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Urinary functional outcomes and toxicity five years after proton therapy for low- and intermediate-risk prostate cancer: Results of two prospective trials

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Abstract

Background. To assess genitourinary (GU) function and toxicity in patients treated with image-guided proton therapy (PT) for early- and intermediate-risk prostate cancer and to analyze the impact of pretreatment urinary obstructive symptoms on urinary function after PT. *Material and methods.* Two prospective trials accrued 171 prostate cancer patients from August 2006 to September 2007. Low-risk patients received 78 cobalt gray equivalent (CGE) in 39 fractions and intermediate-risk patients received 78–82 CGE. Median follow-up was five years. The International Prostate Symptom Score (IPSS) and GU toxicities (per CTCAE v3.0 and v4.0) were documented prospectively. *Results.* Five transient GU events were scored Gr 3 per CTCAE v4.0, for a cumulative late GU toxicity rate of 2.9% at five years. There were no Gr 4 or 5 events. On multivariate analysis (MVA), the only factor predictive of Gr 2 + GU toxicity was pretreatment GU symptom management ($p = 0.0058$). Patients with pretreatment IPSS of 15–25 had a decline (clinical improvement) in median IPSS from 18 before treatment to 10 at their 60-month follow-up. At last follow-up, 18 (54.5%) patients had a ≥ 5-point decline, 14 (42.5%) remained stable, and two patients (3%) had a ≥ 5-point rise (deterioration) in IPSS. Patients with IPSS < 15 had a stable median IPSS of 6 before treatment and at 60 months. *Conclusion.* Urologic toxicity at five years with image-guided PT has been uncommon and transient. Patients with pretreatment IPSS of < 15 had stable urinary function five years after PT, but patients with 15–25 showed substantial improvement (decline) in median IPSS, a finding not explained by initiation or dose adjustment of alpha blockers. This suggests that PT provides a minimally toxic and effective treatment for low and intermediate prostate cancer patients, including those with significant pretreatment GU dysfunction (IPSS 15–25).

Some prostate cancer patients considered for treatment with radiation present with moderate-to-severe bladder outlet obstructive symptoms. Although there is accumulating evidence that proton therapy (PT) is a safe and effective means of delivering high-dose radiation for localized prostate cancer [1–6], there is little information on the genitourinary (GU) outcomes after PT in this group of symptomatic patients.

Two prospective trials were conducted at the University of Florida Proton Therapy Institute (UFPTI; Jacksonville, FL, USA) for patients with low- and intermediate-risk prostate cancer treated between August 2006 and September 2007. Patients on these protocols now have a median five-year follow-up. This study reports the five-year urinary toxicity rates and functional outcomes on these trials, with a focus on the men who had moderate-to-severe pretreatment obstructive GU symptoms.

Patients and methods

The patients

From August 2006 through September 2007, 89 patients enrolled on Institutional Review Board-approved protocol PR-01(UFJ-2005-154) for

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low-risk prostate cancer and 82 on PR-02 (UFJ-2006-63) for intermediate-risk prostate cancer. The median age at enrollment was 66 years (range, 41–86 years).

Both patient-reported quality of life parameters (PROs) and physician-determined function and toxicities were assessed before PT and at six-month intervals using standard tools, including the Expanded Prostate Cancer Index Composite (EPIC), the International Prostate Symptom Score (IPSS), the International Erectile Function Form, and the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) and version 4.0 (CTCAE v4.0). Toxicities were also recorded on a weekly basis throughout treatment.

Data on prior treatment of urinary retentive and obstructive symptoms, prostatitis, and co-morbidities that might impact tolerance of radiation therapy, such as diabetes (DM), hypertension (HTN), blood, cardiovascular (CD) and chronic obstructive pulmonary (COPD) disease, smoking history, and the use of anticoagulants were extracted from patient records and histories and reported previously [3], but reviewed and confirmed for this study. Median prostate volume estimated by transrectal ultrasound at the time of fiducial-marker placement was 36.6 cm^3 (range, 11.3–135.0 cm^3). The prostate volume was less than 60 cm^3 in 144 of 170 patients (85%). CT measured prostate volumes were also calculated. With respect to urologic toxicity, 71 (42%) patients had required management of GU obstructive or prostatitis symptoms before PT with transurethral resection of the prostate (TURP; n = 10, 6%), alpha blockers (n = 58, 34%), hormones and/or avodart (n = 26, 15%), and/or antibiotics (n = 21, 12%). Ninety-seven (57%) patients were on anticoagulant therapy, and 106 (62%) had co-morbidities, including ischemic heart disease, DM, COPD, and HTN.

