Advances in Radiation Oncology (2018) **3**, 163–169

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Outcomes and toxicity from a prospective study of moderately hypofractionated radiation therapy for prostate cancer

Wei Gang Wang MD [a], Di Yan DSc [a], Hong Ye PhD [a], Gary Gustafson MD [b], Michael Ghilezan MD [c], Alvaro Martinez MD [c], Daniel Krauss MD [a,*]

[a] *Department of Radiation Oncology, Beaumont Health, Royal Oak, Michigan*
[b] *Department of Radiation Oncology, Beaumont Health, Sterling Heights, Michigan*
[c] *MHP Radiation Oncology Institute, 21st Century Oncology, Troy, Michigan*

Received 10 August 2017; received in revised form 1 December 2017; accepted 21 December 2017

Abstract

Purpose: The purpose of this study is to report the long-term outcomes and toxicity results of a prospective trial of moderately hypofractionated, image guided radiation therapy (RT) for localized prostate cancer.

Methods and materials: Patients were enrolled between December 2006 and February 2012. Patients in group 1 were stage T1-T2b, had a Gleason score (GS) of 2 to 6 *or* 7 (3 + 4) with only 1 lobe involved, and had prostate-specific antigen levels ≤10 ng/mL. Group 2 patients were stage ≥T2c, had a GS ≥7 (4 + 3), a GS 7 (3 + 4) involving both lobes, or a PSA >10 ng/mL and ≤30 ng/mL. All patients underwent transrectal ultrasound guided fiducial (Visicoil) placement prior to computed tomography/magnetic resonance imaging simulation. Daily cone beam computed tomography with online correction was used. The prescribed dose was 64 Gy in 20 fractions. The primary endpoint was acute and late toxicity. The secondary endpoint was biochemical control.

Results: A total of 40 patients with a median age of 70 years were recruited for the study. Twenty-two patients (55%) were in group 1, and 18 patients (45%) were in group 2. Thirteen patients (32.5%) were classified as low, 26 patients (65%) as intermediate, and 1 patient (2.5%) as high risk per the National Comprehensive Cancer Network criteria. The median follow-up time was 59 months. Five-year biochemical control was 100% and 94.4% for groups 1 and 2, respectively. Thirteen patients (32.5%) developed acute gastrointestinal (GI) toxicities grade ≥2 and 3 (7.5%) developed acute grade 3 GI toxicity. A total of 17 patients (42.5%) developed grade ≥2 acute genitourinary toxicities and 1 (2.5%) developed acute grade 3 dysuria. Two patients (5%) developed late GI toxicities grade ≥2. There was 1 case (2.5%) of grade 4 fistula requiring sigmoid resection. Seven patients

Conflicts of interest: None.

Sources of support: None.

Meeting information: Presented at the 2016 Annual Meeting of the American Society for Radiation Oncology, September 25-28, 2016, in Boston, Massachusetts.

* Corresponding author. Department of Radiation Oncology, Beaumont Health, Oakland University William Beaumont School of Medicine, 3601 West 13 Mile Road, Royal Oak, MI 48073.

E-mail address: Daniel.Krauss@beaumont.edu (D. Krauss).

https://doi.org/10.1016/j.adro.2017.12.006

(17.5%) developed grade ≥2 late genitourinary toxicities; 2 patients (5%) late grade 3 urinary frequency/urgency.

Conclusions: Moderately hypofractionated RT is effective with favorable toxicity and biochemical control, providing further evidence that increasing daily fractional dose can be safely and effectively delivered with contemporary RT techniques.

Introduction

In recent years, technological advances have given us many tools, such as image guidance and conformal radiation therapy, to improve the treatment of prostate cancer. Intensity modulated radiation therapy (IMRT) has allowed for safe dose escalation with proven benefits with respect to biochemical control (BCC).[1-4] This has led to increased interest in moderate and extreme hypofractionated schedules due to the inherent biology of prostate cancer and potential convenience and cost improvements associated with decreased treatment duration. Unlike many other malignancies, prostate cancer has been shown to have a low alpha-beta ratio, possibly as low as 1.5 Gy,[5-7] which suggests a therapeutic advantage to treat prostate cancer with high-dose fractions.

