Postoperative or Salvage Proton Radiotherapy for Prostate Cancer After Radical Prostatectomy

Shivam M. Kharod, MD[1]; Catherine E. Mercado, MD[2]; Christopher G. Morris, MS[1]; Curtis M. Bryant, MD, MPH[1]; Nancy P. Mendenhall, MD[1]; William M. Mendenhall, MD[1]; R. Charles Nichols, MD[1]; Bradford S. Hoppe, MD MPH[3]; Xiaoying Liang, PhD[1]; Zhong Su, PhD[1]; Zuofeng Li, DSc[1]; Randal H. Henderson, MD, MBA[1]

[1]Department of Radiation Oncology, University of Florida, College of Medicine, Jacksonville, FL, USA
[2]Department of Radiation Oncology, Orlando Health, Orlando, FL, USA
[3]Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, USA

Abstract

Purpose: Postprostatectomy radiation improves disease control, but limited data exist regarding outcomes, toxicities, and patient-reported quality of life with proton therapy.
Method and Materials: The first 102 patients who were enrolled on an outcome tracking protocol between 2006 and 2017 and treated with double-scattered proton therapy after prostatectomy were retrospectively reviewed. Eleven (11%) received adjuvant radiation, while 91 (89%) received salvage radiation. Seventy-four received double-scattered proton therapy to the prostate bed only. Twenty-eight received a double-scattered proton therapy prostate-bed boost after prostate-bed and pelvic-node treatment. Eleven adjuvant patients received a median dose of 66.6 GyRBE (range, 66.0-70.2). Ninety-one salvage patients received a median dose of 70.2 GyRBE (range, 66.0-78.0). Forty-five patients received androgen deprivation therapy for a median 9 months (range, 1-30). Toxicities were scored using Common Terminology Criteria for Adverse Events v4.0 criteria, and patient-reported quality-of-life data were reviewed.
Results: The median follow-up was 5.5 years (range, 0.8-11.4 years). Five-year biochemical relapse-free and distant metastases-free survival rates were 72% and 91% for adjuvant patients, 57% and 97% for salvage patients, and 57% and 97% overall. Acute and late grade 3 or higher genitourinary toxicity rates were 1% and 7%. No patients had grade 3 or higher gastrointestinal toxicity. Acute and late grade 2 gastrointestinal toxicities were 5% and 2%. The mean values and SDs of the International Prostate Symptom Score, International Index of Erectile Function, and Expanded Prostate Cancer Index Composite bowel function and bother were 7.5 (SD = 5.9), 10.2 (SD = 8.3), 92.8 (SD = 11.1), and 91.2 (SD = 6.4), respectively, at baseline, and 12.1 (SD = 9.1), 10.1 (SD = 6.7), 87.3 (SD = 18), and 86.7 (SD = 13.8) at the 5-year follow-up.
Conclusion: High-dose postprostatectomy proton therapy provides effective long-term biochemical control and freedom from metastasis, with low acute and long-term gastrointestinal and genitourinary toxicity.

Keywords: proton therapy; radiotherapy; prostate cancer; quality of life

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Corresponding Author:
Randal Henderson, MD, MBA
University of Florida Health
Proton Therapy Institute
2015 North Jefferson St.
Jacksonville, FL 32206, USA
Phone: + 1 (904) 588-1800
rhenderson@floridaproton.org

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Introduction

Although radical prostatectomy is often the initial treatment for prostate cancer, the risk of biochemical recurrence ranges from 40% to 70% based on adverse pathological features, such as seminal vesicle invasion, positive surgical margins, and extracapsular extension [1–5]. Postprostatectomy radiation therapy has been shown to reduce biochemical recurrence in 3 prospective randomized clinical trials—European Organization for Research and Treatment of Cancer (EORTC) 22911 [4], Southwest Oncology Group 8794 [6], and Arbeitsgemeinschaft Radiologische Onkologie 9602 [5]. As a consequence, the American Society for Radiation Oncology and American Urologic Association have published guidelines that recommend discussing adjuvant radiation for patients found to have adverse pathologic features after prostatectomy [7]. Investigators who have retrospectively studied postprostatectomy radiation in the salvage setting have also demonstrated improved long-term prostate-specific antigen (PSA) response if radiation is delivered soon after detection of biochemical progression [8, 9]. In general, toxicities after postprostatectomy radiation using photon-based techniques have been tolerable, although the rates of late grade 2 and gastrointestinal (GI) and genitourinary (GU) toxicities range from 10% to 20% [10–14] with image-guided intensity-modulated radiation therapy (IMRT).

Trends in radical prostatectomy utilization have demonstrated that high-risk disease comprises an increasing share of radical prostatectomies [15], which will likely result in more patients having indications for adjuvant and salvage radiation therapy. As a result, there has been increasing interest in exploring treatment methods that reduce rates of toxicities, while at least maintaining disease control rates, thereby increasing the therapeutic ratio. Proton therapy has unique dose deposition characteristics that allow high doses to be delivered to target volumes while minimizing radiation to normal structures [16]. There is an increase in data supporting the use of proton therapy for primary treatment of the intact prostate [17–19]; however, to the best of our knowledge, only 1 series has reported treatment toxicities with using proton radiation in the postprostatectomy setting [20, 21].

