Original Article

Hypofractionated Stereotactic Body Radiotherapy in Low-Risk Prostate Adenocarcinoma

Preliminary Results of a Multi-Institutional Phase 1 Feasibility Trial

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BACKGROUND: Recent reports using extreme hypofractionated regimens in the treatment of low-risk prostate adenocarcinoma have been encouraging. Here, the authors report on their own multi-institutional experience with extreme hypofractionated stereotactic radiotherapy for early stage disease. **METHODS:** In total, at 4 centers, 45 patients with National Comprehensive Cancer Network-defined, low-risk prostate adenocarcinoma were enrolled in a phase 1, multi-institutional trial of hypofractionated radiosurgery with a proprietary radiosurgical device (CyberKnife). Thirty-four patients received 7.5 grays (Gy) delivered in 5 fractions, 9 patients received 7.25 Gy delivered in 5 fractions, and 2 patients received other regimens. The variables evaluated were biochemical progression-free survival (bPFS), prostate-specific antigen (PSA) bounce, and toxicities. Health-related quality of life was evaluated using the Sexual Health Inventory for Men (SHIM), American Urological Association (AUA), and Expanded Prostate Cancer Index Composite (EPIC) questionnaires. **RESULTS:** The median follow-up for surviving patients was 44.5 months (range, 0-62 months). The bPFS rate at 3 years was 97.7%. The median PSA declined from 4.9 ng/mL at diagnosis to 0.2 ng/mL at last follow-up, and the median percentage PSA decline at 12 months was 80%. Nine patients experienced at least 1 PSA bounce $\geq$0.4 ng/mL, and 4 patients experienced 2 PSA bounces. The median time to first PSA bounce was 11.6 months (range, 7.2-18.2 months), and the mean percentage PSA bounce was 1.07 ng/mL. There was 1 episode of late grade 3 urinary obstruction, and there were 2 episodes of late grade 3 proctitis. There was a significant late decline in SHIM and EPIC sexual scores and a small, late decline in the EPIC Bowel domain score. **CONCLUSIONS:** In a select population, extreme hypofractionation with stereotactic radiosurgery was safe and effective for the treatment of low-risk prostate adenocarcinoma. ***Cancer*** **2012;118:3681-90.** *© 2011 American Cancer Society.*

KEYWORDS: prostate cancer, low risk, stereotactic, hypofractionation, prostate-specific antigen bounce.

INTRODUCTION

External -beam radiation therapy (EBRT) is one of the main-stay, definitive treatments for low-risk prostate adenocarcinoma. Traditional EBRT regimens have involved protracted-course, multiweek, daily radiation treatments, more recently involving doses to the prostate of 78 to 80 grays (Gy) in approximately 40 to 44 fractions.[1,2] A recent pooled analysis of retrospective series that evaluated standard fractionation versus hypofractionation schemes suggests that the α/β ratio for prostate cancer, regardless of risk category, is on the order of 1.4 (95% confidence interval [CI], 0.9-2.2).[3] Although contrary data exist,[4] if true, then this lower α/β ratio argues that tumor control may be improved by the delivery of larger doses per fraction (hypofractionation). In addition to the possibility of decreased recurrence risk, hypofractionation, because of the larger doses delivered per individual treatment, allows for the deposition of dose biologically equivalent to the standard, multiweek regimens over a shorter period of time; for elderly patients with prostate cancer who have

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difficulties traveling, this has obvious quality-of-life (QOL) benefits. Finally, truncating treatment time may carry with it cost benefits compared with now widely adopted, longer course, intensity-modulated radiation therapy (IMRT) regimens.[5]

The studied hypofractionation regimens can be divided into 2 groups: 1) moderate hypofractionation (eg, 60 Gy in 20 fractions) and 2) extreme hypofractionation (eg, 36.25 Gy in 5 fractions). Several randomized controlled trials (RCTs) that compared standard fractionation with moderate hypofractionation have been published, and all of those trials demonstrated a significant improvement in biochemical recurrence-free survival (bRFS) with equivalent toxicities.[6-8]

Extreme hypofractionation, because of the delivery of large doses per fraction, requires stereotactic techniques, including unique beam arrangements, stable immobilization, motion control, and daily image guidance. Initial treatment schemes were based largely on the experience of several institutions with high-dose rate brachytherapy that delivered 38 to 43 Gy in 4 to 6 fractions.[9,10] To our knowledge, no published RCTs exist to date comparing extreme external-beam hypofractionation treatments for low-risk prostate adenocarcinoma versus either standard or moderate hypofractionation regimens. However, several phase 1/2 feasibility studies have been reported. At a median follow-up between 2 and 3 years, those studies have demonstrated that stereotactic, extreme hypofractionation regimens have both acceptable toxicity profiles and excellent rates of biochemical control.[11-14] In the current report, we present the results from a multi-institutional, prospective, phase 1 study using extreme hypofractionation in the treatment of low-risk prostate adenocarcinoma.

