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Effect of modern, high-quality prostate intensity-modulated radiation therapy on outcome: Evidence from a community radiation oncology program

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Abstract. Radiation technique for prostate cancer has continuously evolved over the past several decades. The aim of the present study was to describe the effects of implementing modern prostate intensity-modulated radiation therapy (M-IMRT) on dosimetry and outcome. Between January 2010 and April 2012, 48 consecutive patients were treated with conventional prostate IMRT (C-IMRT) to a dose of 81 Gy. Between May 2012 and April 2015, 50 consecutive patients were treated with M-IMRT to the entire prostate to a dose of 75.6-79.2 Gy, while using prostate magnetic resonance imaging fusion, dose-volume constraints prioritizing normal tissue avoidance above planning target volume coverage, and boosting any dominant intraprostatic masses to 79.2-81 Gy. Rectal Dmax, V75, V60, V65 and V50, bladder Dmax, V75, V70 and V65, and acute and late toxicities were compared between the C-IMRT and M-IMRT groups. The median follow-up for the C-IMRT and M-IMRT groups was 61 vs. 26 months, respectively (P<0.001). M-IMRT resulted in a significant reduction in median rectal Dmax, rectal V75, rectal V70, rectal V65, bladder Dmax, bladder V75, bladder V70 and bladder V65 (P<0.01 for all). There was no significant difference in rectal V50. The 2-year rate of late grade ≥2 rectal bleeding was 13% with C-IMRT vs. 3% with M-IMRT (P=0.03). The 2-year rate of late grade ≥2 genitourinary toxicity was 11% for C-IMRT vs. 5% for M-IMRT (P=0.21). There were no significant differences in acute toxicity, biochemical control or overall survival. Therefore, compared with C-IMRT, M-IMRT was associated with reduced rectal toxicity without compromising disease control.

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Abbreviations: IMRT, intensity-modulated radiation therapy; C-IMRT, conventional IMRT; M-IMRT, modern IMRT

Key words: intensity-modulated radiation therapy, radiation oncology, dosimetry, toxicity, prostate cancer

Introduction

External-beam radiation therapy is a standard treatment option for patients with localized prostate cancer (1). Recent advances in prostate radiotherapy include intensity-modulated radiation therapy (IMRT), image-guided radiation therapy and radiation dose escalation to 75.6-81 Gy (2-5). In recent years, there has been a widespread application of more stringent normal tissue dose-volume constraints, aiming to reduce toxicity from prostate radiotherapy (6). Routine use of prostate magnetic resonance imaging (MRI) for radiation treatment planning is associated with more accurate delineation of the prostate, enabling reductions in planning target volume (PTV) and decreased dose to the bladder and rectum (7). The more recent development of multiparametric MRI enables consideration of a selective boost to the dominant intraprostatic masses (6). While these newer techniques are highly promising and are increasingly utilized, evidence of clinical benefit through quality local registries remains limited (5).

In the modern era, the potential of designing highly reliable radiation oncology protocols to enhance patient safety has been well-described (8). The association between high-quality radiation oncology and improved survival has clearly been demonstrated in studies analyzing 2- and 3-dimensional conformal radiation therapy (9). Since the majority of publications investigating modern quality improvement programs have focused on process and logistics, there are limited data linking contemporary patient safety efforts with the outcome of cancer of the prostate and other common disease sites (10,11).

To address this evidence gap, the aim of the present study was to quantify the effect of implementing various quality initiatives, including routine MRI-based treatment planning, PTV volume reduction and more stringent normal tissue dose-volume constraints on toxicity and outcome in a community hospital-based radiation oncology program.

Patients and methods

Conventional IMRT (C-IMRT) technique. The Institutional Review Board approved this retrospective study. Between January 2010 and April 2012, 48 consecutive patients with T1-3 prostate cancer were treated with IMRT with a dose of 50.4-54 Gy to the prostate and seminal vesicles followed by a boost to 81 Gy in 1.8-Gy fractions to the entire prostate by 3 highly experienced board-certified radiation oncologists. During this time, the prostate volume was expanded by 1 cm with a reduced 6-mm posterior margin to create the PTV. Elective pelvic lymph node treatment was not performed. Patients underwent computed tomography (CT) simulation in the supine position with custom aquaplast immobilization on a Varian 2100 c/d linear accelerator. Modified Memorial Sloan Kettering planning constraints were utilized with <30% of the rectal wall receiving >75.6 Gy and <53% of the rectal wall receiving >47 Gy. The prescription dose was defined by the isodose line covering the PTV with a Dmax <111%. Dosimetrists were instructed to prioritize PTV coverage over normal tissue avoidance.