The purpose of our study was to report the acute and late treatment toxicities, quality-of-life metrics, disease control, and survival outcomes for patients who received postprostatectomy proton radiation.

Materials and Methods

Inclusion and Exclusion Criteria

All patients who received adjuvant or salvage proton radiation treatment at the University of Florida Health Proton Therapy Institute between 2006 and 2017 and consented to our department's institutional review board–approved outcome tracking protocol for prostate cancer patients treated with proton therapy (UFPTI 1306-PRX2) were included in this analysis. All patients underwent primary treatment with open, laparoscopic, or robotically assisted prostatectomy and were treated with double-scattered proton radiation postoperatively due to high-risk features (extracapsular extension, seminal vesicle involvement, positive margins, or detectable PSA postoperatively) or due to recurrent or progressive disease (PSA or clinical progression). Patients with metastatic disease were not included in this analysis.

Before treatment, all patients underwent history and physical examination, including a digital rectal examination, colonoscopy, computed tomography (CT) scan, and 1.5- to 3.0-Tesla magnetic resonance imaging of the pelvis for lymph node evaluation, chest X-ray, and bone scan. Workup also included testosterone, PSA, and alkaline phosphatase measurements. In-house pathology review of surgical specimens was performed for patients from outside institutions. All patients completed the International Index of Erectile Function (IIEF-5 or IIEF-5m), International Prostate Symptom Score (IPSS), and the Expanded Prostate Cancer Index Composite (EPIC) questionnaires before treatment initiation.

Adjuvant radiation was defined as radiation started within 6 months of surgery with at least 1 of the following risk factors as the indication for radiation: extracapsular extension, positive surgical margins, invasion of the seminal vesicles, or a persistently elevated postprostatectomy PSA (> 0.2 ng/mL < 6 weeks after prostatectomy in the absence of detectable distant metastasis). Salvage radiation was defined as radiation delivered following surgery in a patient with at least 1 of the following indications: biopsy-proven and/or radiographically defined local–regional relapse, or biochemical relapse after a nondetectable postprostatectomy PSA (any detectable PSA at least 6 weeks after prostatectomy followed by another higher value, or a single PSA of ≥ 0.2 ng/mL). High-risk patients were those considered at a high risk of lymph node involvement with no nodal sampling, or inadequate lymph node sampling, with at least 1 of the following features: pathologic Gleason score of 8 or higher on biopsy or surgical histology, preoperative PSA of 20 ng/mL or higher, pathologic involvement of the seminal vesicles, or presalvage radiation therapy PSA 2.0 ng/mL or higher.

Table 1. Normal-tissue dose constraints.

Organ	Constraint	Dose or volume, %
Bladder	$V_{65GyRBE}$	< 40
Bladder	$V_{40GyRBE}$	< 60
Rectum	$V_{65GyRBE}$	< 25
Rectum	$V_{40GyRBE}$	< 45
Femoral heads	$V_{50GyRBE}$	< 10
Small bowel	$V_{46GyRBE}$	0
Large bowel	$V_{60GyRBE}$	0

Treatment Simulation, Planning, and Delivery

Our institution's treatment planning procedures have been previously described [22]. Daily rectal balloon filled with 90 cm^3 of saline for proton treatments, or 90 cm^3 of air for X-ray treatment, was used at the treating physician's discretion. When pelvic node irradiation was performed during this era, it was done with IMRT and protons were used solely for the prostate bed. The clinical target volume (CTV)-1 for high-risk patients consisted of the prostate bed and pelvic lymph nodes, as defined by the Radiation Therapy Oncology Group (RTOG) contouring atlases [23, 24]. CTV1 was delivered with photons using IMRT and treated to 45 Gy. In these patients, CTV2 was defined as the prostate bed and was delivered with proton radiation. In patients undergoing adjuvant radiation, a typical dose of 21.6 GyRBE was sequentially delivered to CTV2. In patients undergoing salvage radiation treatment, typically 25.2 GyRBE was sequentially delivered to CTV2. Any patients with evidence of gross disease on imaging underwent an additional boost of 3.6 to 7.8 GyRBE to the area of gross disease. Patients with pathologic lymph node involvement from the time of surgery underwent pelvic lymph node irradiation in addition to prostate bed irradiation. For patients not at high risk of pelvic lymph node involvement, the prostate bed alone was treated entirely with proton radiation. The IMRT planning target volume (PTV) margin expansions were 5-mm axially, 8-mm superiorly to inferiorly for the prostate bed and prostate bed boost, 5 mm for the left/right, 7 mm in the anterior to posterior direction, and 9 mm for the superior to inferior direction of the regional nodal areas. The proton PTV margin expansions were 5 mm in the axial directions and 8 mm in the superior to inferior directions for the prostate bed. Treatment in all cases consisted of 1.8 to 2 GyRBE fractions.

For image guidance, radio-opaque markers were typically placed in the prostate bed. Daily image guidance for proton therapy consisted of orthogonal kilovoltage images and cone-beam CT for plans with an IMRT component. Proton therapy was delivered using lateral or oblique fields. The edge of the brass aperture was placed 1 cm beyond the PTV in the superior, inferior, and anterior directions, and 7 mm in the posterior direction. Treatment was planned on an Eclipse system (Varian Medical Systems, Palo Alto, CA) using a CT Hounsfield conversion algorithm [25], including 5-mm distal and proximal range uncertainty margins and a 19-mm smearing value.