The overall cumulative and/or time-specific GU toxicity scores included the highest single score for any and all symptoms of obstruction, stricture or stenosis, frequency, cystitis, incontinence, hematuria, hesitancy, and retention. Use of an alpha blocker was tabulated, but not counted as a Gr2 + event, consistent with other analyses [7].

Protocol treatment and target and normal-tissue dosimetric specifications

The gross tumor volume (GTV) for patients on PR01 included the prostate but, on PR02, it included the prostate and proximal 2 cm of seminal vesicles. The planning target volume (PTV) expansion was 8 mm in the superior-inferior axis and 5 mm in the axial plane as previously described [2].

The PR01 trial for low-risk prostate cancer delivered 78 cobalt gray equivalent (CGE) in 39 fractions at 2 CGE per fraction to the prostate via opposed lateral or lateral-oblique fields. The PR02 trial for intermediate-risk prostate cancer was a dose-escalation trial of 78–82 CGE delivered at 2 CGE per fraction to the prostate and proximal seminal vesicles depending on normal-tissue constraints. Based on prospective treatment planning guidelines for dose-volume limitations to the bladder, rectum, and femoral heads, 57 (69%) of 82 patients on PR02 received 82 CGE, 13 (16%) received 80 CGE, and 12 (15%) received 78 CGE.

Statistics

All statistical computations were performed with SAS and JMP software (SAS Institute, Cary, NC, USA). Since toxicity is a nominal endpoint, Fisher's exact test provided estimates of statistical significance when the prognostic factor of interest was also nominal. Logistic regression was used for continuous prognostic factors such as age and dose-volume histogram (DVH) data. All p-values below 0.05 were considered statistically significant.

Results

Follow-up

All patients had a minimum potential follow-up of five or more years. Sixteen patients have died of intercurrent disease. Among the 155 living patients, 145 (94%) had follow-up within the past 12 months. Only four patients were lost to follow-up (defined as no follow-up data available after January 2011). The median actual follow-up after completion of PT was five years (range, 0–5.9 years).

Patient-reported IPSS

The median IPSS values prior to PT, at six-months and at yearly intervals after PT are shown in Table I. For the total group, there was a slight improvement in IPSS after PT from a median pretreatment value of 8 to a median value of 7 at five years. In the 34 patients with a pretreatment IPSS of ≥ 15, median pretreatment and five-year IPSS were 18 and 10, respectively. Among these 34 patients, 33 had sufficient IPSS follow-up data for analysis. As shown in Table II, one patient (3%) had a deterioration in urinary function with an increase in IPSS of >5 at last follow-up and 18 (54.5%) had an improvement with a reduction in IPSS of >5 points, leaving 14 (42.4%) who had stable urinary function with changes of <5 points in IPSS.

For the 137 patients who began PT with an IPSS score <15, median pretreatment and

Table I. Median IPSS at six-month intervals.

Pretreatment IPSS	N	Median Pretreatment IPSS (range)	Median post-treatment IPSS (range)					
			6M	12M	24M	36M	48M	60M
<15	137	6 (0–14)	5 (0–35) 130 pts.	7 (0–25) 117 pts.	6 (0–25) 112 pts.	6 (0–23) 95 pts.	6 (0–20) 92 pts.	6 (0–23) 50 pts.
≥ 15	34	18 (15–25)	11 (1–21) 30 pts.	14.5 (2–27) 30 pts.	13.5 (3–28) 26 pts.	12 (3–30) 20 pts.	12 (3–27) 19 pts.	10 (3–21) 12 pts.
Total	171*	8 (0–25)	7 (0–35) 160 pts.	7 (0–27) 147 pts.	7 (0–28) 138 pts.	6 (0–30) 115 pts.	7 (0–27) 111 pts.	7 (0–23) 62 pts.

IPSS, International Prostate Symptom Score; M, month; N, number of patients.
*171 patients available for analysis of pretreatment data.

five-year IPSS were both 6. However, there was a transient increase in IPSS score of 5 or more points in 62 (45.2%) patients with resolution by last follow-up in all but 29 (21.2%). Among the 89 patients with an initial IPSS <15 but more than 5, making them evaluable for IPSS decrease or improvement of ≥ 5 points, 20 (22.5%) had a decrease of more than 5 points in IPSS score at last follow-up. Thus 29 (21.2%) of the 137 patients with pretreatment IPSS of <15 had >5-point deterioration in their urinary function at last follow-up, while 20 (22.5%) of the 89 patients with baseline IPSS of <15 but ≥ 5 had improvement in urinary function of ≥ 5 points, and the remaining 88 (64.2%) had stable urinary function with less than a 5-point change in IPSS.