MATERIALS AND METHODS

In August 2006, we began an institutional review board-approved phase 1 clinical trial of radiosurgery using the CyberKnife radiosurgical device (Accuray Inc., Sunnyvale, Calif) for the treatment of low-risk prostate adenocarcinoma. This trial was opened at 4 geographically diverse centers. Our objectives were to assess acute and long-term toxicity, health-related QOL (HR-QOL), and biochemical outcomes in this patient cohort.

Patient Eligibility

Eligible patients included those with biopsy proven, newly diagnosed, and previously untreated adenocarcinoma of the prostate. Patient had National Comprehensive Cancer Network (NCCN)-defined, low-risk prostate adenocarcinoma (Gleason score, 2-6; clinical stage T1c-T2a; prostate-specific antigen (PSA) level $\leq$10 ng/mL). Prostate size by ultrasound measurement was $\leq$80 cc. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 with American Urological Association (AUA) scores $\leq$15. No lutenizing hormone-releasing hormone antagonistic therapy was permitted within 6 months of treatment initiation. Patients could not have received prior pelvic radiation or a diagnosis of any other cancer within the 5 years preceding enrollment. All patients were required to provide informed consent at the time of enrollment.

Planning

The CyberKnife radiosurgical device (Accuray Inc.), which consists of a 6-megavolt linear accelerator mounted on a robotic arm, was used to deliver all treatments. By using transrectal ultrasound guidance, 4 gold seeds were placed transperineally with attention to requirements for sufficient separation and noncoplanar placement to allow for full CyberKnife tracking. This was accomplished under local anesthesia. Care was taken to keep all fiducials within the substance of the prostate gland to reduce the risk of migration. All patients had a treatment-planning computed tomography (CT) study obtained in the supine position; an alpha cradle (Smithens Medical, North Canton, Ohio) or a similar device was used as needed. If required to observe the urethra, an additional CT study was obtained with an indwelling catheter and/or urethrogram. A mixture of intravenous contrast and sterile normal saline or water was instilled such that the urethra and bladder were observed. CT cuts of 1.0 to 1.5 mm centered approximately at the prostate were taken. When feasible, magnetic resonance imaging (MRI) studies of the prostate were obtained to determine the anatomic borders of the prostate and, if possible, the urethra. MRI studies were then fused to the treatment-planning CT. No endorectal coil was used, and the minimum field strength was 1.5 T. Patients had bowel preparation to eliminate rectal contents before treatment-planning scans.

Inverse treatment planning was used for all patients. The treatment course consisted of 5 fractions of either 7.5 Gy or 7.25 Gy to a total dose of either 37.5 Gy or 36.25 Gy, respectively. Dose regimens were based on previously published studies of high-dose-rate brachytherapy and stereotactic radiosurgery for the treatment of low-risk prostate cancer.[15,16] The ultimate choice between the 2 regimens was left up to the participating institutions. The dose was prescribed to the planning target volume (PTV),

which included the gross target volume (prostate only) with a 3-mm posterior expansion and a 5-mm expansion in all other dimensions. The rectum, urethra, bladder, and penile bulb were contoured as avoidance structures. The volume receiving 37.5 Gy (V37.5) had to include at least 95% of the PTV with a prescribed dose between 70% and 90% of the tissue depth at which the maximum dose was delivered (Dmax). Normal tissue dose constraints were as follows: a rectal V36Gy $<$ 1 cc, a urethral V49Gy $<$ 10%, a bladder V37.5Gy $<$ 5 cc, and a penile bulb V29.5Gy $\leq$ 50%. Treatment had to be completed within 10 days with no less than 12 hours between any 2 fractions. At least 3 fiducials were identified and tracked in real time during all treatments. Two orthogonal kilovoltage x-ray imagers provided real-time stereoscopic image guidance and automatic correction for intratreatment movements of the prostate.

Study Endpoints and Statistics

The primary endpoints of the feasibility study were bPFS, toxicity, and HR-QOL. The Phoenix definition of PSA nadir plus 2 ng/mL was used to determine biochemical failure.[17] The time to biochemical progression was defined as the time from pathologic diagnosis to either biochemical failure or death; the Kaplan-Meier method was used to estimate bPFS. Rectal, urinary, and sexual toxicities/HR-QOL were assessed at baseline; during treatment; and at 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, 36 months, 42 months, 48 months, and 54 months after treatment. HR-QOL endpoints were evaluated using the AUA prostate symptom score,[18] the Expanded Prostate Cancer Index Composite (EPIC) questionnaire,[19] and the Sexual Health Inventory for Men (SHIM) survey[20]; the EPIC questionnaire has 4 domains designed to ascertain sexual, bowel, urinary, and hormone QOL. We investigated scores on the sexual, bowel, and urinary subdomains.