Multiple large randomized trials have recently been published and report comparable disease control with moderate fractionation. However, toxicity results were mixed, with some trials showing worse toxicities. Those protocols did not mandate optimal modern radiation therapy techniques and allowed variable planning target volume (PTV) margins up to 10 mm.[8-10] Our protocol examines the utilization of modern 3-dimensional, image guided radiation therapy (IGRT) with fiducials to minimize PTV margins to 3 mm. We report here the toxicity and BCC outcomes from the prospective, nonrandomized, prostate hypofractionation protocol treating patients to a total dose of 64 Gy in 3.2 Gy daily fractions. We hypothesized that fractional doses of radiation could be increased safely through the use of image guidance and tight PTV margins.

Methods and materials

This trial was approved by our institution's institutional review board. Patients were eligible if they had biopsy-proven prostate adenocarcinoma. Patients were recruited prospectively into 2 groups on the basis of risk factors. Patients in group 1 had stage T1-T2b, a Gleason score (GS) of 2 to 6 *or* 7 (3 + 4) with only 1 lobe involved, and prostate-specific antigen (PSA) levels ≤10 ng/mL. Group 2 patients had stage T2c, GS 7 (4 + 3), GS 7 (3 + 4) involving both lobes, or PSA levels >10 ng/mL and ≤30 ng/mL. Patients needed to be able to undergo a magnetic resonance imaging (MRI) scan during the initial simulation process to generate a computed tomography (CT)-MRI fusion for optimal target delineation. Short term (≤6 months) androgen deprivation therapy was allowed at the physician's discretion.

Patients were excluded if they had severe diabetes mellitus with signs/symptoms of neuropathy or angiopathy; inflammatory bowel disease such as ulcerative colitis or Crohn disease;, prior transurethral resection of the prostate within 2 years of enrollment; or previous anorectal surgery, with the exclusion of external hemorrhoid. Additionally, patients with a maximal lateral separation of >37 cm or those with a visible "apron" were not eligible, nor were patients with a history of hip replacement surgery.

All patients underwent an initial complete history review and physical examination to determine eligibility. A CT scan of the abdomen/pelvis was required for patients in group 2, and bone scan was optional. All patients underwent transrectal ultrasound guided fiducials (Visicoil; IBA, Reston, VA) prior to the CT-MRI simulation. The MRI was not used for staging but was performed for the purpose of target delineation, specifically to aid in the delineation of the apex of the prostate. No treatment stage was changed on the basis of MRI findings. The gross tumor volume (GTV) was defined as the external contour of the prostate gland for group 1 patients, with the addition of the entire seminal vesicles for group 2 patients. The clinical target volume (CTV) was defined as the prostate with a 0 mm margin for group 1 patients and a 2 to 4 mm margin for group 2 patients. The PTV was defined as the CTV with a 3 mm uniform margin. The organs at risk that were contoured included the rectum, bladder, small bowel, penile bulb, prostatic neurovascular bundles, and femoral head.

Patients were treated with IMRT or volumetric modulated arc therapy using high energy (≥6 MV) photon beams. Dose was prescribed such that ≥95% of the PTV received the prescription dose and the maximum dose did not exceed 105% of the prescription. The prescribed dose was 64 Gy in 20 fractions at 3.2 Gy per fraction. This was calculated using a conservative alpha-beta ratio assumption of 4 Gy to an equivalent dose in 2 Gy (EQD2) of 76.8 Gy. For the organs at risk, we used the following constraints during planning: Bladder constraints were $V_{59.4Gy}$ <30% and D_{max} of 64.1 Gy; rectal doses were constrained to a $V_{56.5Gy}$ <40%, $V_{59.4Gy}$ <30%, and $V_{62.6\,Gy}$ <5%; small bowel D_{max} was not

to exceed 48.6 Gy; and femoral head D_{max} was constrained to 48.6 Gy.

Patients were aligned daily, initially with laser and skin tattoo localization. Fiducial alignment was done and verified through the use of daily cone beam CT (CBCT). Bladder filling and rectal position were monitored on the CBCT; administration of daily treatment if either were unsatisfactory was at the discretion of the treating physician. The CBCTs were assessed daily by the physicians.

Acute and late toxicities were recorded in accordance with the National Cancer Institute Common Terminology Criteria, version 3.0.[11] Acute toxicities were scored as any symptoms experienced during the first 90 days from the start of radiation therapy (RT), and late toxicities were recorded as those beyond 90 days. Patients were followed every 3 months with an examination and PSA test for the first 2 years, every 6 months from years 2 to 5, and annually after 5 years. The visits were scheduled to alternate between a radiation oncologist and urologist when possible. All toxicity data were collected during routine radiation oncology follow-up.