Modern MR-guided IMRT (M-IMRT) technique. Between May 2012 and April 2015, 50 consecutive patients with T1-3 prostate cancer were treated by a board-certified radiation oncologist (JK) with reduced-dose IMRT to a dose of 70 Gy to the proximal seminal vesicles, with an integrated prostate boost to 75.6-79.2 Gy in fractions of 1.8-2.0 Gy. The prostate and proximal 1 cm of the seminal vesicles were expanded by 8 mm, with a 5-mm posterior margin. The prostate volume was expanded by 5 mm with a reduced 3-mm posterior margin to create the PTV. For high-to-intermediate- and high-risk patients, the entire seminal vesicles were treated with a separate plan to 46.8-57.6 Gy. For patients with very high-risk disease according to the National Comprehensive Cancer Network (NCCN) guidelines (12), pelvic lymph nodes were treated with 45-46.8 Gy. Grossly positive lymph nodes were treated with 54-59.4 Gy. Patients were simulated and treated with a comfortably full bladder and an empty rectum. Starting in May 2012, the University of Michigan treatment planning constraints for prostate cancer were utilized (Table I). During this period, rectal and bowel avoidance were given higher priority compared with PTV coverage. The prescription dose was >97% of the PTV covered by 100%.

Pelvic MRI with intravenous contrast was offered to all patients from May 2012 onwards. From February 2014 onwards, 3-Tesla multiparametric MRI was routinely available. A minority of patients (22%) was ineligible for MRI, most commonly due to pacemaker or automatic implantable cardioverter-defibrillator. MRI/CT simulation fusion was routinely performed, ensuring alignment of the posterior prostate and anterior rectal interface. An MRI-guided intraprostatic boost was performed when technically feasible. The intraprostatic boost volume was treated with a dose of 79.2-81 Gy using a simultaneous integrated boost approach. The boost PTV was defined as the MRI-defined mass +3 mm, with further volume reductions to avoid overlap with the rectum or bladder.

Image guidance. From February 2014 onwards, the patients were treated on a Varian TrueBeam linear accelerator with cone beam CT. Although fiducial markers were not routinely used, the vast majority of the patients had intraprostatic calcifications that supplemented anatomical information. To reduce imaging dose, cone beam CT was only performed during the first 5 treatments (13). If the average shifts were <5 mm, the frequency of cone beam CT was reduced to twice per week thereafter.

Table I. Treatment planning constraints used at Good Samaritan Hospital Medical Center after May 2012.

	Priority	Dosage
Structures		
Rectum	1	Max dose to 0.1 cc (including PTV overlap) ≤ Rx dose
	1	<15% ≥75 Gy
	1	<25% ≥70 Gy
	1	<35% ≥65 Gy
	1	<50% ≥50 Gy
	3	<5% ≥75 Gy
	3	<15% ≥70 Gy
	3	<17% ≥65 Gy ALARA
Bladder	3	<25% ≥75 Gy
	3	<35% ≥70 Gy
	3	<50% ≥65 Gy
Femur right/left	3	Max ≤45 Gy
	4	ALARA
Penile bulb	3	Mean ≤50 Gy
	4	ALARA
Bowel	1	Max to 1 cc ≤54 Gy
	4	ALARA
Target goals		
PTV (IMRT)	2	Min dose ≥95% Rx dose
	2	Min dose to non-rectal overlap ≥Rx dose
	2	Max dose <110% Rx dose

Adapted with permission from the 'Prostate Treatment Planning Directive' The Regents of the University of Michigan 2008. PTV, planning target volume; ALARA, as low as reasonably achievable; IMRT, intensity-modulated radiation therapy.

Androgen ablation. Androgen ablation was performed for patients with NCCN high-risk and selected patients with intermediate-risk prostate cancer. In general, patients in the intermediate-risk group received 6 months of leuprolide and patients in the high-risk group received 24 months of leuprolide.

