Clinical Investigation: Genitourinary Cancer

Five-Year Outcomes from 3 Prospective Trials of Image-Guided Proton Therapy for Prostate Cancer

Nancy P. Mendenhall, MD,* Bradford S. Hoppe, MD,* Romaine C. Nichols, MD,* William M. Mendenhall, MD,* Christopher G. Morris, MS,* Zuofeng Li, DSc,* Zhong Su, PhD,* Christopher R. Williams, MD,† Joseph Costa, DO,† and Randal H. Henderson, MD, MBA*

*University of Florida Proton Therapy Institute, Jacksonville, Florida; and †Division of Urology, College of Medicine, University of Florida, Jacksonville, Florida

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Introduction

There is interest among patients, physicians, insurers, and government agencies in the relative effectiveness of various strategies for management of prostate cancer, the most common noncutaneous malignancy in men in the United States. One comparative study of patient-reported quality of life outcomes (PRQoLOs) among patients treated with surgery, brachytherapy, or external beam radiation therapy (EBRT) showed variation in

Reprint requests to: Nancy Price Mendenhall, MD, University of Florida Proton Therapy Institute, 2015 North Jefferson St, Jacksonville, FL 32206. Tel: (904) 588-1800; E-mail: menden@shands.ufl.edu

Summary

Proton therapy (PT) for low-, intermediate-, and high-risk prostate cancer patients is highly effective, minimally toxic, and associated with excellent patient-reported outcomes. PT compares favorably with other contemporary radiation modalities used in treating prostate cancer.

Purpose: To report 5-year clinical outcomes of 3 prospective trials of image-guided proton therapy for prostate cancer.

Methods and Materials: A total of 211 prostate cancer patients (89 low-risk, 82 intermediate-risk, and 40 high-risk) were treated in institutional review board-approved trials of 78 cobalt gray equivalent (CGE) in 39 fractions for low-risk disease, 78 to 82 CGE for intermediate-risk disease, and 78 CGE with concomitant docetaxel therapy followed by androgen deprivation therapy for high-risk disease. Toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Median follow-up was 5.2 years.

Results: Five-year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low-, intermediate-, and high-risk patients, respectively. Actuarial 5-year rates of late CTCAE, version 3.0 (or version 4.0) grade 3 gastrointestinal and urologic toxicity were 1.0% (0.5%) and 5.4% (1.0%), respectively. Median pretreatment scores and International Prostate Symptom Scores at >4 years posttreatment were 8 and 7, 6 and 6, and 9 and 8, respectively, among the low-, intermediate-, and high-risk patients. There were no significant changes between median pretreatment summary scores and Expanded Prostate Cancer Index Composite scores at >4 years for bowel, urinary irritative and/or obstructive, and urinary continence.

Conclusions: Five-year clinical outcomes with image-guided proton therapy included extremely high efficacy, minimal physician-assessed toxicity, and excellent patient-reported outcomes. Further follow-up and a larger patient experience are necessary to confirm these favorable outcomes. © 2014 Elsevier Inc.
toxicity profiles (1) but relatively favorable outcomes for EBRT. Most EBRT delivers x-rays using sophisticated techniques (2). There is growing interest in proton therapy (PT) as a radiation source because, compared with x-ray-based therapies, less radiation dose is deposited in normal nontargeted tissues, possibly resulting in less toxicity, better quality of life, and fewer second malignancies (3, 4). Reduction in dose to normal tissues might also make radiation dose escalation or intensification feasible, resulting in greater efficacy and shorter, less expensive treatment schedules. Despite reports of excellent outcomes in prostate cancer patients treated with PT alone (5) or in combination with x-ray therapy (6), many physicians consider the clinical evidence for PT to be insufficient (7, 8), and some investigators have relied on surrogate data from Medicare claims for comparative studies (9), leading to controversial findings.

To establish benchmark outcomes for PT, 3 prospective trials in low-, intermediate-, and high-risk prostate cancer patients were conducted at our institution. Five-year outcomes from these trials are reported below.