Our treatment planning guidelines included target coverage and dose heterogeneity goals as well as constraints for organs at risk, which included the bladder, rectum, small bowel, large bowel, and femoral heads. Normal tissue constraints are shown in **Table 1**. For the IMRT portion of the treatment plan, at least 95% of the PTV1 and PTV2 received the prescribed dose. The maximum dose heterogeneity allowable in the PTV was 15%. For the proton portion of the treatment plan, the maximum dose did not exceed the prescription dose by more than 10%. The entire PTV received a minimum of 95% of the prescribed dose, and a minimum of 95% of the PTV received the full prescribed dose. A minimum of 99% of the CTV was treated to the prescribed dose. If we exceeded our critical dose constraint goals to the organs at risk, we made adjustments to our treatment plan, including reductions in coverage to the PTV and dose per fraction, and treatment of both rather than only 1 field per day.

Androgen deprivation therapy (ADT) was highly encouraged for patients with high-risk disease. If ADT was initiated, it was generally started 2 months before radiation therapy and continued for 2 years if well tolerated.

Patient Assessments, Toxicities, and Adverse Events

During the course of radiation therapy, patients were assessed prospectively by the treating physician weekly, and their grade 2 or higher GI toxicities and grade 3 or higher GU toxicities were scored using the Common Terminology Criteria for Adverse Events (CTCAE; US National Cancer Institute, Bethesda, MD) version 3.0 or version 4.0 after its publication in 2009. All patients with CTCAE v3.0 toxicities were retrospectively categorized to CTCAE v4.0 criteria. Toxicities occurring 6 months or more after proton therapy were scored as "late" and those occurring during treatment or less than 6 months after proton

therapy were scored as "acute." Patients returned for follow-up visits every 6 months for the first year, and then at yearly intervals after treatment. Prostate-specific antigen tests were performed every 6 or 3 months for 3 years and yearly thereafter for low- and high-risk patients, respectively. Patients prospectively completed IPSS, IIEF-5, and EPIC questionnaires at 6-month intervals after treatment for 2 years, and then annually thereafter. The time to reported biochemical outcomes was calculated from the radiation end date. In the event of biochemical failure, patients underwent bone scans, pelvic magnetic resonance imaging, and occasionally positron emission tomography-CT to determine patterns of failure. Clinical failure (local, regional, or distant) was documented based on physical, histologic, or radiographic evidence of clinical disease recurrence.

Statistical Analysis

Statistical analyses were performed using SAS and JMP software (SAS Institute, Cary, NC). The Kaplan-Meier product limit method provided estimates of freedom from biochemical recurrence, freedom from metastases, and death from any cause. The log-rank test statistic assessed the level of statistical significance between levels of selected prognostic factors. Multivariate analysis of biochemical control as a function of margin status, extracapsular extension, seminal vesicle involvement, radiation dose, and hormones was accomplished with proportional hazards regression via the PROC PHREG procedure. The variables of age, radiation to surgery time interval, radiation dose, aspirin/coagulation use, ADT use, metformin use, and baseline IPSS score were evaluated in a univariate analysis in relation to toxicities. Multivariate analysis of toxicity endpoints was not considered owing to relatively few available events that would render overparameterized models. The mean values and SDs of the International Prostate Symptom Score, International Index of Erectile Function, and Expanded Prostate Cancer Index Composite bowel function and bother were also calculated.

Results

Patient, Tumor, and Treatment Characteristics

Table 2 summarizes the patient and tumor characteristics. The median age of patients at the time of radiation treatment was 68 years (range, 48-81 years). Eighty-one patients (79%) were white, 19 patients were black (19%), and 2 declined to identify (2%). The mean preoperative PSA was 9.7 ng/mL (range, 1.0-71.3 ng/mL). The most common pathologic Gleason score was 7 (49%), followed by 8 (25%), 6 (17%), and 9 (6%). Lymph node sampling was not performed at the time of surgery in 39 patients (38%). Three (5%) of 63 patients (62%) with lymph node sampling at the time of surgery had at least 1 positive lymph node while 60 (95%) had no positive lymph nodes. Margins were positive in 57 patients (56%); extracapsular extension was identified in 44 patients (43%); and seminal vesicles were involved in 17 patients (17%). Postoperatively, 82 patients (80%) had a PSA nadir below 0.2, while 20 (20%) patients had a PSA nadir of 0.2 or higher. Twelve patients (12%) had a postoperative, preradiation maximum PSA of 2 or higher. The mean PSA doubling time was 8.0 months (range, 0.7-36.0 months). Disease recurrence was detectable radiographically in 19 patients (19%) and clinically through physical examination in 9 patients (9%).

Table 3 summarizes the treatment characteristics for this cohort. Eleven patients (11%) received adjuvant radiation, while 91 (89%) received salvage radiation. The prostate bed alone was irradiated in 74 patients (73%), while the pelvic lymph nodes and prostate bed were irradiated in 28 patients (27%). The median prescribed dose was 70.2 GyRBE (range, 66.0-78.0 GyRBE) and the median duration of radiation therapy was 56 days (range, 450-65 days).