Follow-up, toxicity scoring and statistical methods. Patients were evaluated for acute toxicity weekly during radiotherapy and at 1 month following treatment. Acute side effects were scored using the Common Toxicity Criteria for Adverse Events v4.0(https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). Late rectal bleeding was scored

Table II. Patient characteristics for patients treated with conventional or modern IMRT.

Characteristics	Conventional IMRT, n (%) (n=48)	Modern IMRT, n (%) (n=50)	P-value
Age (years)			
Median	70.5	71.5	0.76
Range	51-84	50-85	
Race			
White	32 (67)	32 (64)	0.78
Non-white	16 (33)	18 (36)	
Stage			
T1c-T2a	32 (67)	42 (84)	0.09
T2b-c	11 (23)	7 (14)	
T3	5 (19)	1 (2)	
Gleason score			
≤6	22 (46)	13 (26)	0.04
7	20 (42)	22 (44)	
8-10	6 (13)	15 (30)	
PSA (ng/ml)			
0-10	34 (71)	27 (54)	0.23
10-20	10 (21)	17 (34)	
>20	4 (8)	6 (12)	
Pretreatment IPSS			
Median	9	6	0.40
Range	0-31	0-26	
Percentage of positive cores			
Median	25	30	0.88
Range	8-100	6-100	
Hormonal therapy			
Yes	19 (40%)	27 (54%)	0.15
No	29 (60%)	23 (46%)	
NCCN prognostic group			
Low	16 (33)	7 (14)	0.12
Intermediate	20 (42)	24 (28)	
High	6 (13)	12 (24)	
Very high	6 (13)	7 (14)	

IMRT, intensity-modulated radiation therapy; PSA, prostate specific antigen; IPSS, international prostate symptom score; NCCN, National Comprehensive Cancer Network.

using the more widely used modified Radiation Therapy Oncology Group scale (14). Late genitourinary toxicity was defined as urinary incontinence, urethral stricture and/or urinary bleeding requiring intervention. Late effects and disease control were evaluated in follow-up visits every 3-6 months for the first year and every 6-12 months thereafter. Differences between groups were assessed using a two-sided t-test. The treatment outcomes included biochemical control, with failure defined as a prostate-specific antigen (PSA) increase to >2 ng/dl above the nadir, and overall survival. The Kaplan-Meier method was used to estimate disease control and actuarial toxicity rates using Stata 13.1 software (StataCorp, College Station, TX, USA). For actuarial survival and toxicity data, differences between groups were analyzed using the log-rank test. $P<0.05$ was considered to indicate statistically significant differences.

Results

Patient characteristics. The patient characteristics of both cohorts are summarized in Table II. The median follow-up for the C-IMRT cohort was 60.5 months and the median follow-up for the M-IMRT cohort was 25.9 months ($P<0.01$). The patients were well-matched in terms of age, race, percentage of positive core biopsies, pretreatment PSA velocity and pretreatment International Prostate Symptom Score (IPSS) ($P>0.05$). Patients in the C-IMRT cohort were more likely to have Gleason 6 or NCCN low-risk disease ($P=0.03$).