Methods and Materials

Patients

From August 2006 through September 2007, 211 patients were treated with institutional review board-approved protocols PR-01 (UFJ-2005-154), PR-02 (UFJ-2006-63), and PR-03 (UFJ-2006-94) to assess outcomes after undergoing PT for low-risk (n = 89), intermediate-risk (n = 82), and high-risk (n = 40) prostate cancer, respectively. Eligibility criteria and required staging were previously described (10). Patients were staged according to the seventh edition of the AJCC Staging Manual (11).

Prostate-specific antigen (PSA) concentration was assessed before and after treatment and then at 3-month intervals; the Phoenix definition for PSA progression (nadir + 2 ng/mL) was used (12). In all patients with PSA progression, a bone scan and positron emission tomography-computed tomography (CT) and/or magnetic resonance imaging (MRI) of the pelvis were performed to determine patterns of failure. Physician-determined toxicities were assessed weekly throughout treatment and at 6-month intervals, using Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) (13). Serious adverse events were also classified retrospectively according to the 2010 edition of CTCAE v4.0 (14), which is based on instrumental and self-care activities of daily living (ADLs). The Expanded Prostate Cancer Index Composite (EPIC; version 2.2002) score and self-care activities of daily living (ADLs). The Expanded Prostate Cancer Index Composite (EPIC; version 2.2002) score and self-care activities of daily living (ADLs).

Protocol treatment

PR-01 for low-risk patients delivered 78 cobalt gray equivalent (CGE). PR-02 delivered 78 to 82 CGE for intermediate-risk prostate cancer. PR-03 for high-risk patients delivered 78 CGE with weekly concomitant docetaxel (Taxotere, Sanofi-Aventis U.S. LLC, Bridgewater, NJ) (20 mg/m²) therapy, followed by 6 months of androgen deprivation therapy (ADT). The daily dose was 2 CGE. Two PR-03 patients refused ADT after completing PT with Taxotere. Ten low-risk and 7 intermediate-risk patients received neoadjuvant ADT prior to referral (Table 1). No pelvic node irradiation was delivered.

Treatment simulation and planning

Previously reported planning details (10) include customized vacuum-locked body bags, bladder filling, and rectal instillation of saline to reduce intrafractional prostate motion. Fused CT and MRI simulation images were used to define both the clinical target volume (CTV) and organs at risk (OARs). The CTV for PR-01 was the prostate only but the proximal 2 cm of the seminal vesicles were included in PR-02 and PR-03. The planning target volume (PTV) included an expansion beyond the CTV of 8 mm in the superior–inferior axis and 5 mm in the axial plane; beam angles were selected to optimize both target coverage and avoidance of OARs. Brass apertures included the PTV plus 1 cm in all directions except posterior, which was 7 mm. Compensators for distal conformity of target coverage used a smearing value of 1.9 cm and 1.0-cm border smoothing (subsequently reduced to 0 cm following experimental validation). Proton beam stopping power was calculated from the CT Hounsfield unit value (16). Distal and proximal beam margins from the PTV were 0.5 cm.

Target and normal tissue dosimetric specifications

When all dosimetric specifications for target coverage and avoidance of OARs (10) could be met with a single field, only 1 of the 2 fields was treated each day. Both fields were treated each day in only 23 cases (11%).

The intermediate-risk protocol, PR-02, permitted dose escalation to 82 CGE if OAR constraint goals were met; 57 patients (69%) received 82 CGE, 13 (16%) received 80 CGE, and 12 (15%) received 78 CGE.

Image guided treatment delivery

Daily targeting was based on intraprostatic fiducial markers identified by orthogonal orthovoltage imaging. Rectal balloons were added in 8 patients (3.7%) whose daily intrafractional motion exceeded 5 mm.

Statistical analysis

Maximum genitourinary (GU) and gastrointestinal (GI) toxicity scores were assessed at 6-month intervals; cumulative incidence, prevalence, and actuarial rates were calculated.