The primary study endpoint was acute and late toxicity, not to exceed a 7% increase in acute (<3 months post-RT) genitourinary (GU) toxicity relative to the historical, standard fractionation approach. The secondary endpoint was BCC to demonstrate that control rates compared favorably with historical measures in the context of image guidance with a reduced PTV margin. Biochemical failure was defined using the phoenix definition of a PSA level increase of ≥2 ng/mL from the nadir.[12] SPSS software version 22 (IBM, Armonk, NY) was used for statistical analysis. BCC and overall survival were calculated using the Kaplan-Meier estimate. Toxicities are reported as the maximal toxicity (excluding sexual toxicity) that the patient experienced during the follow up period.

Results

A total of 43 patients were enrolled between December 2006 and February 2012. Three patients withdrew consent, leaving 40 patients for inclusion in this analysis. The median follow-up time was 59 months (range, 19-99). Patient characteristics are shown in Table 1. The median patient age was 70 years (range, 54-81 years). The majority of patients had clinical stage T1c (75%). The Gleason score was equally distributed between 6 (32.5%), 7 = 3 + 4 (35%), and 7 = 4 + 3 (32.5%). The median pretreatment PSA was 5.65, and the majority of patients fell into the National Comprehensive Cancer Network intermediate-risk group category (65%). Two patients received androgen deprivation therapy prior to initiation of RT.

A single biochemical failure occurred in group 2 and none in group 1, yielding 5-year cumulative incidence estimates for BCC of 97.4%, 100%, and 94.4% for the entire cohort, group 1, and group 2, respectively. The single biochemical failure event occurred 23 months after completion of treatment (Fig 1). The patient has been started on intermittent androgen deprivation therapy, and PSA remains undetectable without signs of systemic disease at this time. Two patients without prior evidence of biochemical failure died during the follow-up period from causes that were unrelated to prostate cancer.

Acute gastrointestinal (GI) toxicities grade ≥2 were observed in 13 patients (32.5%). Three patients (7.5%)

Table 1 Baseline patient characteristics

Characteristics	Value (%)
Patients (n)	40
Age (y)	
Median	70
Range	54-81
Clinical T stage (n)	
T1c	30 (75)
T2a	8 (20)
T2b	2 (5)
Gleason score (n)	
6	13 (32.5)
1%-25% cores positive	11 (84.6)
26%-50% cores positive	2 (15.4)
>50% cores positive	0
7 (3 + 4)	14 (35)
1%-25% cores positive	7 (50)
26%-50% cores positive	6 (42.9)
>50% cores positive	1 (7.1)
7 (4 + 3)	13 (32.5)
1%-25% cores positive	3 (23.1)
26%-50% cores positive	6 (46.2)
>50% cores positive	4 (30.7)
Pretreatment prostate-specific antigen level (ng/mL)	
Median (range)	5.65 (1.54-24.4)
0-4.99	15 (37.5)
5-9.99	20 (50)
10-19.99	4 (10)
20-30	1 (2.5)
National Comprehensive Cancer Network risk group	
Low	13 (32.5)
Intermediate	26 (65)
High	1 (2.5)
Risk group (n)	
I	22 (55)
II	18 (45)
Androgen depravation therapy	
Yes	2 (5)
No	38 (95)
Baseline International Prostate Symptom Score	
0-10	26 (65)
11-20	12 (30)
>20	2 (5)
Baseline impotence	14 (35)