Disease Control

The median follow-up for all patients was 5.5 years (range, 0.8-11.4 years). The 5-year actuarial rates of freedom from biochemical progression, distant metastasis-free survival, and overall survival were 57% (95% confidence interval [CI], 46-68), 97% (95% CI, 90-99), and 93% (95% CI, 85-97), respectively (**Figure**). The 5-year actuarial rates of freedom from biochemical progression, distant metastasis-free survival, and overall survival were 72% (95% CI, 40-91), 91% (95% CI, 56-99), and 100% in patients who underwent adjuvant radiation ($n = 11$) and 57% (95% CI, 45-68), 97% (95% CI, 90-99) and 93% (95% CI, 84-97) in patients who underwent salvage radiation ($n = 91$).

The median time to PSA nadir after completion of radiation therapy for all patients was 6.2 months (range, 0-125 months). As of the last follow-up, 41 patients (40%) have developed biochemical failure at a median 6.2 months after treatment. Margin status, seminal vesicle invasion, Gleason score, extra capsular extension, bladder neck invasion, perineural invasion, radiotherapy total dose, ADT use, maximum postprostatectomy preradiation PSA, preradiation clinical failure, and preradiation

Table 2. Patient and tumor characteristics.

Characteristic	Value		
	Adjuvant (n = 11)	Salvage (n = 91)	All (N = 102)
Age, median (range), y	70.1 (51.3–75)	67.5 (48–80.8)	67.8 (48–80.8)
Race, n (%)			
White	9 (82)	72 (79)	81 (79)
Black	2 (18)	17 (19)	19 (19)
Patient declined	0	2 (2)	2 (2)
Preoperative PSA, mean ± SD (range), ng/mL	12.6 ± 11.2 (4.6–42.5)	9.4 ± 9.9 (1.0–71.3)	9.7 ± 10 (1.0–71.3)
Pathologic Gleason score, n (%)			
4	0	1 (1)	1 (1)
5	0	2 (2)	2 (2)
6	0	17 (19)	17 (17)
7	9 (82)	41 (45)	50 (49)
8	2 (18)	24 (26)	26 (25)
9	0	6 (7)	6 (6)
Pathologic nodal stage, n (%)			
N0	5 (45)	55 (60)	60 (59)
N1	2 (18)	1 (1)	3 (3)
Unknown	4 (36)	35 (38)	39 (38)
Margin status, n (%)			
Positive	9 (82)	48 (53)	57 (56)
Negative	2 (18)	43 (47)	45 (44)
Extracapsular extension, n (%)			
Yes	8 (73)	36 (40)	44 (43)
No	3 (27)	55 (60)	58 (57)
Seminal vesicle status, n (%)			
Involved	2 (18)	15 (16)	17 (17)
Uninvolved	9 (82)	76 (84)	85 (83)
Bladder neck invasion, n (%)			
Yes	0	6 (7)	6 (6)
No	11 (100)	84 (92)	95 (94)
Missing	0	1 (1)	1 (1)
Perineural invasion, n (%)			
Yes	7 (63)	62 (68)	69 (68)
No	4 (36)	29 (32)	33 (32)
Postoperative PSA nadir, n (%)			
< 0.2	10 (91)	72 (79)	82 (80)
≥ 0.2	1 (9)	19 (21)	20 (20)
Maximum postoperative preradiation PSA, n (%)			
< 0.2	10 (91)	17 (19)	27 (26)
≥ 0.2 and < 2	1 (9)	62 (68)	63 (62)
≥ 2	0	12 (13)	12 (12)
Preradiation PSA doubling time prior, mean ± SD (range), mo	3 (N/A)	8.1 ± 6.1 (0.7–36.0)	8.0 ± 6.1 (0.7–36.0)
Radiographic failure, n (%)			
Yes	0 (0)	19 (21)	19 (19)
No	11 (100)	72 (79)	83 (81)
Clinical failure, n (%)			
Yes	0 (0)	9 (10)	9 (9)
No	11 (100)	82 (90)	93 (91)

Abbreviation: PSA, prostate-specific antigen.

Table 3. Treatment characteristics (N = 102).

Characteristic	Number of patients (%)
Radiation indication	
Adjuvant	11 (11)
Salvage	91 (89)
Radiation fields	
Prostate bed and pelvic nodes	28 (27)
Prostate bed only	74 (73)
Prescribed dose, GyRBE	
< 70.2	27 (26)
70.2–72	45 (44)
73–74	29 (28)
> 74	1 (1)
Androgen deprivation therapy	
Yes	45 (44)
No	57 (56)

radiographic failure were variables that were analyzed in a univariate analysis in relation to biochemical failure. Seminal vesicle invasion was associated with a decline in biochemical control ($P = .002$), while positive margins were associated with improvements in biochemical control ($P = .04$) (**Table 4**). Neither radiation dose ($P = .13$) nor radiographic evidence of local recurrence ($P = .43$) was associated with worse biochemical control in salvage patients. Multiple proportional hazards regression assessed the ability of margin status, extracapsular extension, seminal vesicle involvement, radiation dose ($<$ vs $\geq$ 73 Gy), and use of hormones to predict significant differences in biochemical control relative to one another. Margin status ($P = .04$, hazard ratio 0.5 [95% C.I. 0.3-0.9]) and extracapsular extension ($P < .01$, hazard ratio 1.2 [95% C.I. 1.4-5.7]) were significant predictors of biochemical control, whereas seminal vesicle involvement ($P = .63$), radiation dose ($P = .08$), and use of hormones ($P = .17$) were not significant.

