (ESTRO-ISRS) meta-analysis by Alongi et al[47] reported pooled 1-year and 2-year LC rates of 81% and 77%, respectively, for spine SBRT in the reirradiation setting across approximately 1500 lesions. With a median follow-up of 13 months, the 1- and 2-year local tumor control rate was 74% in our cohort, which is broadly consistent with these contemporary benchmark data, although somewhat lower. Differences in patient and disease characteristics may partially contribute to this observation. Notably, prostate adenocarcinoma was the predominant primary histology in our cohort (53%). Although prostate cancer is not traditionally considered a highly radioresistant tumor type, these patients frequently experience prolonged survival compared with many other metastatic populations represented in historical spine reirradiation series. Consequently, durable LC and minimization of late treatment-related toxicity remain particularly important clinical endpoints, as these patients have a greater opportunity to experience both long-term disease control and late adverse effects.

Conclusions

Spine SPAR is a feasible and well-tolerated treatment for selected patients with spinal metastases. In this retrospective analysis, SPAR achieved acceptable LC rates with low rates of high-grade toxicity, including in reirradiation and anatomically challenging cases. These findings support the feasibility of SPAR as a treatment approach for selected complex spine lesions, particularly in the reirradiation setting. Broader validation in prospective studies will be essential to define optimal patient selection, dosimetric thresholds, and long-term outcomes.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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