All statistical computations were performed with SAS and JMP software (SAS Institute, Cary, NC). The Wilcoxon signed rank sum test was used for paired comparisons of baseline and posttreatment
Table 1  Patient characteristics for low-, intermediate-, and high-risk trials of image-guided proton therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low risk (PR-01)</th>
<th>Intermediate risk (PR-02)</th>
<th>High risk (PR-03)</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>89</td>
<td>82</td>
<td>40</td>
<td>211</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>64 (40-81)</td>
<td>68 (45-86)</td>
<td>72 (53-88)</td>
<td>68 (40-88)</td>
</tr>
<tr>
<td>Median prostate volume (cm³)</td>
<td>41 (11-92)</td>
<td>35 (13-135)</td>
<td>27 (10-80)</td>
<td>36 (10-135)</td>
</tr>
<tr>
<td>Prostate &lt;40 cm³</td>
<td>42 (47%)</td>
<td>54 (66%)</td>
<td>27 (69%)</td>
<td>123 (59%)</td>
</tr>
<tr>
<td>Prostate ≥40 and &lt;60 cm³</td>
<td>33 (38%)</td>
<td>15 (18%)</td>
<td>7 (18%)</td>
<td>55 (26%)</td>
</tr>
<tr>
<td>Prostate ≥60 cm³</td>
<td>13 (15%)</td>
<td>13 (16%)</td>
<td>5 (13%)</td>
<td>31 (15%)</td>
</tr>
<tr>
<td>Medical comorbidity</td>
<td>54 (61%)</td>
<td>52 (63%)</td>
<td>25 (63%)</td>
<td>131 (62%)</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>50 (56%)</td>
<td>47 (57%)</td>
<td>18 (45%)</td>
<td>115 (55%)</td>
</tr>
<tr>
<td>Prior TURP</td>
<td>3 (3%)</td>
<td>7 (9%)</td>
<td>6 (15%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>Prior α-blockers</td>
<td>35 (39%)</td>
<td>26 (32%)</td>
<td>7 (18%)</td>
<td>68 (32%)</td>
</tr>
<tr>
<td>Prior rectal bleeding</td>
<td>5 (6%)</td>
<td>7 (9%)</td>
<td>3 (8%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>neoADT</td>
<td>10 (11%)</td>
<td>7 (9%)</td>
<td>9 (23%)</td>
<td>26 (12%)</td>
</tr>
</tbody>
</table>

Abbreviations: neoADT = neoadjuvant androgen deprivation therapy; in addition, most high-risk prostate cancer patients received neoADT or ADT; TURP = transurethral resection of the prostate or other cytoreductive surgical process to relieve obstructive symptoms.

* Pretreatment prostate volume data were missing in 2 patients.
† Medical comorbidities included diabetes, hypertension, cardiovascular disease, and chronic obstructive pulmonary disease.

QoL data. In the case of urinary incontinence score comparisons, the median test replaced the Wilcoxon signed rank sum test because of heavy skew toward high scores (61% with the highest possible score of 100). The Kaplan-Meier product limit function provided estimates of overall survival, freedom from biochemical and/or clinical progression (FFBP), and freedom from toxicity. The log-rank test was used to estimate significance between strata of selected prognostic factors. Proportional hazards regression was used for multivariate analysis of selected prognostic factors. All P values less than .05 were considered statistically significant.

Results

Survival and disease control

At 5 years, 23 patients had died of intercurrent disease (n = 20) or prostate cancer (n = 3), including 6 PR-01 (7%), 11 PR-02 (13%), and 6 PR-03 (15%) patients. Five-year overall survival rates for PR-01, PR-02, and PR-03 are 93%, 88%, and 86%, respectively (Fig. 1).

Disease progression occurred in 10 patients, including 1 low-risk PR-01 patient, 1 “unfavorable intermediate-risk” PR-02 patient, and 8 PR-03 patients. The median time to PSA and/or clinical progression was 31 months (17-56 months). Five-year FFBP rates were 99% for low-risk, 99% for intermediate-risk, and 76% for high-risk patients (Fig. 2).