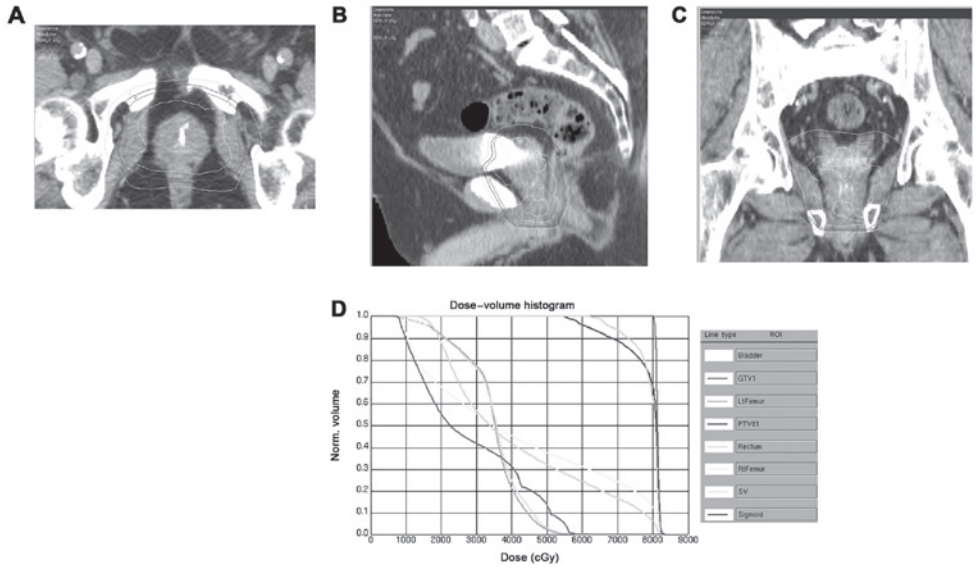

Figure 1. Dose distribution in a representative patient treated with conventional intensity-modulated radiation therapy with 81 Gy to the prostate and 52.2 Gy to the seminal vesicles. The patient developed acute grade 2 urinary and gastrointestinal toxicity and developed grade 3 rectal toxicity requiring laser coagulation. The patient remained alive and biochemically controlled at 5 years. Dose distribution in the (A) axial, (B) sagittal and (C) coronal planes showing excellent coverage of the entire prostate with margin, with a small volume of the anterior rectal wall and the bladder neck receiving >81 Gy. (D) Dose-volume histogram showing a relatively high rectal and bladder Dmax, V75 and V70. ROI, region of interest; GTV, gross tumor volume; PTV, planning target volume.