Two of 3 patients with pathologic node-positive disease from the time of surgery had no evidence of disease at the time of last follow-up. The median follow-up time for these patients was 2.6 years (range, 1.6-11.4 years). Of these 3 patients, 1 underwent orchiectomy; ADT was not initiated in the other 2 patients due to patient preference and comorbidities.

Patterns of Failure

All patients with disease progression had evidence of biochemical progression (n = 41). PSA progression was the sole indication of disease progression in 32 patients (78%), but was accompanied by isolated biopsy-proven local failure in 1 patient (2%), isolated pelvic nodal failure in 2 patients (5%), isolated distant metastases in 4 patients (10%), or a combination of clinical sites in 2 patients (5%). Patterns of failure are summarized in **Table 5**. Two of 3 pelvic nodal failures occurred in patients treated to the prostate bed only. The third pelvic nodal failure was in a patient who had pelvic nodal treatment extending inferiorly in the presacral area to the S3/4 level. The failure occurred outside of the radiation fields in a presacral node anterior to S5. There was no significant difference in the risk of pelvic nodal failure between patients treated with or without pelvic nodal irradiation. The 5-year rate of freedom from pelvic nodal failure in patients treated with and without nodal treatment was 96% (95% CI 76.5-99.4) versus 96.9% (95% CI 88.5-99.2; $P = 0.8637$).

In total, 5 patients (5%) died from disease progression and 6 patients (6%) died from intercurrent disease, defined as competing comorbidities. The median time to death after detection of the first recurrence for patients who died from disease progression was 56 months (range, 37-76 months).

Toxicities and Patient-Reported Outcomes

No patients developed grade 4 or 5 acute or late toxicities. One patient (1%) experienced acute grade 3 GU toxicities in the forms of dysuria, urinary frequency, and urgency. Seven patients (7%) experienced a maximum late grade 3 GU toxicity, including dysuria (1%), frequency (1%), incontinence (2%), retention (1%), and hematuria (2%). The median time to maximum late grade 3 GU toxicity was 25 months (range, 8-97 months). Hematuria resolved in both patients as of last follow-up, as did dysuria for the patient who experienced this toxicity.