Patterns of PSA response and disease progression

Serial PSA data were available for 10 patients with PSA progression and 198 patients coded as biochemically and clinically free of disease. For the 198 patients without progression, median PSA nadir was 0.2 (0-3.6), including 0.2 in low-risk, 0.2 in intermediate-risk, and 0.1 in high-risk patients; 82% of nadirs were <0.5. The median times to nadir were 36, 44, and 8 months for PR-01, PR-02, and PR-03, respectively. In 149 patients who were not receiving ADT, transient pre-nadir PSA “bumps” were observed in 108 patients (72.5%), including PSA bumps of ≥2 ng/mL in 9 patients (6%), ≥1 and <2 ng/mL in 14 (9.4%) patients, and <1 in 85 (57%) patients. Transient postnadir PSA bumps were observed in 77 patients (51.7%), including bumps of ≥2 ng/mL in 1 patient (0.7%), ≥1 ng/mL but <2 ng/mL in 5 patients (3.4%), and <1 ng/mL in 71 patients (47.6%). Transient pre-nadir bumps were observed in 14 (28.6%) of the 49 patients receiving ADT: no bumps were ≥2 ng/mL, 2 of the bumps (4.1%) were ≥1 ng/mL but <2 ng/mL, and 12 bumps (24.5%) were <1 ng/mL. Transient postnadir bumps were observed in 40 patients (81.6%), including bumps ≥2 ng/mL in 4 patients (8.2%), ≥1 ng/mL but <2 ng/mL in 2 patients (4.1%), and <1 ng/mL in 34 patients (69.4%).

Patterns of disease progression are shown in Table 2. PSA progression occurred in all patients, either alone (n = 5) or with isolated pelvic nodal failure (n = 2) and/or distant metastases (n = 3).

Toxicity

There was a single instance of acute grade 3 GU toxicity: 1 patient required catheterization for 10 days during treatment. Late grade 3 GU events, according to CTCAE v3.0 (12), occurred in 4, 4, and 2 patients on PR-01, PR-02, and PR-03, respectively, for an actuarial rate and cumulative incidence at 5 years of 5.4% and 4.8%, respectively; all events were transient. GU events were significantly correlated with pretreatment urologic symptom management (P < .03). Grade 3 GU toxicities included 4 post-treatment prostate reductive procedures, 3 temporary catheterizations, incontinence in a patient with a pretreatment penile implant who developed a posttreatment bulbar urethral stricture, 1 transfusion and urethral cautery for hemorrhage, and 1 case of cystitis requiring hyperbaric oxygen and narcotics. The last 2 events were considered to impact self-care ADLs; thus, the CTCAE v4.0 (13) grade 3 GU toxicity rate was 0.9%.

One acute grade 3 GI event occurred in a PR-03 patient who developed severe constipation, possibly related to docetaxel. Late CTCAE v3.0 grade 3 GI symptoms occurred in 2 PR-02 patients receiving anticoagulant therapy, 1 of whom developed rectal ulceration after undergoing endoscopic biopsy of inflamed rectal mucosa and required temporary colostomy and the other who required transfusion and cautery for rectal bleeding for a 5-year actuarial and cumulative incidence of 1.0%. Only the first of these events impacted self-care ADLs, so the CTCAE v4.0 grade 3 late GI toxicity rate was 0.5%.
Two additional grade 3 toxicities included hot flashes and erectile dysfunction in 2 PR-03 patients undergoing ADT.

**Patient-reported outcomes**

As shown in Table 3, the median baseline and IPSS scores at >4 years were stable: 8 and 7 for low-risk patients, 6 and 6 for intermediate-risk patients, and 9 and 8 for high-risk patients, respectively. Similarly, the median EPIC summary scores for bowel, urinary irritative/obstructive, and urinary incontinence domains remained relatively stable; however, sexual function summary scores in patients declined. The median sexual summary scores in patients <60 years old and not receiving ADT fell from 87.5 to 57.9 and from 61.0 to 27.0 in patients ≥60 years old. Sexual summary scores among the 29 patients treated with ADT rose nonsignificantly from 25.0 (range, 0.0-100.0) to 31.8 (range, 0.0-100.0).