Pair-wise comparisons between baseline values and subsequent measurements of HR-QOL were made using the Wilcoxon ranked sign test for AUA, SHIM, and EPIC scores. Toxicity was evaluated by the treating physician using version 4.0 of the Common Toxicity Criteria for Adverse Events (CTCAEv4.0). Acute toxicity was defined as toxicities that occurred $\leq$3 months after the completion of treatment.

PSA bounce was defined as a PSA increase of $\geq$0.4 ng/mL between any 2 consecutive measurements followed by a subsequent decline to or below the previous nadir.[21] Comparison of ages for those who experienced PSA bounce versus those who did not was done using the *t* test. All statistical analysis was done using the Statistica software package (version 6.0; Statistica, Tulsa, Okla). All reported *P* values are two-sided.

Table 1. Baseline Patient Characteristics

Characteristic	No. of Patients (%)
No. of Patients	45 (100)
Age: Median [range], y	70 [54-83]
Race	
White	40 (89)
African-American	4 (9)
Asian	1 (2)
PSA at diagnosis: Median [range], ng/mL	4.9 [1.36-9.4]
Tumor classification	
T1c	33 (73)
T2a	12 (27)
Gleason score 6 (3+3)	45 (100)
Total no. of cores samples: Median [range]	12.5 [3-20]
No. of involved cores: Median [range]	1 [1-12]
Treatment, Gy	
7.25×5 Fractions	34 (76)
7.5×5 Fractions	10 (22)
Other	1 (3)
Time elapses: Median [range], d	7 [4-20]

Abbreviations: Gy, grays; PSA, prostate-specific antigen.

RESULTS

Patients

In total, 45 patients were enrolled between August 2006 and August 2008. The median age was 70 years (range, 54-83 years). All of our patients had NCCN-defined, low-risk prostate adenocarcinoma with T1 or T2a tumors and Gleason 6 disease. The median pretreatment PSA level was 4.9 ng/mL (range, 1.4-9.4 ng/mL). Nearly all patients (97%) received 5 fractions of either 7.25 Gy or 7.5 Gy over a median of 7 elapsed days (range, 4-20 days). For completeness, the 1 enrolled patient who received a nonprotocol dose regimen was included in the analysis. None received androgen deprivation. Table 1 provides pertinent patient information.

Prostate-Specific Antigen Response

The median follow-up for surviving patients was 44.5 months (range, 0-62 months). The bPFS rate at 3 years was 97.7%; 1 patient died of unrelated causes at 13.6 months (Fig. 1). There were no biochemical failures. The median PSA declined from an initial value of 4.9 ng/mL to a final value at follow-up for surviving patients of 0.2 ng/mL (range, 0-1.5 ng/mL). At 12 months, the

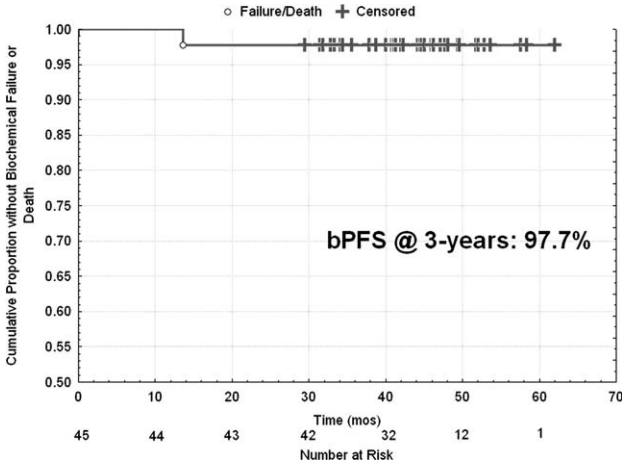

Figure 1. Biochemical progression-free survival (bPFS) is illustrated. This curve was calculated using the Kaplan-Meier product-limit method. Patients were censored at last follow-up. Biochemical failure was defined using the nadir prostate-specific antigen level plus 2 ng/mL. One patient died of unrelated causes at 13.6 months; there were no biochemical failures.

median PSA was 0.91 ng/mL, representing a median decline of approximately 80% over the course of the first year. The trend in median PSA over time is illustrated in Figure 2. Although the Phoenix definition of nadir plus 2 ng/mL was used to report bPFS, had we used the older American Society of Radiation Oncology (ASTRO) definition, 3 patients would have failed at 9.0 months, 31.2 months, and 39.0 months. The patient who "failed" at 9 months had his PSA value subsequently decline to a new nadir. For the remaining 2 patients, their third consecutive PSA rise was at their date of last follow-up.

Nine patients experienced at least 1 PSA bounce $\geq$0.4 ng/mL, including the aforementioned ASTRO-defined failure; 4 of those patients experienced 2 PSA bounces, and 1 experienced 3 PSA bounces. The median time to first PSA bounce was 11.6 months (range, 7.2-18.2 months). The mean PSA bounce was 1.07 ng/mL (range, 0.4-2.8 ng/mL). The mean age of those who experienced a bounce was significantly younger than those who did not (65.1 years vs 71.1 years; $P = .04$). All patients had their PSA return to prebounce nadir levels or below by 6 months.