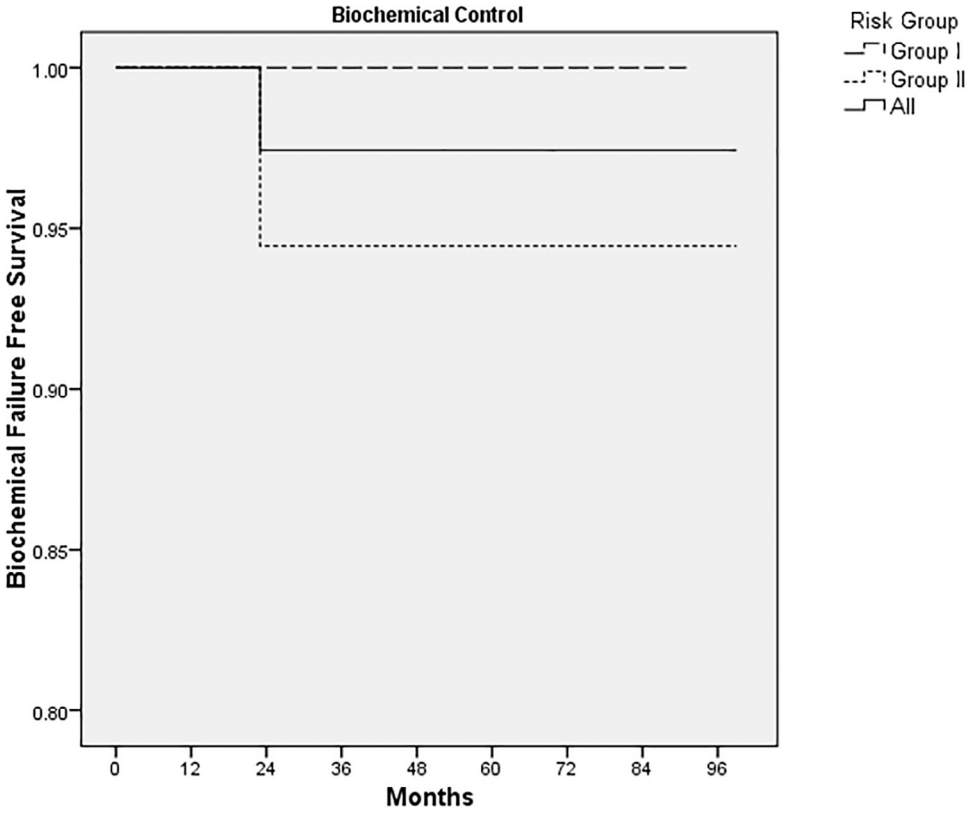

Figure 1 Biochemical failure-free survival in months of patients in the entire cohort (solid), group 1 (wide dash), and group 2 (fine dash).

developed grade 3 GI toxicity (2 with grade 3 diarrhea and 1 with grade 3 rectal bleeding); no acute grade 4 toxicity occurred. Acute grade ≥2 urinary toxicity occurred in 17 patients (42.5%), 1 patient (2.5%) developed grade 3 dysuria, and no acute grade 4 toxicities were recorded. The primary objective of the study was met because the historic control had an acute grade 2 + GU toxicity rate of 41.5% and acute grade 3 + GU toxicity of 3.3%.

Chronic GI toxicities grade ≥2 were observed in 2 patients (5%). No patients developed grade 3 toxicities. One case (2.5%) of grade 4 fistula was recorded. The patient with grade 4 toxicity originally completed treatment in June 2007 and started to develop recurrent urinary tract infections in 2009. Cystoscopy revealed possible colorectal fistula in the left trigone of the bladder. The patient underwent sigmoid resection and repair and has been asymptomatic since that time. The patient had a history of diverticulosis. On review of the radiation plan, the maximum hot spot was 106% of the prescription dose (68 Gy) at the base of the bladder and did exceed the protocol recommended maximum of 64.1 Gy. Subsequently, strict adherence to the protocol-specific organ constraints were mandated.

For chronic GU toxicities, 7 patients (17.5%) developed chronic grade ≥2 toxicities, 2 (5%) developed grade 3 urinary frequency/urgency, and no grade 4 toxicities were recorded. All acute and chronic toxicities are listed in Tables 2 and 3. With regard to sexual function, 14 patients (35%) were impotent at baseline. During the follow-up for those who had sexual function prior to the trial, 9 patients (34.6%) retained function. Ten patients (38.5%),

Table 2 Gastrointestinal toxicity

Acute gastrointestinal toxicity n (%)					Late gastrointestinal toxicity n (%)				
Toxicity grade	0	1	2	3	0	1	2	3	4
Diarrhea	12 (29)	19 (46)	8 (20)	2 (5)	34 (85)	5 (13)	1 (2)	0 (0)	0 (0)
Rectal bleeding	36 (88)	4 (10)	0 (0)	1 (2)	36 (90)	4 (10)	0 (0)	0 (0)	0 (0)
Proctitis	37 (90)	3 (7)	1 (3)	0 (0)	39 (98)	1 (2)	0 (0)	0 (0)	0 (0)
Rectal pain/tenesmus	24 (59)	16 (39)	1 (2)	0 (0)	39 (98)	1 (2)	0 (0)	0 (0)	0 (0)
Fistula/fissure	41 (100)	0 (0)	0 (0)	0 (0)	39 (98)	0 (0)	0 (0)	0 (0)	1 (2)