**Special subset analysis**

In the 42 brachytherapy candidates, 1 grade 3 GU toxicity occurred but no grade 3 GI toxicities; 5-year FFBP was 97%. In the 20 “very low-risk” patients, no grade 3 toxicities occurred; 5-year FFBP was 100%. In the 54 “favorable intermediate-risk” patients, there were 2 grade 3 GU toxicities and no grade 3 GI toxicities; 5-year FFBP was 100%. In the 28 “unfavorable intermediate-risk” patients, 3 grade 3 GU toxicities and 2 grade 3 GI toxicities occurred; 5-year FFBP was 96%.

**Discussion**

Efficacy, toxicity, and quality of life are the most important clinical endpoints for patients selecting a management strategy for prostate cancer. This PT study reports 5-year FFBP rates of 99%, 99%, and 76% in low-, intermediate- and high-risk patients, respectively. CTCAE v3.0 grade 3 GU toxicity occurred in only 5.4% of patients and, as in previous studies, was correlated with pretreatment urologic dysfunction (10, 17, 18). Late grade 3 GI toxicity occurred in only 2 patients, both of whom were receiving anticoagulation therapy, a factor previously associated with rectal bleeding (19); and 1 event was precipitated by rectal mucosal biopsy. This study also provides the first published analysis of 5-year patient-reported EPIC outcomes after PT alone, documenting excellent, sustained PRQoLs in the bowel, urinary irritative, and urinary obstructive/retentive domains, with some decline in the sexual domain, similar to earlier reports (20). These clinical outcomes with PT confirm earlier observations (5, 6) and should obviate further questions regarding the efficacy, low risk of toxicity, and preserved quality of life with PT (7, 8).

Concerns regarding relative comparative effectiveness, however, remain. Few trials prospectively compare competing local therapies. One comparing PT with intensity modulated RT (IMRT) is ongoing, but results will not be available for several years. A prospective 2-year comparison of PRQoLs among surgery, brachytherapy, and EBRT patients reported by Sanda et al (1) has shown that EBRT patients were older and had more rectal dysfunction; surgery patients had more urinary incontinence; and brachytherapy patients had more urinary irritative symptoms. None of the EBRT patients were treated with PT, but some received IMRT. One comparison of PRQoLs outcomes between the IMRT patients in the study by Sanda et al (1) and those from a PT cohort (using different PRQoL assessment tools) showed no significant early differences between IMRT and PT (21). However, another comparison of PRQoLs outcomes between the IMRT patients in the Sanda et al study and those of another PT cohort which used the same prospective assessments as the study by Sanda et al (1) showed similar summary scores but specific differences in rectal urgency, favoring the PT cohort (22). Thus far, no disease control data from the various cohorts in the Sanda et al study have been provided.

An early Memorial Sloan-Kettering Cancer Center (MSKCC) experience (23) with transperineal CT-planned permanent iodine-125 prostate implantation showed 5-year FFBP rates of 88%, 77%, and 38% for favorable-, intermediate-, and unfavorable-risk disease, respectively, with an overall 5-year rate of urethral stricture of 10%. A Fox Chase Cancer Center retrospective comparative study of iodine-125 permanent implantation versus IMRT in low-risk prostate cancer patients showed 4-year FFBP rates of 93.4% versus 99.5%, respectively, and significantly higher toxicity with brachytherapy (24). In the 42 brachytherapy-eligible patients in the current PT study, a single grade 3 GU and no grade 3 GI events occurred, and 5-year FFBP was 97%.