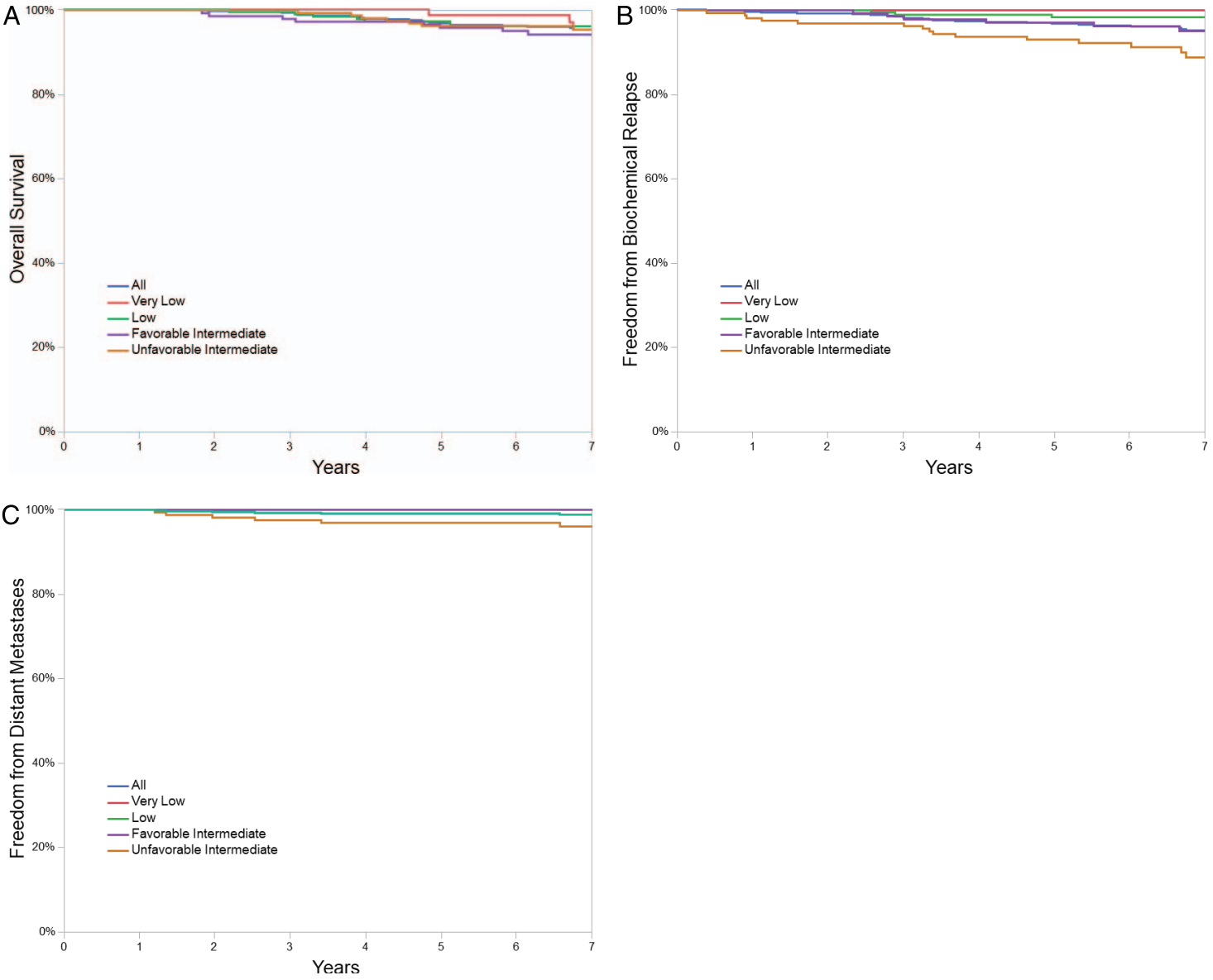

Figure. Actuarial rates of (A) overall survival, (B) freedom from biochemical progression, and (C) distant metastasis-free survival.

There was no grade 3 or higher acute or late GI toxicities. Five patients (5%) experienced acute grade 2 GI toxicity as follows: diarrhea (3%), abdominal cramping (1%), and proctitis (1%). All 5 received treatment to their pelvic lymph nodes with IMRT. One patient with acute grade 2 diarrhea developed a late grade 2 GI toxicity. Two patients experienced late grade 2 GI toxicities, both in the form of rectal hemorrhage. One patient received treatment to his pelvic lymph nodes with IMRT, while the other received treatment with protons only to the prostate bed alone. The latter had resolution of his late grade 2 GI toxicity as of last follow-up. The median time to maximum late grade 2 GI toxicity was 20 months (range, 12-29 months). Age, radiation to surgery time interval, radiation dose, aspirin/coagulation use, ADT use, metformin use, and baseline IPSS score were variables that were analyzed in a univariate analysis in relation to toxicities (**Table 6**). On univariate analysis, the incidence of grade 2 or higher GI and grade 3 or higher GU toxicities was unrelated to patient age ($P = .77$ and $P = .86$, respectively), radiation to surgery time interval ($P = .63$ and $P = .83$, respectively), radiation dose ($P = .21$ and $P = .44$, respectively), aspirin/anticoagulation use ($P = .24$ and $P = .88$, respectively), ADT use ($P = .55$ and $P = .27$, respectively), metformin use ($P = .55$ and $P = .49$, respectively), and baseline IPSS score ($P = .85$ and $P = .58$, respectively). Multivariate analysis was not performed for toxicities, as there were too few events for this analysis.

Table 4. Univariable Kaplan-Meier analysis for freedom from biochemical recurrence according to subgroup characteristics.

Variables	5-y rate (%)	95% confidence interval	*P* value
Margin			.04[a]
Positive	67.1	50.9–80.0	
Negative	45.7	30.7–61.5	
Extracapsular extension			.34
Present	52.2	34.8–69.0	
Absent	60.7	46.0–73.8	
Seminal vesicle invasion			.002[a]
Present	41.2	21.0–64.8	
Absent	61.2	48.6–72.5	
Bladder neck invasion			.84
Present	55.6	14.8–90.0	
Absent	57.1	45.5–68.0	
Perineural invasion			.99
Present	56.0	41.9–69.2	
Absent	59.1	40.3–75.5	
Radiotherapy total dose, GyRBE			.13
< 70.2	62.3	48.3–74.6	
> 70.2	49.4	31.7–67.2	
ADT			.08
Received	47.9	31.5–64.8	
Not received	64.3	49.4–77.0	
Preradiation clinical failure			.23
Present	32.4	5.1–80.9	
Absent	58.9	47.2–69.7	
Preradiation radiographic failure			.43
Present	53.7	30.4–75.5	
Absent	58.2	45.5–70.0	
Pelvic nodal treatment			.46
No	55.8	42.9–68.0	
Yes	60.6	37.7–79.6	
Gleason score			.17
4–6	70.1	40.4–89.0	
7–10	54.2	42.0–66.0	
Maximum postoperative, preradiation prostate-specific antigen			.09
< 0.2	74.8	45.8–91.2	
≤ 0.2	53.2	41.0 - 65.1	

Abbreviation: ADT, androgen deprivation therapy.

[a]Indicates statistically significant values.

Baseline, 6-month, 1-year, and 5-year patient-reported quality-of-life scores are shown in **Table 7** for patients with appropriate follow-up. Over 5 years, the mean IPSS score increased from 7.5 (SD = 5.9) to 12.1 (9.1), both of which would be characterized as scores that fall in the ‘‘moderate’’ symptoms [26] range. The mean IIEF-5, EPIC bowel function, and EPIC bowel bother scores remained relatively stable at 5 years.

Discussion

This study presents long-term treatment outcomes and toxicities for patients who received postprostatectomy proton radiation. The main objective of our investigation was to establish benchmark outcomes for treatment efficacy and toxicities for

Table 5. Patterns of failure.

	Number of patients (%)		
Type of progression	**Adjuvant (n = 11)**	**Salvage (n = 91)**	**All (N = 102)**
None	8 (73)	53 (58)	61 (60)
PSA failure only	2 (18)	30 (33)	32 (31)
PSA failure with biopsy-proven local recurrence	0	1 (1)	1 (1)
PSA failure with isolated pelvic nodal failure	0	2 (2)	2 (2)
PSA failure with isolated distant metastatic disease	1 (9)	3 (3)	4 (4)
PSA failure with pelvic nodal and distant metastatic disease	0	1 (1)	1 (1)
PSA failure with local recurrence and distant metastatic disease	0	1 (1)	1 (1)

Abbreviation: PSA, prostate-specific antigen.

postprostatectomy proton radiation. It is our hope that these results can guide future strategies to improve outcomes, either by mitigating toxicity or improving disease control.