Table 3 Genitourinary toxicity

Acute genitourinary toxicity n (%)					Late genitourinary toxicity n (%)			
Toxicity grade	0	1	2	3	0	1	2	3
Dysuria	19 (46)	19 (46)	2 (5)	1 (3)	34 (85)	6 (15)	0 (0)	0 (0)
Frequency/urgency	6 (15)	25 (61)	10 (24)	0 (0)	17 (43)	17 (43)	4 (10)	2 (5)
Retention	27 (66)	14 (34)	0 (0)	0 (0)	26 (65)	14 (35)	0 (0)	0 (0)
Incontinence	40 (98)	0 (0)	1 (2)	0 (0)	36 (90)	4 (10)	0 (0)	0 (0)
Hematuria	39 (95)	1 (2)	1 (2)	0 (0)	35 (88)	4 (10)	1 (2)	0 (0)
Urethral stricture	41 (100)	0 (0)	0 (0)	0 (0)	39 (98)	1 (2)	0 (0)	0 (0)

6 patients (23.1%), and 1 patient (3.8%) had grade 1, grade 2, and grade 3 sexual toxicity, respectively.

Discussion

Our results show that moderate hypofractionation with 64 Gy in 20 fractions is feasible and safe in patients with low- to intermediate-risk prostate cancer. Severe late toxicities are rare, with 1 case of grade 4 rectal fistula and 2 cases of grade 3 urinary frequency/urgency. With a median follow-up of 59 months, 5-year BCC was favorable at 97.1%. Our primary and secondary objectives were also met based on the favorable results of our study. The single grade 4 toxicity in our cohort demonstrates the importance of adhering to the prespecified protocol constrains.

A number of randomized trials have compared traditional fractionation with moderate hypofractionation and have reported early results (3-5 years). Most of the trials do not show a difference in biochemical control, and toxicities are comparable. These trials all have variable inclusion criteria with slight differences in the hypofractionation schedule. Recently, Radiation Therapy Oncology Group (RTOG) 0415 was published, having included 1101 men with low-risk prostate cancer who were randomized to 73.8 Gy in 41 fractions or 70 Gy in 28 fractions. The 5-year disease-free survival was 85.3% in the conventional arm versus 86.3% in the hypofractionated arm. The study concluded that the hypofractionated regimen was noninferior to the standard treatment arm.[8]

The Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial in the United Kingdom enrolled 2100 all-risk-group patients with prostate cancer, randomizing them to 74 Gy in 37 fractions, 60 Gy in 20 fractions, or 57 Gy in 19 fractions. With a median follow-up time of 62.4 months, the 5-year biochemical or clinical control rate was 88.3% in the 74 Gy arm, 90.6% in the 60 Gy arm, and 85.9% in the 57 Gy arm. The 60 Gy dose was noninferior to the 74 Gy, but noninferiority could not be established for the 57 Gy dose compared with 74 Gy[9]

In addition, the HYpofractionated irradiation for PROstate cancer (HYPRO) trial was also recently published. The study randomized 820 intermediate- to high-risk patients to 78 Gy in 39 fractions versus 64.6 Gy in 19 fractions. The median follow-up time was 60 months. The 5-year relapse-free survival was 80.5% in the hypofractionation arm and 77.1% in the conventional fractionation arm, which was not significantly different.[10] Our favorable BCC at 5 years could be a reflection of favorable patient selection because a majority of the patients had GS 6 and GS 7 = 3 + 4 (77.5%). In addition, our BED is higher than that of the RTOG 0415 regimen if an alpha-beta ratio of 2 Gy is selected but is equivalent if an alpha-beta of 4 Gy is used. This raises the possibility that the true alpha/beta ratio of prostate cancer could be on the lower end of the literature's estimate. Finally, given the small sample size of the cohort, the higher BCC may simply be due to statistical variance.