Another study of high-dose rate brachytherapy and external beam radiation therapy from MSKCC reported 7-year FFBP rates...
of 95%, 90%, and 57% in patients with low-, intermediate-, and high-risk prostate cancer, respectively (25). Two retrospective studies from the Cancer Center of Irvine (26) and MSKCC (27) compared IMRT alone versus IMRT combined with high-dose-rate brachytherapy. Neither study demonstrated a difference in FFBP in low-risk disease, but Deutsch et al (27) found an improvement in FFBB in intermediate-risk patients with the addition of brachytherapy (84% vs 98%, respectively). Investigators from Beaumont Health (28) also identified a subgroup of intermediate-risk patients with perineural invasion, CST2B-C, or percentage core involvement >50% with improved 5-year FFBB with the addition of brachytherapy to image guided RT (IGRT; 96% vs 87%, respectively). However, results for IMRT plus brachytherapy in both studies appear comparable (27, 28) to those achieved with PT alone in the current study.

No randomized controlled trials comparing IMRT with 3-dimensional conformal radiation therapy (3DCRT) have been published, but several retrospective studies of clinical (29) or surrogate outcomes (9) show lower toxicity rates with IMRT. Recently, the MSKCC group reported an IMRT experience with follow-up (median of 5.5 years) similar to the current PT study (2). The MSKCC radiation dose was 86.4 Gy in 48 daily fractions of 1.8 Gy over 9.5 weeks (biologically equivalent dose [BED] of 164 Gy) compared with 78 to 82 CGE in 39 to 41 daily fractions of 2.0 CGE over 8 weeks (BED of 156-164 Gy) in the current PT cohort. “Very-low-risk” patients were more common in the MSKCC series (49% vs 22%) and the use of ADT in MSKCC low- and intermediate-risk patients was higher: 27% and 48% versus 11% and 9%, respectively, in the current PT cohort. The proportion of “unfavorable” intermediate-risk patients was 34% in the PT cohort but unknown in the MSKCC experience. The MSKCC high-risk patients received 6 or more months of ADT compared with patients receiving concurrent docetaxel during PT and only 6 months of ADT. Five-year FFBB rates were 97%, 85%, and 67% in low-, intermediate-, and high-risk patients, respectively, at MSKCC compared with 99%, 99%, and 76%, respectively, in the current series. Toxicity rates were similar, using the same retrospectively applied CTCAE v4.0 scoring system.

Given excellent disease control and toxicity rates in low-risk prostate cancer patients with a variety of modalities, one appropriate goal is cost reduction via hypofractionation. A comparison of the MSKCC and current studies suggests similar FFBP rates in low-risk patients with the 39 fractions of PT compared to 48 fractions of IMRT. It is unclear whether similar toxicity outcomes with the 10% increase in daily dose (2 CGE rather than 1.8 Gy) and approximate 20% reduction in treatments indicate more potential for hypofractionation with PT than IMRT. Earlier 3DCRT data from the Radiation Therapy Oncology Group showed increased grade 3 GI toxicity with 2 Gy fractions to 78 Gy compared with other regimens using either 1.8-Gy fractions or lower total doses (30), which led to typical 1.8-Gy fractions in both 3DCRT and IMRT. Dosimetry studies in prostate cancer have shown that the primary difference between IMRT and PT is a reduction in low to moderate radiation dose to non-targeted pelvic tissue with PT (31). The clinical impact of this dosimetric difference has been questioned (32). Testosterone suppression, which occurs after x-ray-based EBRT (33, 34), has not been observed after PT (35, 36), suggesting at least one relevant clinical consequence of reducing low-dose exposure. A second consequence of reduced low-dose exposure is fewer anticipated second malignancies (2). A third potential consequence may be an impact on grade 3 toxicities in adjacent normal tissues receiving higher doses, that is, because less rectal volume receives low to moderate doses of radiation with PT, more aggressive radiation dose fractionation schemes may be tolerated. Numerous ongoing studies of hypofractionation with both PT and IMRT will shed light on the relative safety of hypofractionation with each modality, but the minimal toxicity observed with 2 CGE fractions in this study is promising and lays the groundwork for hypofractionation studies in PT.