Interpreting toxicities after postprostatectomy radiation can pose several challenges. It is often difficult to determine to what degree a toxicity is caused by radiation in a patient who previously had prostatectomy. To mitigate this challenge, we tabulated baseline functioning before radiation treatment, and prospectively collected toxicity data. In our cohort, few patients experienced acute or late toxicities. Acute toxicities did not commonly evolve into late toxicities, and no patients experienced grade 3 or higher GI toxicities or grade 4 or higher GU toxicities. Of the 6 patients who experienced grade 2 or higher acute and

Table 6. Five-year rates of Grade ≥ 2 gastrointestinal toxicity and Grade ≥ 3 genitourinary toxicity according to subgroup characteristics.

	Grade 2 and gastrointestinal toxicity			Grade 3 and genitourinary toxicity		
Variables	**Toxicity rate (%)**	**95% confidence interval**	***P* value**	**Toxicity rate (%)**	**95% confidence interval**	***P* value**
Androgen deprivation therapy			.55			.27
Received	2.3	0.3–14.4		7.1	2.3–19.9	
Not received	1.8	0.2–11.4		0.0	N/A	
Age			.77			.86
< median 67 y	2.1	0.3–13.6		2.1	0.3–13.6	
≥ median 67 y	1.9	0.3–12.2		4.0	1–14.7	
Aspirin/anticoagulant?			.24			.88
At consult or consult and last follow-up	0.0	N/A		5.9	1.5–20.7	
Only at last follow-up or none	3.0	0.7–11.2		1.7	0.2–11.1	
Radiation dose			.21			.44
< 73 Gy	1.4	0.2–9.4		4.5	1.4–13	
≥ 73 Gy	3.3	0.5–20.2		0.0	N/A	
Metformin			.55			.49
At consult or consult and last follow-up	0.0	N/A		0.0	N/A	
Only at last follow-up or none	2.2	0.6–8.4		3.4	1.1–10.1	
Modality			.62			.42
Postoperative	0.0	N/A		12.5	1.7–53.7	
Salvage	2.2	0.6–8.5		2.2	0.6–8.4	
Surgery to radiation start interval			.63			.83
< median 2.7 years	0.0	N/A		4.3	1.1–15.7	
≥ median 2.7 years	4.0	1–14.7		2.0	0.3–12.6	
Pelvic nodal treatment			.74			.63
No	1.4	0.2–9.3		1.4	0.2–9	
Yes	3.6	0.5–21.4		7.6	1.9–25.9	
IPSS score	-	-	-			.58
< 5	-	-	-	5.3	1.3–18.9	
≥ 5	-	-	-	1.7	0.2–11.2	

Abbreviation: IPSS, International Prostate Symptom Score.

Table 7. Patient-reported outcomes.

	Baseline (mean ± SD)			At 6 mo (mean ± SD)			At 1 y (mean ± SD)			At 5 y (mean ± SD)		
Measure	Adjuvant (n = 11)	Salvage (n = 91)	All (n = 102)	Adjuvant	Salvage	All	Adjuvant	Salvage	All	Adjuvant	Salvage	All
IPSS	8.0 ± 6.2	7.5 ± 6.0	7.5 ± 5.9	9 ± 7.7	8.3 ± 6.2	8.4 ± 6.4	8 ± 4.7	8.8 ± 7.4	8.7 ± 7.2	10.3 ± 9.1	12.2 ± 9.2	12.1 ± 9.1
n	11	87	98	11	81	92	9	69	78	3	34	37
IIEF-5	6.0 ± 6.9	10.7 ± 8.5	10.2 ± 8.3	7.2 ± 4.4	9.8 ± 8.2	9.5 ± 7.8	7.7 ± 4.6	9.5 ± 7.4	9.3 ± 7.2	14.0 ± 9.5	9.6 ± 6.3	10.1 ± 6.7
n	10	81	91	10	69	79	7	58	65	3	23	26
EPIC bowel function	98.8 ± 2.1	92.2 ± 11.5	92.8 ± 11.1	93 ± 8.3	89.9 ± 13.7	90.3 ± 13.2	90.6 ± 18.8	88.2 ± 15.5	88.5 ± 15.8	95.2 ± 4.1	86.6 ± 18.6	87.3 ± 18
n	10	85	95	11	75	86	8	63	71	3	32	35
EPIC bowel bother	97.6 ± 2.1	90.6 ± 6.4	91.2 ± 6.4	90.4 ± 6.5	88.2 ± 13.7	88.4 ± 13	92.3 ± 8.6	88.1 ± 11.9	88.5 ± 11.7	94.0 ± 10.3	86.1 ± 14.0	86.7 ± 13.8
n	11	85	96	10	80	90	7	68	75	3	33	36

Abbreviations: IPSS, International Prostate Symptom Score; IIEF, International Index of Erectile Function; EPIC, Expanded Prostate Cancer Index Composite.