A total of 58, 54, and 67 patients received alpha blockers before, during, and after PT. There were 18 and nine patients who received their first prescription for alpha blockers during and after radiotherapy, respectively. Administration of alpha blockers was associated with improved IPSS in three of 29 (10.3%) patients, but the IPSS improvement in the remaining 26 (89.6%) patients appeared to be related to tumor and/or prostate shrinkage after PT.

CTCAE V3.0 GU toxicity and prevalence of GU symptom management

Table III shows both the prevalence and rate of CTCAE v3 Gr2 + GU toxicity at five-year follow-up according to whether or not patients required pretreatment GU symptom management. In each group, the percentages of patients developing Gr2 + toxicity during treatment were similar at 10.0% and 9.9%, respectively. With respect to late toxicity, the 100 men with no pretreatment GU symptom management had a five-year Gr2 + GU toxicity prevalence of 2.4% and cumulative incidence of Gr 2 + events of 15.2%. The 71 men who had pretreatment GU symptom management had a five-year Gr2 + GU toxicity prevalence of 5.5% and cumulative incidence of 33.8%.

Table II. Post-treatment changes in International Prostate Symptom Score (IPSS; up to 60 months of follow-up).

Increase in post-treatment IPSS

Baseline IPSS	N*	No. of patients with ≥ 5-point increase at any point after treatment (%)	No. of patients with ≥ 5-point increase at last follow-up (%)	No. of patients with ≥ 5-point increase resolved at last follow-up (%)
<15	137	62 (45.2%)	29 (21.2%)	33 (24.1%)
15–25	33	4 (12.1%)	1 (3.0%)	3 (9.1%)
Total	170	66 (38.8%)	30 (17.6%)	36 (21.2%)

Decrease in post-treatment IPSS

Baseline IPSS	N	No. of patients with ≥ 5-point decrease at any point after treatment (%)	No. of patients with ≥ 5-point decrease at last follow-up (%)	No. of patients with ≥ 5-point decrease in IPSS no longer present at last follow-up (%)
<15	89**	35 (39.3%)	20 (22.5%)	15 (16.9%)
15–25	33	29 (87.9%)	18 (54.5%)	11 (33.3%)
Total	122	64 (52.5%)	38 (31.1%)	26 (21.3%)

*One patient died during treatment, leaving 170 available for follow-up analysis. **48 patients of the 137 with IPSS <15 had baseline. IPSS <5 and thus could not be assessed for a decrease in IPSS of ≥ 5.

Table III. Prevalence and cumulative incidence of grade (Gr) 2 + genitourinary (GU) toxicity per Common Terminology Criteria for Adverse Events (CTCAE) v3.0*.

GU intervention required prior to PT	No. of patients developing Gr2 + toxicity during PT/no. of patients	No. of patients developing Gr2 + toxicity at a given point in time (months) after PT/no. of patients treated						Cumulative incidence of Gr 2 + GU toxicity at 5 years
		6M	12M	24M	36M	48M	60M	
All patients (N = 171)	17 (9.9%)	5 (2.9%)	6 (3.6%)	13 (8.1%)	17 (10.7%)	5 (3.3%)	5 (3.6%)	39 (22.9%)
None (N = 100)	10 (10.0%)	2 (2.0%)	0 (0.0%)	3 (3.1%)	6 (6.3%)	2 (2.2%)	2 (2.4%)	15 (15.2%)
Any GU Symptom management** (N = 71)	7 (9.9%)	3 (4.2%)	6 (8.5%)	10 (15.4%)	11 (17.2%)	3 (5.0%)	3 (5.5%)	24 (33.8%)
Alpha blockers (N = 58)	4 (6.9%)	1 (1.7%)	5 (8.6%)	6 (11.3%)	10 (18.9%)	3 (6.1%)	3 (6.8%)	20 (34.5%)
Antibiotics (N = 21)	3 (14.3%)	2 (9.5%)	2 (9.5%)	3 (15.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (23.8%)
TURP*** (N = 10)	1 (10.0%)	1 (10.0%)	1 (10.0%)	2 (22.2%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	3 (30.0%)
Hormones (N = 26)	1 (3.8%)	0 (0.0%)	1 (3.8%)	4 (18.2%)	3 (13.6%)	1 (4.8%)	1 (5.3%)	7 (26.9%)

PT, proton therapy; TURP, transurethral resection of the prostate.
*Each patient coded once only at each time interval for highest grade symptom present. **Includes alpha blockers, antibiotics, TURP, or hormones. ***Transurethral resection of prostate tissue or other ablative procedure such as suprapubic prostate resection, green light laser, prostiva, etc.