Several studies have suggested mixed toxicity results associated with hypofractionated treatment. A randomized control trial from Italy with 168 patients and 3-dimensional chemo-RT randomized to 80 Gy in 40 fractions versus 62 Gy in 20 fractions found worse acute and late GI toxicity in the conventional arm.[13] Another trial from MD Anderson randomized 203 patients treated with IMRT to 75.6 Gy in 42 fractions versus 72 Gy in 30 fractions and found a nonsignificant trend toward inferior GI toxicity in the hypofractionated arm.[14] In addition, Fox Chase conducted a trial enrolling 303 patients and IMRT planning, randomizing patients between 76 Gy in 36 fractions versus 70.2 Gy in 26 fractions. They found no significant difference in late toxicity, although subgroup analysis showed that those with compromised urinary function prior to treatment had worse urinary function after hypofractionated RT.[15]

Our toxicity profile compares favorably with data from other institutions and large clinical trials. The CHHiP trial published their toxicity and quality of life (QOL) data. Using patient-reported QOL questionnaires as well as physician-graded toxicity, no differences were found among the 3 arms.[16,17] RTOG 0415 reported an increase in late grade 2 and 3 GI/GU toxicity in the hypofractionated arm.[8] Their hypofractionated arm had chronic grade ≥2 GI and GU toxicities at 22.4% and 29.7%, respectively, and chronic grade ≥3 GI and GU toxicities at 4.1% and 3.5%, respectively.

The HYPRO trial showed higher acute GI grade 2 or higher toxicity in the hypofractionation group (42% vs. 31%), and noninferiority could not be established.[18] For their late toxicities, noninferiority could not be established with

Table 4 Summary of moderate hypofractionation results comapred with large randomized trials

	Current study[a]	RTOG 0415 trial[a]	CHHiP trial[b]	HYPRO trial[b]
Fractionation	64 Gy in 20 fractions	70 Gy in 28 fractions	60 Gy in 20 fractions	64.6 Gy in 19 fractions
NCCN risk group				
Low	32.5%	100%	16%	0%
Intermediate	65%	0%	73%	26%
High	2.5%	0%	11%	74%
ADT use	5% (6 mo)	Not allowed	100% (3-6 mo)	67%
5-y control	97.1% (BCC)	85.3% (DFS)	90.6% (BCC)	80.5% (RFS)
Late grade ≥2 GU	17.5%	29.7%	13.2%	41.3%
Late grade ≥3 GU	5%	3.5%	4.2%	19%
Late grade ≥2 GI	5%	22.4%	6.9%	21.9%
Late grade ≥3 GI	2.5%	4.1%	0.7%	2.6%

ADT, androgen deprivation therapy; BCC, biochemical control; CHHiP, Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy for Prostate Cancer; DFS, disease-free survival; GI, gastrointestinal; GU, genitourinary; HYPRO, HYpofractionated irradiation for PROstate cancer; NCCN, National Comprehensive Cancer Network; RFS, recurrence-free survival; RTOG, Radiation Therapy Oncology Group.

[a] The present study and the RTOG 0415 trial utilized the National Cancer Institute, Common Terminology Criteria, Version 3.

[b] The CHHiP and HYPRO trials used the RTOG toxicity scales.

grade 2 or worse GI/GU toxicity.[19] Our prospective series compared favorably with the results from these trials with regard to chronic grade ≥2 GI and GU toxicities at 5% and 17.5%, respectively, and chronic grade ≥3 GI and GU toxicities at 2.5% and 5%, respectively. A cross-trial comparison is not possible with the CHHiP and HYPRO trials because different toxicity scales were used. RTOG 0415 used the same toxicity scale, and our results compare favorably with the lower rates of late grade ≥2 GI (5% vs. 22.4%) and GU (17.5% vs. 29.7%). This may in part be due to the use of tight margins in our study.

The favorable toxicity in our series could in part be explained by our delivery techniques, many of which are now commonly implemented in standard RT practice. Specifically, 3-dimensional imaging with CBCT was used in conjunction with fiducial marker placement to minimize PTV expansion needs; consequently, a 3 mm margin on the CTV was used. This is significantly less than those used in previously reported studies, and the favorable BCC rates observed in our series suggest that the techniques implemented in the current series are sufficient.

RTOG 0415 allowed a 4 to 10 mm applied margin for the PTV and did not require the use of IMRT. Studies have shown that use of IMRT compared with 3D conformal radiation therapy resulted in decreased late GI toxicities.[20] Our protocol required fiducial placement in all patients with daily CBCT for online correction. Previous studies have shown that marker placement increases the accuracy of daily setup and allows tighter margins to be applied.[21] Similarly, daily CBCT has been shown to allow for a reduction of PTV margins while still adequately treating the target.[22] The precision in radiation delivery and our ability to reduce PTV margins is the likely explanation for the reduced rectal toxicity observed relative to those reported in the randomized trials. Clinics with available resources may be able to achieve lower toxicities, such as in our series, with the use of modern IGRT with fiducial placements.

