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Scientific Article

Effect of Large Prostate Volume on Efficacy and Toxicity of Moderately Hypofractionated Radiation Therapy in Patients With Prostate Cancer

Divya Natesan, MD,[a,*] David J. Carpenter, MD, MHS,[a] Warren Floyd, BS,[b] Taofik Oyekunle, MS,[c] Donna Niedzwiecki, PhD,[c] Laura Waters, NP,[d] Devon Godfrey, PhD,[a,d] Michael J. Moravan, MD, PhD,[a,d] William Robert Lee, MD,[a] and Joseph K. Salama, MD[a,d]

[a]*Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina;* [b]*Duke University School of Medicine, Durham, North Carolina;* [c]*Biostatistics, Duke Cancer Institute, Durham, North Carolina;* [d]*Durham Veterans Affairs Medical Center, Durham, North Carolina*

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Abstract

Purpose: To evaluate the effect of prostate volume on outcomes after moderately hypofractionated radiation therapy (mHFRT) for prostate cancer.

Methods and Materials: Prostate cancer patients treated with mHFRT at a Veteran's Affairs Medical Center from August 20, 2008, to January 31, 2018, were identified. Patients were placed into a large prostate planning target volume (LPTV) cohort if their prostate PTV was in the highest quartile. Acute/late genitourinary (GU) and gastrointestinal toxicity events among patients with and without LPTV were compared. Multivariable analyses estimated the effect of factors on toxicity. Overall survival, biochemical recurrence-free survival, and freedom from late GU/gastrointestinal toxicity of patients with and without LPTV were estimated via Kaplan-Meier.

Results: Four hundred and seventy-two patients were included. Ninety-three percent received 70 Gy in 2.5 Gy fractions; 75% received androgen deprivation therapy. Median follow-up was 69 months. Patients with LPTV (PTV >138.4 cm^3) had a higher late 2 + GU toxicity compared with those without (59% vs 48%, $P = .03$). Earlier time to late 2 + GU toxicity was associated with LPTV (hazard ratio 1.36; 95% confidence interval [CI], 1.00-1.86; $P = .047$), androgen deprivation therapy use (hazard ratio 1.60; 95% CI, 1.13-2.27; $P = .01$), and higher baseline American Urologic Association symptom score (odds ratio 1.03; 95% CI, 1.02-1.05; $P < .001$). At 2 years, freedom from late 2 + GU toxicity was 46% (95% CI, 47%-54%) for those with LPTV versus 61% (95% CI, 55%-65%) for those without ($P = .04$). Late grade 3 GU toxicity was 7% for those with LPTV and 4% for those without. No differences in overall survival or biochemical recurrence-free survival were observed between patients with or without LPTV.

Conclusions: LPTV did not affect efficacy of mHFRT for prostate cancer; however, it was associated with increased risk and earlier onset of late grade 2 + GU toxicity.

Introduction

Moderately hypofractionated radiation therapy (mHFRT) for the treatment of prostate cancer has been shown to have similar safety and efficacy compared with

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*Corresponding author: Divya Natesan, MD; E-mail: divya.natesan@duke.edu

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conventionally fractionated radiation therapy (CFRT) in multiple large randomized controlled trials (RCTs).[1-4] These trials support the use of mHFRT as a standard treatment[5] for men with low,[3] intermediate,[2] and high-risk[1,4] prostate cancers.

The effect of prostate volume has not been well studied in the setting of mHFRT. The clinical significance of large prostate volume (LPV) has been evaluated in other prostate cancer radiotherapies. For example, LPV has generally been a relative contraindication to brachytherapy, on the basis of historical series which reported higher rates of acute and late genitourinary (GU) toxicity.[6-8] Similarly, LPV has also been associated with an increased risk of acute GU symptoms after CFRT.[9,10] It is unknown whether the efficacy and toxicity of mHFRT differs according to prostate volume, questioning the utility of this technique in patients with large volume prostate glands. Therefore, we conducted a single institution retrospective study of prostate cancer patients treated with mHFRT, analyzing the effect of prostate volume (specifically prostate planning target volume) on patient outcomes.