Univariate (UVA) and multivariate analyses (MVA) were performed to identify potential associations between Gr 2 + GU toxicity and various clinical and DVH factors, including prostate volume [by ultrasound measurement and by three-dimensional computed tomography (3D-CT) simulation calculation], pretreatment symptom management, age, anticoagulation, dose, protocol, pretreatment IPSS, and various bladder dosimetric parameters. On MVA, the only factor predictive of Gr 2 + GU toxicity was pretreatment GU symptom management ($p = 0.0058$). There was no correlation between dose-volume parameters for bladder or bladder wall and Gr 2 + GU toxicity.

Table IV shows the Gr2 + toxicity rate (CTCAE v3.0) at the five-year follow-up according to pretreatment IPSS. There was no difference between the rate of acute Gr2 + toxicity between men with pretreatment IPSS of < 15 versus those with IPSS of 15–25 (9.5% vs. 11.8%, $p = 0.7491$). However, there was a higher rate of late Gr2 + toxicity in men with pretreatment IPSS of ≥ 15 compared with those with IPSS < 15 (39.4% vs. 19%, $p = 0.014$).

Among CTCAE v3.0 Gr 2 + events were two acute Gr3 GU toxicities (1.2%) and eight late Gr 3 events for a cumulative rate of Gr 3 events of 4.7% at five years. All Gr3 events were transient. One patient with an acute Gr 3 event was among the eight patients with late Gr 3 events. Six of the eight patients with late Gr3 toxicity had GU symptom intervention prior to PT and three of the patients had prior late Gr2 toxicity. Two of the 8 Gr 3 events occurred among patients with pretreatment IPSS ≥ 15 and 6 among patients with pretreatment IPSS < 15. The cumulative incidences of Gr3 + GU events per CTCAE v3.0 and v4.0 were 4.5% and 2.2%, respectively, for patients treated to 78 CGE to the prostate only on the PR 01 protocol and 4.9% and 3.7% for patients treated on PR 02 with 78–82 CGE to the prostate and proximal seminal vesicles. There were no Gr4 or Gr5 GU toxicities.

CTCAE v4.0 versus v3.0 Gr3 + GU toxicity

In the CTCAE v3.0, the toxicity-severity scoring is primarily dependent on the intervention selected by the treating physician, whereas the focus in CTCAE v4.0 is the impact of the toxicity on the patient's

Table IV. Cumulative incidence of Gr2 + acute and late events (CTCAE v.3.0).

Acute GU 2 +			
International Prostate Symptom Score	None	Events	p-Value
0–14	124 (90.5%)	13 (9.5%)	0.7491
15–25	30 (88.2%)	4 (11.8%)	
Late GU 2 +			
International Prostate Symptom Score	None	Events	p-Value
0–14	111 (81.0%)	26 (19.0%)	0.014
15–25	20 (60.6%)	13 (39.4%)	

ability to perform activities of daily living (ADL). In v4.0, the designation of Gr 3 requires an impact on the patient's ability to perform self-care ADL. With v4.0, both acute v3.0 Gr3+ GU toxicities and three of the eight late toxicities were downgraded to Gr 2+, for a cumulative late Gr3 toxicity incidence of 2.9%, including four among the 137 patients with IPSS <15 and one among the 33 patients with IPSS ≥ 15. Three downgraded toxicities were dysuria affecting instrumental, but not self-care ADL and two temporary foley catheter placements that did not affect self-care ADL. One patient with a 240-cm^3 prostate with indwelling suprapubic catheter had a preradiation TURP with reduction to 110 cm^3. He required a second TURP shortly after PT and was then able to discontinue alpha blockers. A second patient with an 80-cm^3 prostate developed post-treatment hematuria and obstruction caused by necrotic tissue and dystrophic calcification that resolved following transurethral resection of the bladder abnormality. A third patient developed probable prostatitis and hematuria at 31 months after treatment with urinary obstruction requiring catherization and antibiotics; the symptoms of prostatitis resolved with the antibiotics and the hematuria resolved following cauterization of the prostatic urethra. The fourth patient developed unilateral hydronephrosis with 'fluffy tissue' obstructing the ureteral orifice; he had transurethral resection and HBO with resolution of symptoms. The fifth patient developed hematuria that resolved with a transurethral microwave procedure.