Dosimetrics

For the 31 patients who had dosimetric data available, the mean $\pm$ standard deviation (SD) rectal V80 was 14.53% $\pm$ 7.37%, the rectal D5cc was 27.6 $\pm$ 5.06 Gy, and the rectal D10cc was 21.6 $\pm$ 7.16 Gy. The mean $\pm$ SD urethral V100 was 93% $\pm$ 7.94%, the bladder V80 was

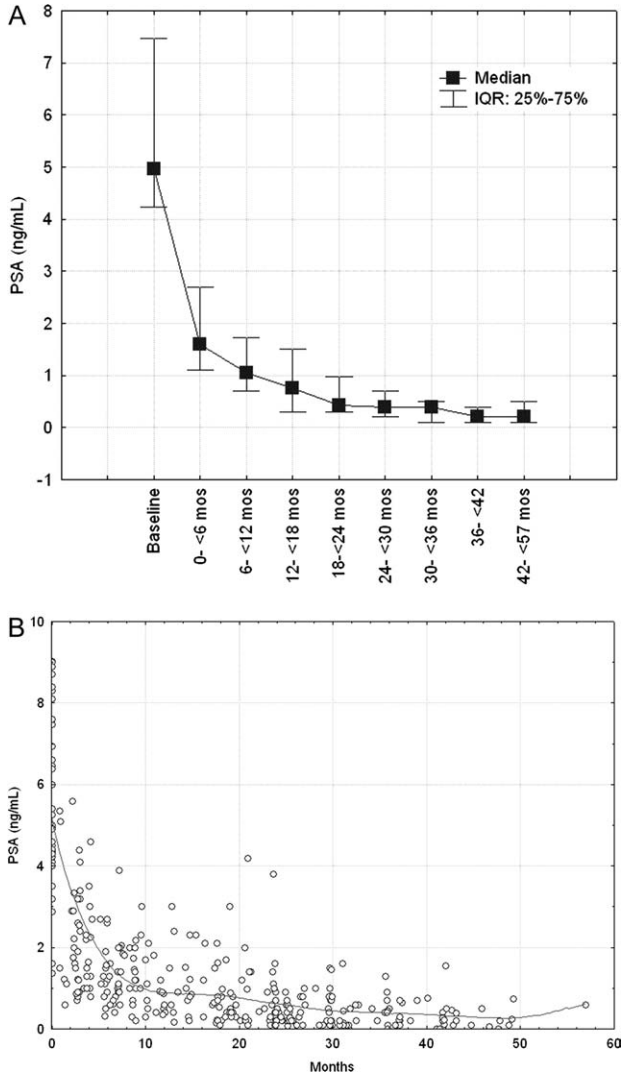

Figure 2. (*Top*) Median prostate-specific antigen (PSA) values are illustrated. Each PSA value that fell within the stated time range (x-axis) was used to tabulate the median PSA for that given range, and the median is graphed for each time range. IQR indicates interquartile range (25% to 75%). (*Bottom*) This is a scatter plot of PSA values. All PSA measurements for the cohort are plotted. A negative, exponentially weighted function fit the data best; the graph of that function is superimposed on the scatter plot.

12% $\pm$ 7.30%, and the bladder D10cc was 32 $\pm$ 5.70 Gy. Penile bulb constraints were used in planning but were not explicitly collected by our trial data managers.

Toxicity

Forty-two patients (93%) had collected data for acute and late, CTCAEv4.0-defined toxicities. Of these, 25 patients (59%) experienced acute grade 1 urinary toxicities, and 8 (19%) experienced acute grade 2 urinary toxicities. Seven patients (17%) experienced late (>3 months) grade 1

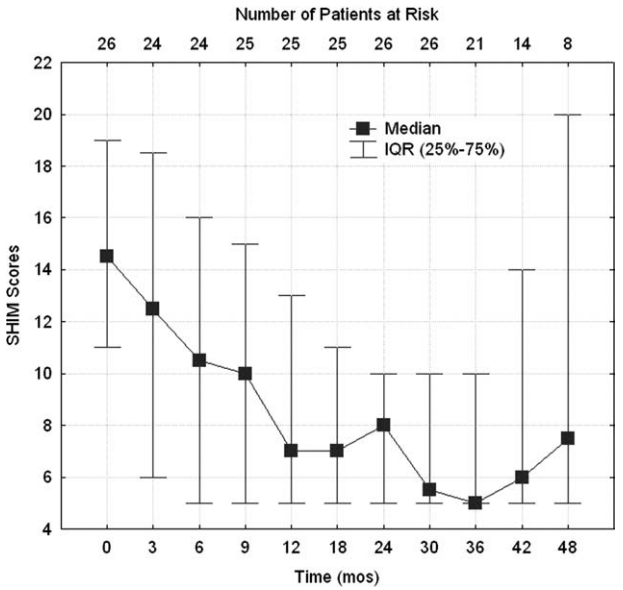

Figure 3. Median scores on the Sexual Health Inventory for Men (SHIM) are illustrated. This is a graph of median SHIM scores for given time points. SHIM scores at 36 months and at last follow-up were significantly lower than at baseline, indicating overall worse sexual function. IQR indicates interquartile range (25% to 75%).