The favorable 8% difference in FFBB between the MSK and current studies in high-risk PT patients is promising but could be related to differences in prognostic factors, concomitant docetaxel, or simply the small sample size; further study is necessary.

In intermediate-risk disease, contemporary IMRT 5-year FFBB rates range from 70% (36) to 85% to 87% (2, 37), possibly because of variations in dose prescription (38) and/or use of ADT. The FFBB of 99% observed in 82 intermediate-risk patients in the

### Table 2 Patterns of disease progression

<table>
<thead>
<tr>
<th>Protocol</th>
<th>No. of patients</th>
<th>PSA only</th>
<th>PSA and regional lymph nodes</th>
<th>PSA with or without regional lymph nodes plus distant metastases</th>
<th>No. of patients with disease progression/total no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR-01</td>
<td>89</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1/89</td>
</tr>
<tr>
<td>Very low risk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/20</td>
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<tr>
<td>Low risk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>69</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1/69</td>
</tr>
<tr>
<td>PR-02</td>
<td>82</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1/82</td>
</tr>
<tr>
<td>Favorable intermediate risk&lt;sup&gt;c&lt;/sup&gt;</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/54</td>
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<td>36</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>5/36</td>
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<tr>
<td>Very high&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Total</td>
<td>211</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>10/211</td>
</tr>
</tbody>
</table>

<sup>a</sup> Very low risk included low-risk patients with stage T1 C, Gleason score of 6, prostate-specific antigen (PSA) <10, <3 cores involved, and <50% maximum core involvement. Low risk included all other low-risk patients with Gleason score of 6, PSA <10, and CS ≤ T2 A.

<sup>b</sup> Intermediate risk included all patients with Gleason score <8, PSA <20, CS < T3, and at least 1 of the following: Gleason score 7, PSA >10, or CST2B-C. Favorable patients included the subset with Gleason score 3 + 3 or 3 + 4, PSA <15, and CST2 B. Unfavorable patients included those patients with Gleason score 4 + 3 and PSA ≥ 15 or CST2 C.

<sup>c</sup> High risk included any patient with Gleason score ≥8, PSA ≥20, or CS ≥T3. Very-high-risk patients were those with 2 or more of the high-risk factors listed above.
current PT study is very promising and may reflect disease control that is improved compared with that in contemporary IMRT experiences; this finding must be confirmed with both a larger population and longer follow-up.

Several factors may be contributing to the favorable comparative outcomes with PT. One is daily image guidance, which may enhance treatment accuracy. A second is the 2 CGE daily dose compared with 1.8 Gy often used in IMRT. Higher daily doses (39) and shorter overall treatment times have been associated with increased efficacy in prostate cancer (38). A third factor is inclusion of some anterior rectal wall in the PTV and PTV dose homogeneity requirements in the current study, which may differ from some IMRT practices and could impact disease control (38, 40). A fourth possibility is that relative biological effectiveness factors may not be fully accounted for in dose calculations and BED conversions. Regardless of reasons, the outcomes with PT in this study have been extremely favorable compared with those in available contemporary IMRT data.

A recent report based on surrogate data from Medicare claims suggested that PT might be more toxic than IMRT (9). The study lacked actual clinical outcome data (disease control, physician-assessed toxicity, and PRQoLs), and conclusions were drawn entirely from Medicare claims data. The discordance between the actual clinical outcomes reported in this paper and outcomes inferred from Medicare claims highlights the dangers of using surrogate data to infer or predict clinical outcomes.

### Conclusions

Five-year clinical outcomes with image-guided proton therapy included extremely high efficacy, minimal physician-assessed toxicity, and excellent patient-reported outcomes. Further follow-up and a larger patient experience are necessary to confirm these favorable outcomes.

### References

3. Fontenot JD, Lee AK, Newhauser WD. Risk of secondary malignant neoplasms from proton therapy and intensity-modulated x-ray therapy