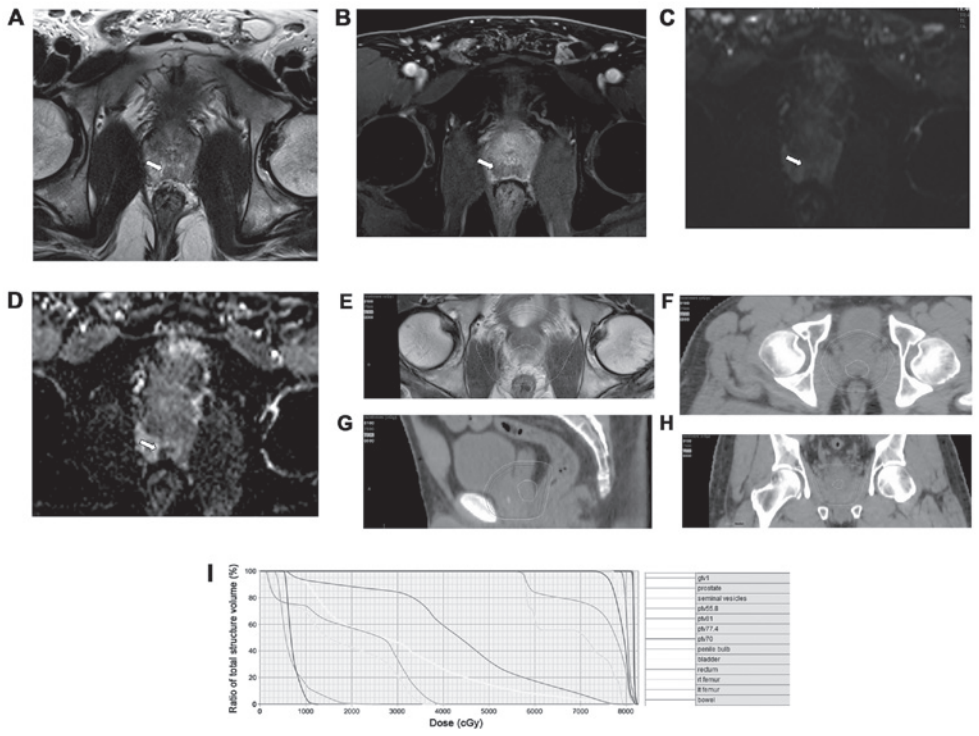

Figure 2. Dose distribution in a representative patient treated with modern intensity-modulated radiation therapy of 81 Gy to the magnetic resonance imaging (MRI) tumor, 77.4 Gy to the prostate, 70 Gy to the proximal seminal vesicles and 55.8 Gy to the seminal vesicles. The patient developed grade 1 acute urinary toxicity and remained alive and biochemically controlled at 17 months after treatment, without late toxicity. Multiparametric prostate MRI showing a dominant mass in the (A) right posterior midline apex on T2-weighted imaging, (B) early dynamic contrast enhancement on T1-weighted imaging, (C) diffusion-weighted imaging and (D) restricted diffusion on the apparent diffusion coefficient map. (E) Axial isodose distribution demonstrating excellent coverage of the MRI nodule to a dose of 81 Gy. (F) Axial, (G) sagittal and (H) coronal dose distribution demonstrated excellent coverage of the prostate >75 Gy, while limiting the maximum rectal and bladder dose to <81 Gy. (I) Dose-volume histogram demonstrates excellent coverage of the PTV81, PTV77.4, PTV70 and PTV54 with selective sparing of the rectal, bladder and penile bulb. GTV, gross tumor volume; PTV, planning target volume.

Treatment characteristics (Figs. 1 and 2). Compared with the conventional cohort, patients in the modern cohort had smaller median prostate volumes (65.6 vs. 50.0 cc, P<0.01), reflecting routine use of MRI. Among patients who received MRI, ≥1 dominant prostatic masses were noted in 70% of the patients. In the modern cohort, 44% of patients underwent

Table III. Treatment characteristics for patients treated with conventional or modern IMRT.

Characteristics	Conventional IMRT (n=48)	Modern IMRT (n=50)	P-value
Median prostate volume, cc	65.6	50	<0.001
Range	16.4-170.5	13.2-144.8	
Maximum rectal dose, Gy	83.2 (SD ± 2.1)	79.27 (SD ± 1.5)	<0.001
Range	76.7-86.9	75.3-81.5	
Rectal volume receiving 75 Gy	11% (SD ± 4)	3% (SD ± 2)	<0.001
Range	5-19%	1-8%	
Rectal volume receiving 70 Gy	16% (SD ± 3)	9% (SD ± 3)	<0.001
Range	9-23%	1-15%	
Rectal volume receiving 65 Gy	21% (SD ± 3)	16% (SD ± 5)	<0.001
Range	13-28%	5-24%	
Rectal volume receiving 50 Gy	36% (SD ± 4)	34% (SD ± 9)	0.52
Range	27-47%	18-58%	
Maximum bladder dose, Gy	84.0 (SD ± 2.8)	80.28 (SD ± 1.6)	<0.001
Range	75.8-88.2	76.1-83.3	
Bladder volume receiving 75 Gy	16% (SD ± 4)	5% (SD ± 4)	<0.001
Range	1-25%	1-17%	
Bladder volume receiving 70 Gy	21% (SD ± 5)	9% (SD ± 6)	<0.001
Range	6-30%	1-20%	
Bladder volume receiving 65 Gy	26% (SD ± 7)	13% (SD ± 8)	<0.001
Range	11-50%	2-32%	

IMRT, intensity-modulated radiation therapy; SD, standard deviation.

MRI-guided boost treatment to a median dose of 3.6 Gy (range, 2-4 Gy). The median boost volume was 10.4 cc (range, 3.7-33.9 cc). The treatment parameters are summarized in Table III. Patients in the M-IMRT cohort exhibited a significant reduction in median rectal Dmax, rectal V75, rectal V70, rectal V65, bladder Dmax, bladder V75, bladder V70 and bladder V65 (P<0.01 for all). There was no significant difference in rectal V50.

Impact of modern technique on acute and late toxicity (Fig. 3). The rate of grade 2 acute gastrointestinal (GI) toxicity was 29% for C-IMRT vs. 16% for M-IMRT (P=0.12). The rate of grade 2 acute GU toxicity was 42% for C-IMRT vs. 56% for modern IMRT (P=0.16).

