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Scientific Article

# Five-Year Prostate-Specific Membrane Antigen Positron Emission Tomography-Based Outcomes of Spot-Scanning Proton Radiation Therapy for Localized Prostate Cancer: A Single Institution Experience

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**Purpose:** We report 5-year oncologic outcomes of a prospective series of patients with prostate cancer treated with spot-scanning proton therapy (SSPT).

**Methods and Materials:** A prospective registry identified patients with prostate cancer treated with SSPT between January 2016 and December 2018. Five-year overall survival, local control, biochemical failure, regional and distant failures, and adverse events (AEs) were assessed. Biochemical failure was defined as rise in prostate-specific antigen ≥ 2.0 ng/mL above nadir prostate-specific antigen. Baseline-adjusted toxicities were assigned using the Common Terminology Criteria for Adverse Events version 5.0.

**Results:** With a median follow-up of 4.4 years, 284 patients with prostate cancer were treated with SSPT. Median total radiation dose was 79.2 Gy over 44 fractions, 70 Gy over 28 fractions, and 38 Gy over 5 fractions for conventional fractionation (CF), hypofractionation (HF), and stereotactic body radiation therapy (SBRT), respectively. Biochemical failure rate for all patients was 6.7%. Five-year local control rates for CF, HF, and SBRT were 100%, 100%, and 97.3%, respectively ($P = .07$). Regional recurrences occurred in 12 (4.2%) patients: 8 treated with CF, 2 with HF, and 2 with SBRT ($P = .62$). Distant failures occurred in 12 patients (4.2%): 5 treated with CF, 7 with HF, and none with SBRT ($P = .05$). Five-year overall survival for patients treated with CF, HF, and SBRT SSPT were 88.1%, 86.1%, and 97.2%, respectively ($P = .1$). Acute and chronic grade 2+ gastrointestinal AEs occurred in 8 (2.8%) and 51 (18.0%)

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patients, respectively. Acute and chronic grade 3+ gastrointestinal AEs occurred in 3 (1.1%) and 4 (1.4%) patients, respectively. Acute and chronic grade 2+ genitourinary-related AEs were observed in 71 (25%) and 63 (22.2%) patients, respectively. Acute and chronic grade 3+ genitourinary toxicity were observed in 3 (1.1%) and 6 (2.1%) patients, respectively.

**Conclusions:** SSPT provides high local control rates and excellent oncologic outcomes across different fractionation schedules with low long-term AE rates.



## Introduction

In the United States, prostate cancer is the most common cancer with an annual incidence of 299,010 and is the second leading cause of cancer death in men.[1] Numerous curative-intent treatment options for prostate cancer are available based on the disease risk groups and include surgery, radiation therapy, and/or androgen deprivation therapy (ADT). Although photon radiation therapy for prostate cancer is the historical standard of care radiation therapy option, contemporary groups are investigating the value of proton therapy. Commensurate outcomes between photons and protons have been reported, and the long-term superiority of protons over photons in prostate cancer management has yet to be clearly defined.

With the establishment of new centers in recent years, proton beam therapy (PBT) is becoming a more widely available treatment for patients with prostate cancer. Proton therapy can be delivered using passive scatter ("double scattered" and "uniform scanning") or active scatter ("pencil beam scanning"—PBS, "spot scanning," and "intensity modulated") techniques. Each proton beam has inherent range uncertainty and needs its own planning target volume to maximize target coverage.[2] Passive scattering involves modulating a fixed-energy beam and achieving precise conformity to the distal target edge; that said, this approach conforms poorly to the proximal target edge and causes disadvantageous neutron production.[3,4] In contrast, current proton delivery techniques involve the use of spot-scanning proton therapy (SSPT), which has more dimensions of freedom, and the dose distribution of each beam conforms precisely to the proximal and distal target edges.[3] The treatment is delivered energy layer by layer and spot by spot, where beam spot indicates the location of the beam's Bragg peak. One preclinical study performed Monte Carlo simulations and found no significant differences in beam quality or biologic effectiveness between passive and active proton beams.[5] Active pencil beams have higher dose rates than passive beams and should achieve more conformal dose distributions.