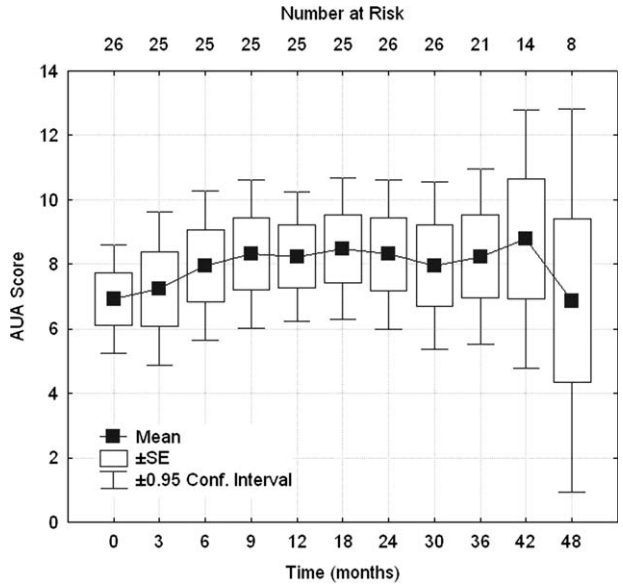

Figure 4. Median scores on the American Urological Association (AUA) questionnaire are illustrated. This is a graph of median AUA scores for given time points. There was no significant difference between baseline values and values at 3 months, 36 months, and last follow-up. IQR indicates interquartile range (25% to 75%); SE, standard error; Conf, confidence.

Table 2. Expanded Prostate Cancer Index Composite Domain Scores[a]

	Median EPIC Score (*P*)			
EPIC Domain	Baseline, n = 26	3 Months, n = 26	36 Months, n = 23	Last Follow-Up
Sexual	43	42 (.5)	17 (.03)[b]	21 (.01)[b]
Urinary	92	88.5 (.08)	86 (.10)	91 (.39)
Bowel	95.5	95 (.08)	95 (.05)[b]	93 (.04)[b]

Abbreviations: EPIC, Expanded Prostate Cancer Index Composite.
[a] Median EPIC scores are display for each time point. The number of evaluable patients at each time point is also listed. All *P* values are for comparisons with baseline.
[b] Statistically significant.

urinary toxicities, and 7 (17%) experienced late grade 2 urinary toxicities. The vast majority of the grade 1 and 2 acute and late toxicities were frequency and dysuria. One patient experienced late grade 3 urinary obstruction requiring transurethral prostatic resection (TURP); pathology from the TURP revealed only radiation effect without evidence of residual disease.

Rectal toxicities were less frequent. Thirteen patients (31%) experienced acute grade 1 rectal toxicities, and 3 patients (7%) experienced acute grade 2 rectal toxicities. The vast majority of these were mild proctitis and diarrhea. Three patients (7%) experienced late rectal grade 1 toxicities, and the same number experienced late grade 2 rectal toxicities. Two patients (5%) experienced grade 3 late proctitis that required and resolved with argon plasma laser ablation.

The scores on the 3 instruments (SHIM, AUA, and EPIC) that we used to analyze HR-QOL were available for 26 patients (58%). The median follow-up for evaluable patients was 45.7 months (range, 32.8-59.0 months). The SHIM score was used to evaluate sexual side effects. The median SHIM score at baseline for the total evaluable population was 14.5. There was no significant decrement in SHIM score at 3 months (median SHIM score, 12.5; $P = .26$). However, at 36 months of follow-up, the median SHIM score of 5.0 was significantly lower than the baseline value ($P = .006$). The SHIM score at last follow-up also was significantly lower than the baseline score (median SHIM score, 7.5; $P = .008$). Figure 3 illustrates the trend in median SHIM score over time for the total population.

We reasoned that, for the patients who had baseline SHIM scores that evidenced full potency or only mild-to-moderate erectile dysfunction (SHIM scores >11), decrements in sexual function may have a more profound impact on their overall HR-QOL. Thus, we performed a subset analysis on the 17 patients who had SHIM scores >11. The median baseline SHIM score in this group was