The 2-year rate of late grade 2 rectal bleeding was 13% with C-IMRT vs. 3% with M-IMRT (P=0.03). One patient in the conventional cohort developed grade 4 rectal toxicity requiring transfusion and 1 patient in the conventional cohort developed rectal bleeding requiring laser coagulation. No patient in the modern cohort developed late grade >2 GI toxicity. The 2-year rate of late grade ≥2 genitourinary toxicity was 11% for C-IMRT vs. 5% for M-IMRT (P=0.21). The cumulative 2-year incidence of grade ≥2 bowel or bladder adverse events was 22% with C-IMRT vs. 8% with M-IMRT (P=0.02). After M-IMRT, there was no significant change in mean IPSS scores compared with baseline (7.9 prior to M-IMRT vs. 6.8 following M-IMRT; P=0.32). After modern radiotherapy, there was a decrease in mean Sexual Health Inventory For Men score compared with baseline (10.9 prior to M-IMRT vs. 6.8 following M-IMRT, P<0.01).

Effect of M-IMRT on survival (Fig. 4). The biochemical control at 2 years was 97% with C-IMRT vs. 98% with M-IMRT (P=0.79). The overall survival at 2 years was 96% with C-IMRT vs. 93% with M-IMRT (P=0.24). There was 1 death from metastatic prostate cancer in the conventional group.

Discussion

In this single-institution study, significantly lower rates of grade ≥2 rectal bleeding were observed following implementation of the modern, higher-quality IMRT technique for the treatment of localized prostate cancer. The observed decline in toxicity was attributed to the routine adoption of multiple quality improvement initiatives, including more stringent treatment planning dose volume constraints for normal tissues, MRI-based treatment planning with simultaneous integrated boosts, and use of image-guided radiation therapy.

The current standard of care for prostate radiotherapy is a minimum dose of 75.6 Gy to the entire prostate. Within a dynamic range of 75.6-81 Gy, there are no data from randomized trials to determine the optimal prostate dose (15). A dose escalation study from the Memorial Sloan Kettering Cancer Center demonstrated a lower positive biopsy rate of 10% following 81 Gy compared with 23% for patients treated with 75.6 Gy (16). For patients receiving dose-escalated radiation therapy >75.6 Gy, IMRT has been shown by investigators at the Memorial Sloan Kettering Cancer Center to decrease late grade ≥2 rectal toxicity compared with 3-dimensional conformal radiation (2,16). However, other centers have

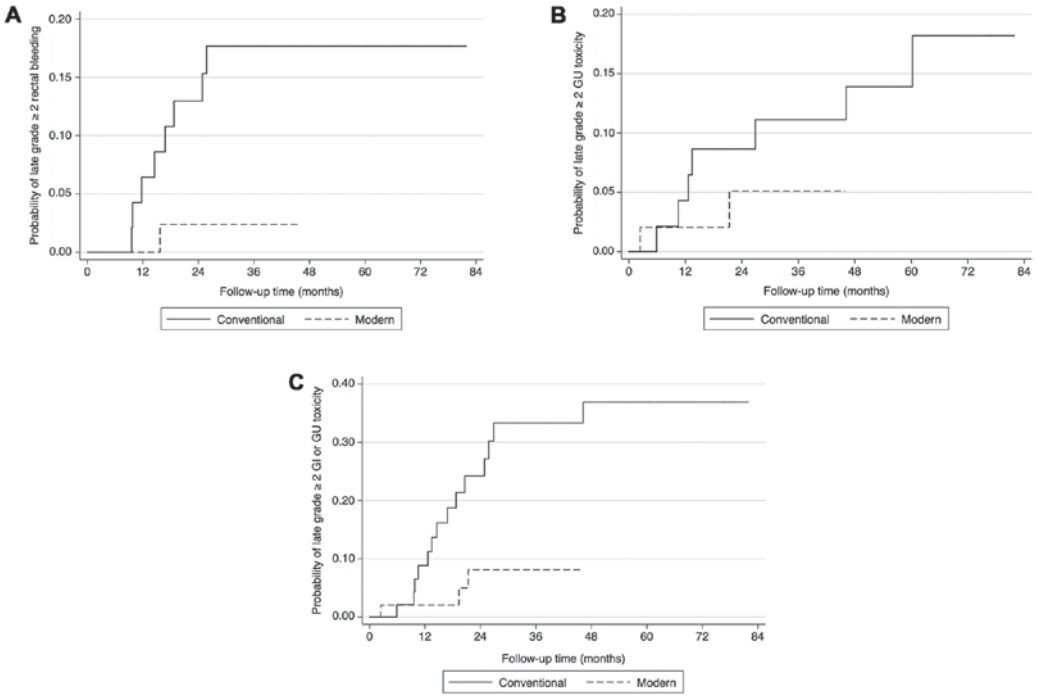

Figure 3. Late toxicity. (A) Estimate of late grade ≥2 rectal bleeding in patients treated with conventional vs. modern intensity-modulated radiation therapy (IMRT). (B) Estimate of late grade ≥2 genitourinary (GU) toxicity in patients treated with conventional vs. modern IMRT. (C) Estimate of late grade ≥2 gastrointestinal (GI) or GU toxicity in patients treated with conventional vs. modern IMRT.