The clinical benefit of active over passive scatter proton therapy has yet to be shown. To date, no prospective randomized clinical trial has compared head-to-head passive and active scatter proton therapy delivery techniques. When compared with intensity modulated radiation therapy (IMRT), active and passive scatter proton therapy reduced the maximum hot spot dose and significantly reduced the rectum and bladder volume receiving 30 Gy or greater (V30).[6] A similar IMRT versus proton treatment plan comparison study reported significant reductions in rectal V10 to V80 Gy and bladder V10 to V35 Gy with protons.[7] Intensity modulated proton therapy has outperformed IMRT by significantly reducing low-to-medium dose to nontarget tissues.[8] Additional longer-term investigation will elucidate whether these theoretical benefits translate into clinically meaningful improvements. The purpose of the current study is to report the 5-year oncologic outcomes of a prospective series of patients with clinically localized prostate cancer treated with SSPT.

## Materials and Methods

### Patient population

An institutional review board-approved, multiinstitutional prospective Proton Collaborative Group registry study was conducted. Adult patients with histologically confirmed prostate adenocarcinoma treated with definitive spot-scanning PBT between January 2016 and December 2018 were included. Patients with metastatic disease were excluded. No patients had previously undergone prostatectomy or pelvic radiation treatment.

### Radiation treatment

All patients received curative-intent, pencil beam scanning proton therapy for localized prostate cancer. Hypofractionation (HF) was defined as treatment to a total dose of 60 to 70 Gy using 2.5 to 3 Gy per fraction. Stereotactic body radiation therapy (SBRT) was delivered as 38 Gy over 5 fractions. Conventional fractionation (CF) was defined as 39 to 44 fractions using $\leq$ 2 Gy per fraction. Before simulation, patients were referred to urology for carbon fiducial marker placement. Hydrogel rectal spacer placement was used in some patients based on patient and physician preference. Simulation was performed with patients in the supine position with a full bladder, empty rectum, and pelvic immobilization device. A rectal balloon was placed for each SBRT treatment. Computed

tomography (CT) and 1.5 to 3 Tesla magnetic resonance imaging scans were obtained and coregistered for planning purposes. Institutional guidelines informed target volume contours, expansions, organs-at-risk dose constraints, and treatment planning details (see Supplementary Material). Every treatment involved initial kilovolt and pelvic bony setup followed by kilovolt image guidance aligned to the fiducial markers before each beam delivery.

## Outcomes

At 5 years, disease-free survival (DFS), clinical failure-free (local, regional, or distant) rates, biochemical failure (BF) rates, and physician-reported adverse events (AEs) were assessed. DFS was measured as the time interval after treatment completion during which no biochemical or radiographic evidence of cancer was found. Clinical failures were identified radiographically. The D'Amico classification for clinically localized prostate cancer was used to assign patients into risk groups. DFS and clinical failure-free rate were stratified by fractionation (HF, SBRT, and conventional), risk group (low, intermediate, and high), and grade group (1, 2-3, and 4-5). BF was defined as rise in prostate-specific antigen (PSA) $\geq$ 2.0 ng/mL above the nadir PSA. Acute and chronic gastrointestinal (GI) and genitourinary (GU) grade 2+ and grade 3+ baseline-adjusted AEs were assigned using the Common Terminology Criteria for Adverse Events version 5.0. Restaging evaluation using PSMA positron emission tomography (PET)-CT scans was performed for all patients who experienced BF.

## Statistical analysis

Kaplan-Meier analysis was performed to estimate overall survival, DFS, and clinical failure-free rates. *P* values were generated between groups to check for statistical significance ($P < .05$) using the log rank test. Descriptive statistics were calculated: counts and percentages for categorical variables and mean, SD, median, and IQR for continuous variables. Analyses were performed using R Statistical Software v4.2.2.[9]

# Results

## Patient, disease, and treatment characteristics

Two hundred and eighty-four patients with prostate cancer, with a median age of 72 years (IQR, 67.5-77.1) were treated with spot-scanning proton radiation. Patients were classified by prostate cancer risk category: 31 (10.9%) low-risk, 156 (54.9%) intermediate-risk, and 97 (34.2%) high-risk. The HF group contained 1 (1.1%) low-risk, 55 (58.5%) intermediate-risk, and 38 (40.4%) high-risk patients. The SBRT group had 19 (40.4%) low-risk, 23 (48.9%) intermediate-risk, and 5 (10.6%) high-risk patients. The CF group included 11 (7.7%) low-risk, 78 (54.5%) intermediate-risk, and 54 (37.8%) high-risk patients. Median follow-up was 4.4 years (IQR, 3.7-5.0). Patient, disease, and treatment characteristics are summarized in Table 1. Over 94% of the patients were White and not Hispanic. The median Gleason grade group was 3 (IQR, 2-4). The median pre-radiation therapy PSA was 6.9 ng/mL (IQR, 4.3-10.5). Median clinical T-stage was T1c. For this population of mostly intermediate- and high-risk patients, a relatively low percentage (64%) of all patients were on ADT at the time of initiating radiation treatment and total ADT duration ranged from 1 to 63+ months. This reflects patient and physician preferences. Hydrogel rectal spacer was placed in 159 (56%) of our patients: 34 HF (36.2%), 33 SBRT (70.2%), and 92 CF (64.3%). The median total radiation dose was 79.2 Gy delivered over 44 fractions, 70 Gy over 28 fractions, and 38 Gy over 5 fractions for CF, HF, and SBRT regimens, respectively.