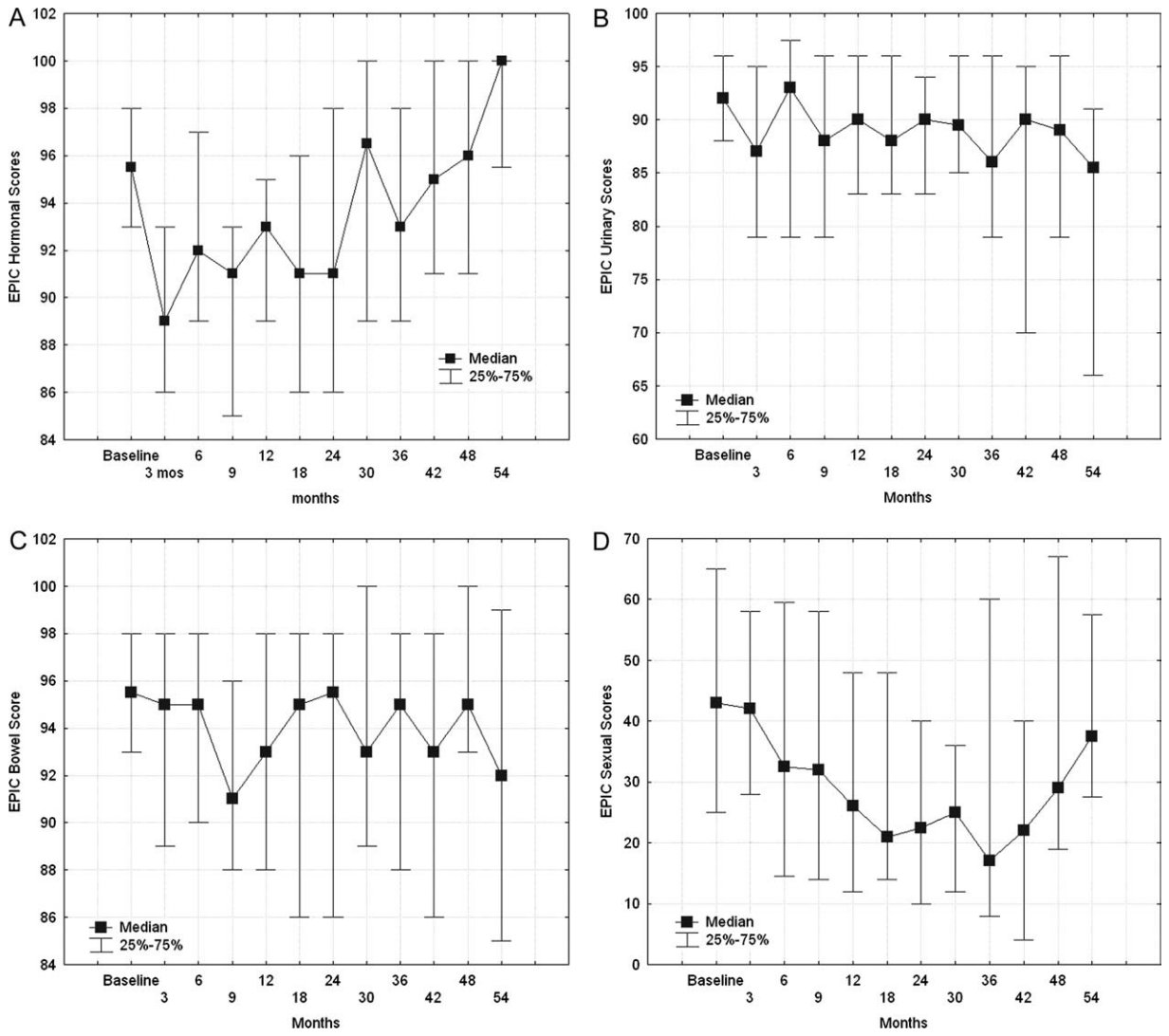

Figure 5. These are graphs of median Expanded Prostate Cancer Index Composite (EPIC) scores for each time point for (*Top Left*) the hormone domain, (*Top Right*) the urinary domain, (*Bottom Left*) the bowel domain, and (*Bottom Right*) the sexual domain. The interquartile range (25%-75%) is indicate for each domain.

17 (range, 12-25). There was no statistically significant decrement in the median SHIM score at 3 months. However, there were statistically significant declines in the SHIM score at 36 months (median SHIM score, 9; $P = .004$) and at the last follow-up (median SHIM score, 10; $P = .001$). At the time of last follow-up, 8 of 17 patients were categorized as having moderate or severe erectile dysfunction.

The AUA score was one of the metrics used to evaluate urinary bother, and increased AUA scores suggested worsening urinary symptoms. The median AUA scores at baseline, 3 months, and 36 months were 7.5, 6.0, and 7.0, respectively. The median AUA score at last follow-up was 6.5. The AUA scores at the follow-up points were not statistically significantly different from the baseline values (Fig. 4).

Finally, we evaluated scores on 3 subdomains of the EPIC instrument, which is a global QOL metric (Table 2, Fig. 5). There were no statistically significant decrements, either acutely or long term, in the EPIC Urinary score. Compared with baseline, the EPIC Bowel scores were statistically significantly lower at 36 months and at the last follow-up, but these differences were small. The EPIC Sexual score revealed a statistically significant late decline, with a decrease in the median score from 42 at baseline to 21 at last follow-up. The baseline sexual scores in the subpopulation on whom we had EPIC data were surprisingly low.