Discussion

The primary objectives of this study were to examine the late urinary function in patients treated in two prospective trials of PT for low- and intermediate-risk prostate cancer, using both patient-reported and provider-assessed data with a focus on those patients who presented with pretreatment urinary dysfunction. A secondary goal was to identify factors associated with the development of Gr2 + GU toxicity and the requirement for continued urologic symptom management after prostate cancer treatment.

Prostate cancer patients with significant obstructive symptoms at the time of diagnosis require special consideration as they are at risk for increased symptoms with radiation treatment that may require catheterization. Historically, concern for increased radiation toxicity has sometimes led to consideration of preradiation TURP or even definitive treatment with radical prostatectomy; however, patients who have a TURP prior to radiation require a several-month delay for healing before beginning radiation and may also have an increased risk of GU toxicity [8,9]. The surgical alternative of radical prostatectomy carries a higher risk of urinary incontinence than radiation [10,11].

There are few data in the literature regarding patients with significant pretreatment obstructive symptoms or post-treatment urinary function in patients treated with intensity-modulated radiation therapy (IMRT) or PT. Malik et al. [7] from the University of Chicago reported a retrospective review of 368 patients treated with external-beam radiotherapy with a focus on GU outcomes in 80 men with a pretreatment IPSS ≥ 15. The median follow-up was 44 months. The median radiation dose was 75.6 Gy and IMRT was used in 311 men (85%). Toxicity was scored according to Radiation Therapy Oncology Group (RTOG) criteria and CTCAE v3.0. The use of alpha blockers and antispasmodics were reported, but not counted as Gr2 events. Patients with pretreatment IPSS ≥ 15 had a median baseline IPSS of 18, which improved to a median IPSS of 13 at last follow-up. Improvement in urinary function, as evidenced by a 5-point decline or greater between baseline and last follow-up, was seen in 59% of men. A rise in IPSS, or decline in urinary function, between baseline and last follow-up was observed in only 16 men (21%) with a median rise of 3.5 points.

In the study reported herein, the 34 proton patients with pretreatment IPSS ≥ 15 had urinary functional outcomes similar to the Chicago experience with IMRT. The median baseline IPSS of this group was also 18 and improved to a median IPSS of 10 at 60 months of follow-up. Eighteen patients (54.5%) had ≥ 5-point decline (improvement) in IPSS, 14 (42.4%) remained stable with a <5-point change in IPSS, and only one patient (3.0%) had an increase (decline) in IPSS >5 points. For patients with moderate to severe pretreatment obstructive symptoms, (IPSS of 15–25), it appears that improvement in long-term urinary function is common and functional deterioration is unusual after either IMRT or protons.

There was little change in IPSS score for Chicago patients with pretreatment IPSS <15; median pretreatment IPSS was 6 compared to a median of 5 at last follow-up. Similarly, in the 137 patients with IPSS <15 reported in our prospective proton trials, the median IPSS was 6 at baseline and 6 at 5-year follow-up, although transient increases of ≥ 5 points were seen in 45.2% of patients. Overall, median IPSS in patients with good pretreatment urinary function remained stable both in the IMRT series as well as in the proton series.

In comparison with the IMRT experience at Chicago, this proton experience reported herein is a prospectively tracked outcome study and radiation doses were substantially higher and delivered at a higher

dose per fraction over a shorter time interval. In prospective RTOG trials of dose escalation with 3D conventional radiation therapy (CRT) [12], similar increases in dose and dose per fraction have resulted in increases in urologic and rectal toxicity. The observation of low rates of both patient- and physician-reported toxicity with IMRT and proton therapy may indicate that urologic toxicity with contemporary IMRT or protons is minimal and not related to radiation dose and dose per fraction than other factors. Alternatively, the similar rates of urologic toxicity with IMRT and PT, despite the higher dose and dose per fraction used in the proton regimens, might also suggest a greater potential for dose escalation and intensification via hypofractionation with PT than feasible with x-ray-based therapy.