## Failures and survival

The 5-year BF rate across the entire cohort was 6.7%. Figure 1B shows 5-year clinical failure-free rates for patients with low-, intermediate, and high-risk disease of 100%, 96.1%, and 82%, respectively. The 5-year local control rates for the CF, HF, and SBRT groups were 100% (95% CI: 100-100), 100% (95% CI: 100-100), and 97.3% (95% CI, 92.2-100), respectively ($P = .07$). Regional recurrences occurred in 12 (4.2%) patients: 8 (5.6%) treated with CF, 2 (2.1%) with HF, and 2 (4.3%) with SBRT ($P = .62$). Distant metastatic failure occurred in 12 patients (4.2%): 5 (3.5%) treated with CF, 7 (7.4%) with HF, and none with SBRT (0%) ($P = .05$). In our cohort, 19 of 284 (6.7%) patients experienced BFs. Disease recurrence sites were identified on PSMA PET/CT scans in 18 of these patients, and 6 (33.3%) of these patients—2 with bone and 4 with lymph node recurrences—underwent salvage radiation therapy and had undetectable PSA levels after salvage treatment. The 19 failures occurred in 5 patients (26%) with intermediate-risk disease and 14 patients (74%) with high-risk disease. The 18 radiographically identified recurrences (3 of which were confirmed with biopsy) were located in bones (8), lymph nodes (8), prostate (1), seminal vesicles (1), and penis (1). The 5-year overall survival rates for patients treated with CF, HF, and SBRT SSPT were 88.1% (95% CI, 81.8-95.0), 86.1% (95% CI, 77.5-95.6), and 97.2% (95% CI, 92-100), respectively ($P = .1$).

**Table 1 Patient, disease, and treatment characteristics**

| | Hypofractionation (N = 94) | SBRT (N = 47) | Conventional (N = 143) | Total (N = 284) |
|---|---|---|---|---|
| Age at RT | | | | |
| Median (y) | 72.0 | 64.9 | 72.9 | 71.8 |
| Range (y) | 57.2-84.9 | 52.2-83.1 | 60.8-91.5 | 52.2-91.5 |
| Race | | | | |
| White | 87 (92.6%) | 44 (93.6%) | 136 (95.1%) | 267 (94.0%) |
| Other | 7 (7.4%) | 3 (6.4%) | 7 (4.9%) | 17 (6.0%) |
| Gleason grade group | | | | |
| 1 | 3 (3.2%) | 22 (46.8%) | 14 (9.8%) | 39 (13.7%) |
| 2 | 35 (37.2%) | 21 (44.7%) | 47 (32.9%) | 103 (36.3%) |
| 3 | 29 (30.9%) | 1 (2.1%) | 37 (25.9%) | 67 (23.6%) |
| 4 | 12 (12.8%) | 2 (4.3%) | 27 (18.9%) | 41 (14.4%) |
| 5 | 15 (16.0%) | 1 (2.1%) | 18 (12.6%) | 34 (12.0%) |
| Pre-RT PSA | | | | |
| Median (ng/mL) | 6.3 | 6.9 | 7.4 | 6.9 |
| IQR (ng/mL) | 4.3-11.6 | 4.3-9.1 | 4.5-10.5 | 4.3-10.5 |
| Clinical TNM staging | | | | |
| T | | | | |
| T1 | 46 (48.9%) | 35 (74.5%) | 67 (46.9%) | 148 (52.1%) |
| T2 | 34 (36.2%) | 12 (25.5%) | 56 (39.2%) | 102 (35.9%) |
| T3+ | 12 (12.8%) | 0 (0%) | 13 (9.1%) | 25 (8.8%) |
| NA | 2 (2.1%) | 0 (0%) | 7 (4.9%) | 9 (3.2%) |
| N | | | | |
| N0 | 90 (95.7%) | 44 (93.6%) | 132 (92.3%) | 266 (93.7%) |
| N1 | 1 (1.1%) | 0 (0%) | 1 (0.7%) | 2 (0.7%) |
| NA | 3 (3.2%) | 3 (6.4%) | 10 (7.0%) | 16 (5.6%) |
| M | | | | |
| M0 | 94 (100%) | 47 (100%) | 143 (100%) | 284 (100%) |
| Pelvic MRI | | | | |
| Yes | 88 (93.6%) | 47 (100%) | 136 (95.1%) | 271 (95.4%) |
| No | 6 (6.4%) | 0 (0%) | 7 (4.9%) | 13 (4.6%) |
| AUASS | | | | |
| Mean (SD) | 8.2 (5.9) | 5.7 (4.1) | 8.0 (6.2) | 7.7 (5.8) |
| Prior chemotherapy | | | | |
| Yes | 0 (0%) | 3 (6.4%) | 1 (0.7%) | 4 (1.4%) |
| No | 94 (100%) | 44 (93.6%) | 142 (99.3%) | 280 (98.6%) |
| Prior ADT | | | | |
| Yes | 63 (67.0%) | 20 (42.6%) | 98 (68.5%) | 181 (63.7%) |
| No | 31 (33.0%) | 27 (57.4%) | 45 (31.5%) | 103 (36.3%) |
| Median total RT dose (Gy)/fraction | 70/28 | 38/5 | 79.2/44 | |