DISCUSSION

Our cohort of 45 patients represents only the second prospective, multi-institutional, phase 1 study of extreme hypofractionated stereotactic body radiotherapy in men with low-risk prostate adenocarcinoma. Whereas the prior study enrolled low-risk and intermediate-risk patients, we limited enrollment to low-risk patients and had longer median follow-up (44.5 months vs 30 months).

With a 44.5-month median follow-up, none of our patients experienced biochemical failure; only 1 patient died of a comorbid and unrelated condition. The median percentage PSA decline at 1-year for those with sufficient follow-up was 80.2%, suggesting a relatively rapid rate of decline. At last follow-up, the median PSA in our cohort was 0.2 ng/mL.

King et al recently updated the Stanford CyberKnife experience treating 65 men with low-risk prostate adenocarcinoma using 36.25 Gy in 5 fractions using either every-day or every-other-day dosing regimens.[12] With a median follow-up of 2.7 years, those authors reported 2 biopsy-proven PSA failures with a 4-year PSA relapse-free survival rate of 94%. Their median PSA at last follow-up for those without failure was 0.5 ng/mL.

Boike et al published their dose-escalation outcomes (45 Gy, 47.5 Gy, and 50 Gy in 5 fractions) and toxicity data in 45 patients with low-risk and intermediate-risk prostate adenocarcinoma.[11] Their median follow-up was 30 months, 18 months, and 12 months in the 45-Gy, 47.5-Gy, and 50-Gy groups, respectively. At the time of publication, all of their patients had declining or stable PSA, and none had experienced biochemical failure (as defined by the Phoenix Consortium).

Finally, Madsen et al investigated the use of extreme hypofractionation in 40 men with low-risk disease.[13] At their median follow-up of 41 months, the 48-month rate of biochemical freedom from relapse was 90% using the Phoenix definition and 70% using the older ASTRO definition of 3 consecutive PSA increases. Their discordant numbers were because of late PSA bounces observed in several patients.

The question of PSA bounce with high-dose regimens is of significant interest because benign rises in PSA may lead to unnecessary interventions and significant patient anxiety. To date, this phenomenon has been examined almost exclusively in patients who received either brachytherapy alone or brachytherapy in combination with EBRT.[24] Recently, Caloglu and Ciezki investigated various PSA bounce cutoff values in 820 patients who received I-125 brachytherapy. By defining PSA bounce as a rise $\geq$0.4 ng/mL with a subsequent return to nadir, 19.6% of patients experienced a bounce at a median of 16.3 months. However, only a PSA bounce $\geq$0.2 ng/mL predicted worse bPFS, although it does not appear that the authors evaluated this in multivariate modeling.

The utility of PSA bounce as a prognostic factor was complicated by a recent publication by Hinnen et al, who investigated the relation between overall survival and PSA bounces $\geq$0.2 ng/mL in 975 patients who received I-125 implants between 1992 and 2006.[25] Somewhat surprisingly, those authors observed that, after adjusting for confounders, the patients who experienced a bounce actually had improved overall survival (hazard ratio, 0.31; 95% confidence interval 0.20-0.48).

Only the Stanford group, looking at the same low-risk cohort that they recently updated, investigated PSA bounce after extreme hypofractionation. Similar to the articles described above, those authors used a PSA cutoff of $\geq$0.2 ng/mL with subsequent decline to previous nadir. By using this definition, 12 patients (29%) experienced a PSA bounce. The median time to PSA bounce was 18 months after radiotherapy, and the median bounce was 0.39 ng/mL.

We chose a conservative definition of PSA bounce ($\geq$0.4 ng/mL) to avoid any differences caused by variation in the test itself. According to this definition, 9 patients (19.5%) in our series experienced a PSA bounce at a median of 11.6 months post-treatment, and all of those patients returned to PSA levels below their prior nadir by 6 months. None went on to experience biochemical failure. In keeping with previous reports, our patients who experienced a bounce were significantly younger than those who did not. Because of our more conservative bounce definition, not unsurprisingly, compared with King et al, the magnitude of our median bounce was larger. The time to first bounce also was shorter. Despite these differences, both studies evidenced excellent rates of biochemical control in those patients who experienced a bounce.

Overall, our reported PSA kinetics, including the rate of biochemical control and PSA bounce, are in keeping with the aforementioned published, single-institutional and multi-institutional reports of extreme stereotactic hypofractionation in low-risk patients. We continue to believe that the Phoenix definition of failure is the best metric for assaying biochemical recurrence in a population treated with extreme hypofractionation, in which PSA bounce may lead to a significant false-positive rate using the old ASTRO definition. Indeed, this was a

major impetus behind the decision to revamp the definition of biochemical failure. However, despite our excellent rates of bPFS, given the indolent nature of low-risk prostate cancer, even longer follow-up is needed ascertain the true rate of control.