late GI toxicities, 5 received treatment to their pelvic nodes with IMRT; only 1 patient who was treated with protons alone experienced a grade 2 or higher GI toxicity. In a published report of toxicities after postprostatectomy proton radiation from the University of Pennsylvania, investigators found no grade 3 or higher GU toxicities or grade 2 or higher GI toxicities using CTCAE v4.0 scoring criteria [20]. These rates of toxicity are slightly lower than our cohort's toxicity rates, perhaps owing to a shorter median follow-up time of 2 years in comparison to our 5.5-year median follow-up. Our toxicity data compared favorably with data from the largest IMRT postprostatectomy radiation study published by investigators at the City of Hope National Medical Center who reported that 10% of patients experienced late grade 3 GU toxicities and 18% experienced late grade 2 or higher GI toxicities, using CTCAE v4.0 criteria [27]. The second challenge with interpreting toxicity data is that the criteria used to measure toxicities can vary from study to study. For example, in the "wait and see" arm of EORTC 22911, the incidence of grade 3 or higher late toxicities was 2.5% while the rates of late grade 2 or higher GU and GI toxicities were 13.5% and 1.9%, respectively, using the RTOG/EORTC toxicity scoring scale [4]. Of note, the RTOG/EORTC toxicity scoring scale does not include urinary incontinence as a criterion, which is critically important for postoperative cases. With these caveats, the patient-reported quality-of-life scores in the current study suggest that quality of life with respect to sexual, urinary, and bowel function is comparable before and after radiation treatment and physician-scored toxicity rates were extremely low.

In our cohort, which was comprised almost exclusively of patients who received salvage rather than adjuvant radiation, the freedom from biochemical progression, distant metastases-free survival, and overall survival were 57%, 97%, and 93%, respectively. The treatment indication of positive margins was associated with an improvement in biochemical control on univariate analysis, a similar finding as in an analysis from Stephenson et al [8]. Our outcomes compare favorably with those reported in a large multi-institutional retrospective study of salvage photon radiation therapy after radical prostatectomy, where the 6-year rate of progression-free survival was 32% [8] using a median dose of 64.8 Gy, with an interquartile range of 63.0 to 66.0 Gy. The difference in disease control may in part be attributable to our higher doses of radiation, as our cohort received a median dose of 70.2 GyRBE. Data from a retrospective study from investigators at Stanford University would seem to corroborate this conjecture, as the 5-year rates of biochemical control with doses of 60 Gy versus 70 Gy were 25% versus 58% [28]. With respect to prospective trials, in the "wait and see" arm of EORTC 22911 (most similar to our cohort), the 5-year rate of biochemical progression-free survival in those receiving salvage radiotherapy was 52.6% [4]. In the salvage radiotherapy alone arm of GETUG-AFU 16, the 5-year rate of progression-free survival was 62% [29]. In our cohort, the 5-year rate of biochemical progression-free survival was 57%. While the disease control rates in the current study are in keeping with other trials, there is certainly room for improvement.

The current standard of care recommended by the National Comprehensive Cancer Network for postoperative radiation is a dose between 64 and 72 Gy [30]; however, there are data suggesting improved disease control with each incremental Gray of radiation delivered [31]. Given these findings, and evidence from Southwest Oncology Group 8794 demonstrating that the most common treatment failure in the postprostatectomy setting is local [32], dose escalation is an area of active interest. Yet, dose escalation may also increase the risk of radiation-related toxicities, which can be particularly debilitating in patients who have undergone radical prostatectomy. The unique dose deposition characteristics proton therapy allow high doses to be

delivered to the target area while minimizing radiation dose to normal structures, which may facilitate safe dose escalation. The low-toxicity rates observed in our study suggest an opportunity for safe-dose escalation with proton therapy.

It has been our practice to offer ADT to patients with a high risk of disease recurrence, given the overall survival benefit demonstrated in RTOG 9601 [33] and the improvement in biochemical progression-free survival demonstrated in GETUG-AFU 16 [33].

There are several limitations to the present study. The study population was mixed with respect to the use of adjuvant versus salvage radiation, ADT, and pelvic node irradiation. However, treatment decisions were guided by consistent criteria and patient input, so we believe these results will be generalizable to other practice settings and institutions. Because the overwhelming majority of patients received salvage radiation as opposed to adjuvant radiation, our ability to draw conclusions on adjuvant treatment is limited. The strengths of this study are its relatively large cohort size, consistent treatment methods based on institutional treatment guidelines, prospective outcome assessment by an experienced clinical staff, and consistent and extensive follow-up.

In conclusion, image-guided postprostatectomy proton therapy for the treatment of prostate cancer offers rates of biochemical control and metastases-free survival that compare favorably with other reported radiation strategies. This treatment is associated with low rates of acute and late grade 3 or higher GU toxicities, acute and late grade 2 or higher GI toxicities, and excellent patient-reported quality-of-life outcomes.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Nancy P. Mendenhall, MD, and William M. Mendenhall, MD, are Editor-in-Chief and Operating Editor of the *International Journal of Particle Therapy*, respectively. Bradford S. Hoppe, MD, MPH, is an Associate Editor of the *International Journal of Particle Therapy* and a Scientific Consultant for Merck & Co., Inc., and Bristol-Myers Squibb
Ethical Approval: All patient data were collected under internal review board–approved protocol.

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