*Abbreviations:* Age at RT = age at start of radiation therapy; TNM = Tumor, Node, Metastasis; AUASS = American Urological Association Symptom Score; MRI = magnetic resonance imaging; Pre-RT PSA = pre-radiation therapy prostate-specific antigen; Prior ADT = on androgen deprivation therapy at the start of RT; SBRT = stereotactic body radiation therapy.

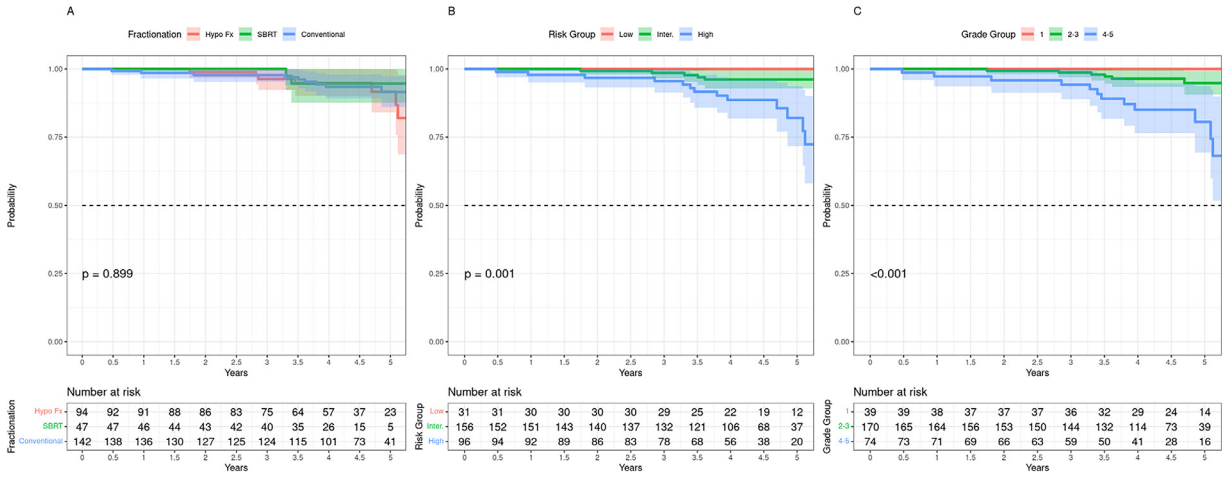


**Figure 1** Clinical failure-free rate by fractionation, risk group, and grade group. Clinical failure-free rate by fractionation (A), risk group (B), and grade group (C).
*Abbreviation:* SBRT = stereotactic body radiation therapy.

## Toxicity

Acute and chronic grade 2+ GI baseline-adjusted AEs occurred in 8 (2.8%) and 51 (18.0%) patients, respectively. Acute and chronic grade 3+ GI baseline-adjusted AEs occurred in 3 (1.1%) and 4 (1.4%) patients, respectively. Acute and chronic grade 2+ GU-related AEs were observed in 71 (25.0%) and 63 (22.2%) patients, respectively. Acute and chronic grade 3+ GU toxicity was observed in 3 (1.1%) and 6 (2.1%) patients, respectively. Toxicities are summarized by fractionation regimen in Table 2.