Furthermore, in low-risk prostate adenocarcinoma, where disease-specific mortality is low, minimizing treatment-related morbidity becomes critical. Our evaluation of toxicity and HR-QOL was extensive, and we used multiple metrics to determine the impact of extreme hypofractionation on these outcomes.

One patient in our cohort did experience grade 3 urinary obstruction and was treated successfully with TURP. Two patients experienced late grade 3 proctitis that also resolved with intervention. Because only 56% of our patients filled out SHIM, AUA, and EPIC questionnaires, the possibility of bias obviously exists. This limits the generalizability of our results. However, the compliance issue was related to a lack of institutional follow-up by specific participating centers and not to individual patient refusal. Within the subsites where patients filled out the questionnaires, compliance was near 100%. This may mitigate some of the potential bias involved. Furthermore, patient characteristics and treatments did not differ significantly between institutions. Thus, we would expect toxicity outcomes at the institutions that had their enrollees fill out SHIM and EPIC questionnaires to mirror those that did not.

Given this qualification, we did observe a statistically significant, late decrement in sexual function as measured by both the SHIM and EPIC Sexual questionnaires. The decrement in SHIM scores was more significant for those who originally were potent or who had only mild-to-moderate erectile dysfunction at baseline. Our reported magnitude of decline in SHIM scores for potent patients or for those with only mild-to-moderate dysfunction is similar to those reported in patients with low baseline sexual morbidity who received standard fractionation IMRT.[26]

In addition to the decrease in sexual function, our patients also evidenced a late decline in EPIC Bowel scores, although the magnitude of the decline was quite small, calling into question its clinical relevance. It is noteworthy that there were no statistically significant decrements in AUA scores or EPIC Urinary scores, thus indicating relatively low rates of treatment-related urinary morbidity.

Overall, our toxicity levels mirror the currently published data on extreme hypofractionation in the low-risk cohort of patients. King et al, in their latest update, reported grade 3 genitourinary (GU) toxicities in only 6% of patients who received consecutive treatment and in only 2% of patients who received every-other-day fractionation. Late grade 1 and 2 GU toxicity was present in 23% and 5% of patients, respectively. Late grade 1 and grade 2 rectal toxicities occurred in 14% and 2% of patients, respectively. There were no grade 3 rectal toxicities in their cohort. They did not report sexual side effects in their patients.

In the cohort of low-risk patients reported by Madsen et al, acute grade 1 and 2 rectal and GU toxicities were was present in 39% and 48.5% of their patients, respectively. There was 1 acute grade 3 GU toxic event. Late grade 1 and 2 rectal and GU toxicities were observed in 45% and 37% of patients, respectively. They reported no late grade 3 toxicities.

Boike et al evaluated both toxicity and HR-QOL using the AUA and EPIC questionnaires. One patient in their 47.5-Gy group experienced grade 3 dysuria; and 2 patients in the 50-Gy group experienced grade $\geq$3 toxicity, including 1 grade 3 GU event and 1 grade 4 rectal ulcer requiring hospitalization. The EPIC bowel-related QOL scores decreased initially at 6 months but were back to baseline at 18 months; the 45-Gy dose arm experienced significantly worse gastrointestinal toxicity than the other 2 dose arms. AUA scores returned to baseline in the 45-Gy and 50-Gy groups but were persistently elevated in the 47.5-Gy arm. Boike et al used total doses much higher than ours, which may explain in part the difference in HR-QOL outcomes between our 2 studies.

With the outcomes and toxicities described, it is clear that extreme hypofractionation using stereotactic techniques is a promising technology in the treatment of low-risk prostate adenocarcinoma. Including our own study, to our knowledge, only 2 multi-institutional phase 1 studies of this treatment in this population exist. With the longest reported follow-up of these 2 studies, we have demonstrated excellent rates of biochemical control and toxicity outcomes commensurate with previously reported hypofractionated stereotactic series. However, our patient population represents a very-low-risk cohort, with a median PSA of 4.9 ng/mL and a low median number of positive cores. Because of this, caution must be used in attempts to extrapolate our findings to the broader cohort of low-risk patients.

Ideally, the success of these phase 1 trials would be confirmed in a randomized controlled setting. However,

in men with low-risk prostate adenocarcinoma, the time required to adequately evaluate treatment noninferiority is daunting. The pressure to decrease treatment cost while maintaining value in a health care system in which there are limited resources is significant. With most radiation oncologists using IMRT in the treatment of low-risk prostate cancer, costs for this relatively indolent disease have increased. A recent American Society of Clinical Oncology abstract using Markov modeling suggests that the total life-time cost of using the CyberKnife is significantly lower than that of IMRT ($25,904 vs $38,915).[5] That model also projects higher quality-adjusted life-years for CyberKnife compared with IMRT.

Ultimately, the relative costs-benefits of stereotactic radiosurgery, coupled with the continued demonstration of excellent outcomes and toxicities that appear to be similar or very close to normal fractionation in updates of already existing phase 1 and 2 trials, soon may change the standard of care for EBRT in men with low-risk prostate adenocarcinoma.

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