Contemporary series reporting physician scored urologic toxicity may use either CTCAE v3.0 or v4.0. Using CTCAE v3.0, Malik et al. [7] reported four-year rates for freedom-from-late-Gr2 + and 3 + toxicity of 69% and 93%, respectively, in patients with pre-RT IPSS ≥ 15. The overall cumulative incidences of CTCAE v3.0 late Gr2 + and 3 + events in our series at 60 months were 22.9% and 4.7%. Only 3.6% of patients had Gr2 + toxicity remaining at 60 months of follow-up. MVA of the current series showed that pretreatment GU intervention was the only statistically significant factor associated with GU 2 + toxicity. The five-year cumulative incidences of Gr 2 + GU events were 15.2% in patients with no pretreatment GU symptom management and 33.8% in those requiring GU symptom management before PT; only 2.4% and 5.5% of patients in these respective groups still had Gr 2 + symptoms at their 60-month follow-up.

Late Gr3 GU toxicity was infrequent and transient. The overall late Gr3 + GU cumulative toxicity rates in our patients were 4.6% and 2.9% per CTCAE v3.0 and 4.0, respectively. The CTCAE v3.0 late Vr3 + toxicity rate for patients with pretreatment IPSS ≥ 15 was 3% and 2.9% for patients with pretreatment IPSS < 15. These numbers compare favorably with the University of Chicago CTCAE v3.0 rates of 6.25% (5 of 80) and 2.8% (8 of 288) in the same IPSS groups [7].

The difference between v3.0 and 4.0 was mainly due to the new v4.0 distinction between impact on instrumental ADL (Gr2) and self-care ADL (Gr3). This change illustrates the possibility of score migration between different classification versions and underscores the importance of consistent toxicity scoring criteria. The CTCAE v4.0 late Gr3 + overall toxicity rate was 2.9%, including 3.0% (1 of 33) for patients with pretreatment IPSS ≥ 15 versus 2.9% (4 of 137) for patients with pretreatment IPSS < 15. These rates also compare favorably with other published reports using CTCAE version 4.0 toxicity scoring**.** Spratt et al. [13] recently reported on a series of 1002 patients treated at Memorial Sloan-Kettering Cancer Center (New York, NY, USA) to a dose of 86.4 Gy at 1.8 Gy per fraction with IMRT with a median follow-up of 5.5 years. The late Gr3 GU toxicity per CTCAE v4.0 was 2.2%.

Nihei et al. [14] reported the results of a multi-institutional phase II study of 151 patients with organ-confined prostate cancer treated with PT to 74 GyE (Gray equivalent) in 37 fractions (using CTCAE version 2.0). The median follow-up was 43.4 months. In total, 8% of the patients experienced late Grade 2 or higher toxicity and 2% experienced Grade 3 or higher toxicity with a regimen that was less aggressive than the one used in our protocols. Cohen et al. [5] reported the toxicity results from a multi-institutional trial (ACR 03-12) of 82 GyE conformal PT for localized prostate cancer. Late Grade 3 + GU toxicity scored by the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity schema was 8.3%. With the caveat of different GU toxicity scoring systems, the Gr 3 + toxicity rate in the Cohen experience may be somewhat higher than the 2.9% rate in the current series. A possible explanation for the difference is the use of normal-tissue constraints in determining which patients were candidates for dose escalation from 78 to 82 CGE on the PR 02 protocol.

Major strengths of the studies reported herein include: 1) the prospective design and relatively complete long-term follow-up, which assure a low probability of missing events; 2) the use of both patient-reported outcomes and physician-assessed outcomes to describe treatment effects; and 3) the use of two different toxicity scoring systems, making the data comparable to other series and underscoring the importance of consistent criteria for toxicity assessment across trials. These results will serve as a baseline for future proton studies at our institution. A weakness of this study is the limited number of patients with pretreatment IPSS of 15–25, and the absence of patients with pretreatment IPSS scores over 25.

Conclusion

PT provides a minimally toxic treatment for low and intermediate prostate cancer patients, including those with significant pretreatment GU dysfunction (IPSS 15–25). Moderate-to-severe pretreatment urinary obstructive symptoms often improve after radiation treatment, and patients with baseline IPSS scores of 15–25 appear to be at only a small risk of significant late obstructive problems. Pretreatment GU intervention is associated with an increase in Gr 2 + toxicity. This information may be useful in

the design of future studies and in the selection of treatment for this group of patients. Proton therapy may safely permit further dose intensification through approaches such as hypofractionation.

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