## Discussion

Our report provides long-term oncologic outcomes for a cohort of patients with predominantly intermediate- and high-risk prostate cancer treated with PBS PBT over a variety of fractionation regimens. Excellent 5-year clinical failure-free rates of 100%, 96.1%, and 82% were achieved for patients with low-, intermediate-, and high-risk prostate cancer, respectively. Our rates are comparable to those reported in the University of Florida studies using standard fractionation proton therapy.[10,11] No significant differences in clinical failure-free rates were found across our three fractionation regimens (Fig. 1A). Our 5-year clinical failure-free rates for patients with intermediate-risk disease were significantly different than those of low-risk (HR 3.29; 95% CI, 1.58-6.87; $P$ = .002) but not of high-risk disease (HR 3.88; 95% CI, 0.67-22.42; $P$ = .130) (Fig. 1B). Similarly, 5-year clinical failure-free rates for grade groups 2 to 3 were significantly different than grade group 1 but not than grade groups 4 to 5 (Fig. 1C).

To make PBT more accessible without sacrificing efficacy, shorter fractionation regimens have been studied. In a prospective clinical registry study, 284 patients with prostate cancer received ultrahypofractionated (36.25 Gy in 5 fractions) PBS proton therapy. Five-year biochemical DFS rates were 96.9%, 91.7%, and 83.5% for low-risk, favorable intermediate-risk, and unfavorable intermediate-risk disease groups.[12] These DFS rates were similar to our 42 patients with low- and intermediate-risk disease who received proton SBRT. No significant differences in

**Table 2 Baseline-adjusted adverse events by fractionation regimen**

| | | Hypofractionation (N = 94) | | SBRT (N = 47) | | Conventional (N = 143) | | Total (N = 284) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Acute | Chronic | Acute | Chronic | Acute | Chronic | Acute | Chronic |
| GI | G2+ | 3 (3.2%) | 15 (16.0%) | 1 (2.1%) | 8 (17.0%) | 4 (2.8%) | 28 (19.6%) | 8 (2.8%) | 51 (18.0%) |
| | G3+ | 2 (2.1%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (0.7%) | 4 (2.8%) | 3 (1.1%) | 4 (1.4%) |
| GU | G2+ | 23 (24.5%) | 20 (21.3%) | 10 (21.3%) | 14 (28.0%) | 38 (26.6%) | 29 (20.3%) | 71 (25.0%) | 63 (22.2%) |
| | G3+ | 2 (2.1%) | 1 (1.1%) | 0 (0%) | 2 (4.3%) | 1 (0.7%) | 3 (2.1%) | 3 (1.1%) | 6 (2.1%) |

*Abbreviations:* G2+ = grade 2+; G3+ = grade 3+; GI = gastrointestinal; GU = genitourinary; SBRT = stereotactic body radiation therapy.