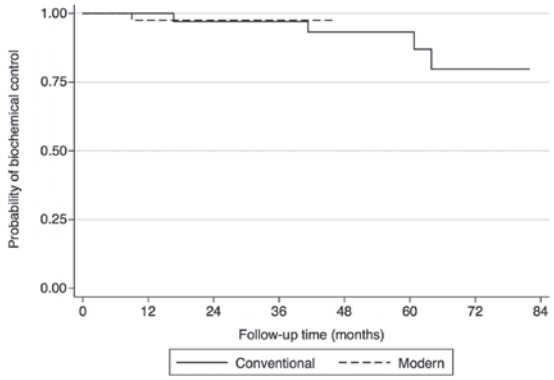

Figure 4. Estimate of biochemical control in patients treated with conventional vs. modern intensity-modulated radiation therapy.

reported significantly higher rates of rectal bleeding with dose-escalated IMRT (17-19). A recent analysis from Emory University suggests that patients treated with IMRT to a dose of 81 Gy had higher acute grade 2 GI and genitourinary (GU) toxicity and higher rates of late grade 2 GU toxicity compared with patients treated with IMRT to a dose of 75.6 Gy (19).

If validated, an elegant solution would be to reduce the dose to the clinically uninvolved prostate to <81 Gy, while maintaining or increasing the radiation dose to the dominant prostatic nodule by employing a non-uniform dose distribution (20,21). The development of multiparametric MRI, consisting of T2-weighted imaging, diffusion-weighted imaging and dynamic contrast enhancement, potentially allows the clinician to selectively target clinically significant dominant prostatic masses with a reasonable level of confidence (22). The widespread availability of cone beam CT increases confidence that the boost volume will be accurately targeted. Several investigators have treated the entire prostate with 72-78 Gy, while boosting the dominant MRI nodule to 80-83 Gy (20,21). These studies demonstrated 33-53% acute grade ≥2 GU toxicity, 8-20% acute grade ≥2 GI toxicity, 8-29% late grade ≥2 GU toxicity and 4-10% late grade ≥2 GI toxicity, with promising efficacy results. The present study provides further evidence that boosting the dominant intraprostatic nodule is feasible and well-tolerated.

Other approaches employed in this study to reduce normal tissue toxicity include limiting the volume of seminal vesicles treated and using more stringent normal tissue dose-volume constraints (23). In this hypothesis-generating study, routine use of MRI-fusion, implementing strict dose-volume constraints and reducing dose to the uninvolved prostate to <80 Gy was associated with reduced late grade ≥2 rectal bleeding compared with historical controls treated with 81 Gy. This study clearly demonstrates the feasibility of achieving higher-quality prostate radiation within a moderate volume community hospital center (24). Of note, these changes were rapidly implemented by a single physician in May 2012, without requiring turnover in dosimetry or physics staff. As a result, this dataset serves as a unique natural experiment of two distinct approaches to IMRT for prostate cancer.

Significant limitations of this study include its retrospective methodology, small sample size, short median follow-up and significant evolution in patient management from 2010 to 2015. Specifically, the cohort treated between January 2010 and April 2012 were more likely to have low-risk disease, reflecting the increased application of active surveillance after 2012. The patients treated between May 2012 and April 2015 benefited from the implementation of strict normal tissue constraints, available image guidance and the development of

multiparametric MRI. As a result, it is not possible to attribute the observed reduction in toxicity to any single technical factor. While M-IMRT for prostate cancer requires increased resources, there may be a benefit in terms of reduced toxicity without compromising disease control, possibly suggesting improved therapeutic ratio. Confirmatory studies will be useful to validate these hypothesis-generating findings.

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