Finally, the importance of precise image guidance in the context of hypofractionated RT for prostate cancer cannot be underestimated. Although the authors acknowledge the relatively small sample size in the current series, the 5-year BCC rate of 97% is notably superior to any of the large, prospective series published to date, the vast majority of which did not require CBCT image guidance (Table 4). This protocol included optimal target delineation through the use of magnetic resonance–based simulation and daily alignment to fiducials under the guidance of CBCT scan. Although intrafraction motion was not specifically taken into account, every other source of setup inaccuracy was addressed prior to the delivery of each treatment fraction and although IGRT offers immense potential advantages in any treatment setting, such are augmented in the hypofractionation context in which any setup inaccuracy on a given day results in a larger proportion of the treatment being delivered suboptimally.

Conclusions

Our results add to the growing body of literature supporting the safety and efficacy of moderately hypofractionated RT for prostate cancer. The limitations of our study include the relatively small patient cohort, lack of high-risk patients, physician- as opposed to patient-reported outcomes, and the lack of a control arm for direct comparison. However, our prospective results show excellent control, with favorably low long-term toxicity rates. The data from previously reported randomized trials support the implementation of hypofractionated RT as a standard treatment approach option, albeit with a slightly increased toxicity risk. This series suggests that the use of optimal target localization resulting in limited PTV expansion, along with IMRT/volumetric modulated arc therapy

delivery techniques, can limit toxicity while preserving highly favorable disease control rates.

References

1. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2007;8:475-487.
2. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the MD Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70:67-74.
3. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol*. 2006;24:1990-1996.
4. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: Long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol*. 2010;28:1106-1111.
5. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys*. 1999;43:1095-1101.
6. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys*. 2002;52:6-13.
7. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5969 patients in seven international institutional datasets: α/β = 1.4 (0.9-2.2) Gy. *Int J Radiat Oncol Biol Phys*. 2012;82:e17-e24.
8. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol*. 2016;34:2325-2332.
9. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;17:1047-1060.
10. Incrocci L, Wortel RC, Alemayehu WG, et al. HYpofractionated versus conventionally fractionated radiotherapy for patients with localised PROstate cancer (HYPRO): Final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2016;17:1061-1069.
11. National Cancer Institute, Division of Cancer Treatment & Diagnosis. Cancer therapy evaluation program, common terminology criteria for adverse events, version 3.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed January 20, 2016.
12. Roach M 3rd, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65:965-974.
13. Arcangeli G, Saracino B, Gomellini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2010;78:11-18.
14. Hoffman KE, Voong KR, Pugh TJ, et al. Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: Results from a randomized trial. *Int J Radiat Oncol Biol Phys*. 2014;88:1074-1084.
15. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol*. 2013;31:3860-3868.
16. Dearnaley D, Syndikus I, Sumo G, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: Preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol*. 2012;13:43-54.
17. Wilkins A, Mossop H, Syndikus I, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2015;16:1605-1616.
18. Aluwini S, Pos F, Schimmel E, et al. HYpofractionated versus conventionally fractionated radiotherapy for patients with PROstate cancer (HYPRO): Acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol*. 2015;16:274-283.
19. Aluwini S, Pos F, Schimmel E, et al. HYpofractionated versus conventionally fractionated radiotherapy for patients with PROstate cancer (HYPRO): Late toxicity results from a randomised, non-inferiority, phase 3 trial. *Lancet Oncol*. 2016;17:464-474.
20. Wortel RC, Incrocci L, Pos FJ, et al. Late side effects after image guided intensity modulated radiation therapy compared to 3D-conformal radiation therapy for prostate cancer: Results from 2 prospective cohorts. *Int J Radiat Oncol Biol Phys*. 2016;95:680-689.
21. Shirato H, Harada T, Harabayashi T, et al. Feasibility of insertion/implantation of 2.0-mm-diameter gold internal fiducial markers for precise setup and real-time tumor tracking in radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003;56:240-247.
22. Ariyaratne H, Chesham H, Pettingell J, Alonzi R. Image-guided radiotherapy for prostate cancer with cone beam CT: Dosimetric effects of imaging frequency and PTV margin. *Radiother Oncol*. 2016;121:103-108.