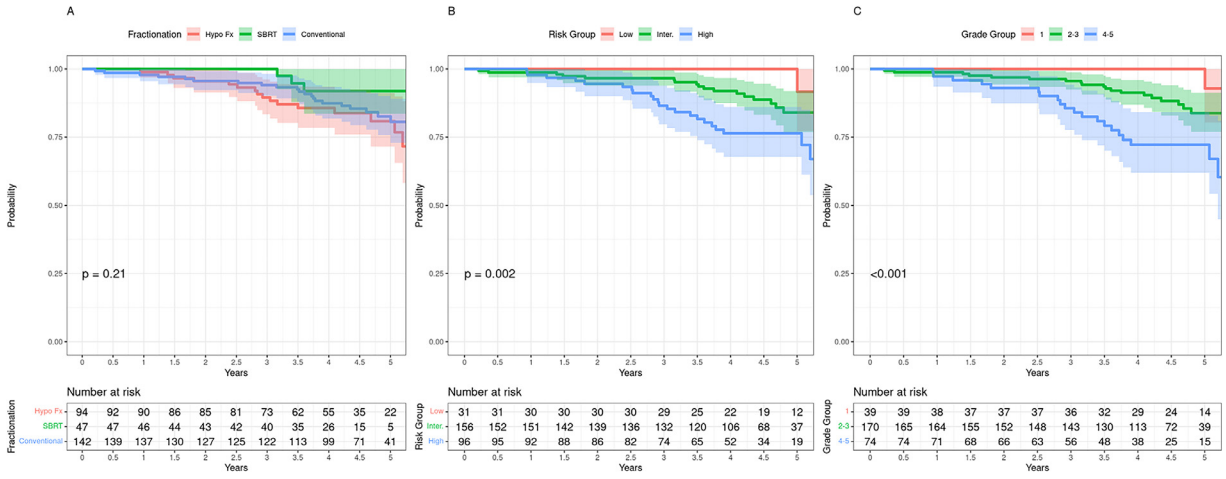


**Figure 2** Disease-free survival by fractionation, risk group, and grade group. Disease-free survival by fractionation (A), risk group (B), and grade group (C).
*Abbreviation:* SBRT = stereotactic body radiation therapy.

DFS were found across our 3 fractionation regimens ($P = .21$) (Fig. 2A). Figure 2B and 2C highlight DFS trends by risk and grade groups, respectively.

Although pencil beam proton therapy has been increasingly used in the management of prostate cancer, most published studies include retrospective data and randomized trials are lacking. The Prostate Advanced Radiation Technologies Investigating Quality of Life (NCT01617161) trial is a multiinstitutional, randomized study comparing double-scattered or PBS PBT versus IMRT as definitive management for localized low- or intermediate-risk prostate cancer. The study has completed accrual of 450 patients and the results are eagerly awaited.

In our cohort, only 19 of 284 (6.7%) patients experienced BFs; 18 of these failures were identified on PSMA PET/CT scan, most of which represented recurrences in bone or lymph nodes. Six of these 18 patients (33%) received salvage radiation therapy and achieved undetectable PSA levels. In biochemically recurrent prostate cancer, $^{68}$Ga-PSMA-11 PET significantly outperformed $^{18}$F-fluciclovine PET when identifying pelvic nodes and extrapelvic lesions.[13] PSMA PET achieves a high positive predictive value and specificity but a low sensitivity[14,15]; it is PSA-dependent and remains an important tool to detect recurrences in intermediate- and high-risk prostate cancer.

Protons interact with the body differently than photons; their lack of an exit dose gives them a theoretical ability to reduce toxicity, but the optimal proton delivery technique is unknown. A prospective multicenter registry study, Proton Collaborative Group 001-09, suggested that passive scatter PBT might achieve lower acute grade 2+ GU toxicity rates than PBS PBT but was limited by lack of dosimetric correlations and short follow-up.[16] In Proton Collaborative Group 001-09, patients who received PBS PBT had acute and chronic grade 2+ GU toxicity rates of 21.4% and 6.3% compared with our rates of 25.2% and 2.8%, respectively (Table 2).[16] Patient-reported urinary quality of life scores at 12 months revealed 2-fold minimally important differences for PBS and passive scatter/uniform scanning of 26.9% and 13.2%, respectively.[17] In terms of acute and chronic grade 2+ GI toxicity rates, Mishra et al[16] reported 2.9% and 4.2% compared with our rates of 2.8% and 17.8%, respectively.[16] The lower rate of chronic grade 2+ GI toxicities may be secondary to the use of conventionally fractionated radiation only by due Mishra et al,[16] whereas the current report involves predominantly hypofractionated and SBRT regimens.[16] Grade 3 toxicities were rare in both studies.[16] Two years out from SSPT or passive scatter proton therapy for localized prostate cancer, toxicity and patient-reported quality of life are comparable.[18] Slight toxicity differences across the literature may be due to variable rectal spacer and balloon usage. Some early evidence supports the use of rectal spacer without endorectal balloon in conventionally fractionated PBS PBT for localized prostate cancer.[19]

Certain limitations must be considered. The retrospective nature of our analysis makes it susceptible to confounding variables and biases. All patients were treated at a single institution, which raises concern about generalizability in other institutions. Only 11% of our cohort had low-risk disease, so limited conclusions can be drawn about these patients. Patients with intermediate- and high-risk disease received varying durations of ADT (1 to 63+ months), which can affect the results of treatment and side effects. Toxicity grading can be subjective and may vary by provider. The current report only includes clinician-reported not patient-reported toxicities.

Our results show that spot-scanning proton radiation for localized prostate cancer provides favorable 5-year clinical failure-free, DFS, and overall survival rates. PSMA PET/CT remains an excellent tool for detecting biochemical recurrences. The acute and chronic GI and GU

toxicities are low and acceptable. Randomized studies are warranted to clearly define the long-term efficacy and side effects of PBS PBT as a treatment modality for prostate cancer.

## Disclosures

None.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101639.

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