Methods

Patients with prostate cancer treated definitively with mHFRT (2.5-3.0 Gy per fraction) at a Veteran's Affairs Medical Center from August 20, 2008 to January 31, 2018 were identified from a prospectively maintained database. This study was approved by the Durham Veteran's Affairs Institutional Review Board (MIRB #01677). Patients were excluded if they did not receive mHFRT, had metastatic disease, had incomplete records, or if follow-up was less than 1 year. The electronic medical record was reviewed for patient demographic, tumor, treatment, toxicity, biochemical and distant recurrence, and death variables. Biochemical recurrence was defined as PSA rise 2 ng/mL from nadir or initiation of ADT. Dose volume histogram information was obtained from individual treatment plans. The percentage and absolute volume (cc) of the bladder and the rectum receiving 70 Gy, 50 Gy, and 31 Gy were recorded.

Patients underwent radiation planning with CT simulation in standard immobilization devices. Prostate glands were contoured on a slice-by-slice basis by the treating radiation oncologist. Prostate magnetic resonance imaging was fused to the computed tomography simulation scan to aid in target delineation. The seminal vesicles (SV) were contoured separately, and not included in the prostate contour. Prostate volume (PV) was obtained as a volumetric calculation from the prostate contour. Prostate planning target volume (PTV) was defined as the prostate contour with a symmetrical 5 to 7 mm volumetric expansion. Patients with low risk disease received radiation to the prostate alone, in either 70 Gy in 2.5 Gy per fraction (earlier in the study period) or 60 Gy in 3.0 Gy per fraction (later in the period). Patients with intermediate or high-risk disease received radiation to the prostate gland and SV, with a simultaneous integrated boost (SIB) to the prostate. They received either (1) 58.8 Gy in 2.1 Gy per fraction to SV, with an SIB of 70 Gy in 2.5 Gy per fraction to the prostate or (2) 50 Gy in 2.5 Gy per fraction to the SV, with an SIB of 60 Gy in 3 Gy per fraction to the prostate. Daily image guidance was used with either daily CBCT soft tissue matching or alignment to fiducials seen on daily orthogonal kV imaging. Androgen deprivation therapy (ADT) was typically given to those with intermediate and high-risk prostate cancer, at the discretion of the treating radiation oncologist. After completion of radiation therapy, patients were typically seen in follow-up within 6 to 8 weeks. Thereafter, patients were typically seen every 6 to 12 months, alternating with other providers as needed. Large prostate PTV (LPTV) was defined a priori as prostate PTVs in the highest quartile. Given the variability in prostate to PTV expansions (5-7 mm) during the study period and possible resulting differences in toxicity and efficacy which might obscure the effects of PV, LPTV was selected over PV as the primary parameter of interest.

Acute GU/GI toxicities were defined as occurring during radiation or within 3 months of completing radiation. Late GU/GI toxicities were defined as occurring greater than 3 months after completing radiation. All GU toxicities were assessed qualitatively and quantitatively with the American Urologic Association (AUA) Symptom Score questionnaire at every follow-up visit. All GI toxicities were assessed qualitatively and documented at every follow-up visit. For this study, toxicities were scored retrospectively in a standard fashion per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Generally, per CTCAE, mild GI or GU symptoms not necessitating medical intervention were assigned grade 1. Symptoms which limited activities of daily living or required medical intervention (new or increased dose from baseline) were assigned a grade 2. Grade 3 toxicities were those which required invasive intervention or hospitalization.

Demographic, tumor, and treatment characteristics of patients with and without LPTV were compared using the Wilcoxon rank-sum and χ^2 tests. Acute and late GU/GI toxicities between patients with and without LPTV was compared with χ^2 or Fisher's exact tests. Volume of bladder and rectum receiving 70 Gy, 50 Gy, and 31 Gy between patients with and without LPTV were compared via the Wilcoxon rank-sum test.

Univariate/multivariate logistic and Cox regression models were used to assess demographic, tumor, treatment, and dosimetric factors associated with acute and late GI/GU toxicities, respectively. Multivariable models were adjusted for age, risk group, ADT use, pre-RT AUA score, RT total dose, selected a priori to adjust for factors

which may influence GU and GI radiation toxicity. Models for GU toxicity were adjusted for baseline AUA score and bladder dosimetric factors which were determined to be most relevant based on the univariate analysis. Models for GI toxicity were adjusted for rectal dosimetric factors which were significant on univariate analysis.

The Kaplan-Meier method was used to estimate overall survival (OS), biochemical recurrence free survival (BRFS), prostate cancer specific survival, distant metastatic free survival (DMFS), and freedom from late grade 2 or higher (2 +) GU and GI toxicities for all patients and compared by LPTV status using the log-rank test. All tests were 2-tailed, and a P value of $< .05$ was assumed to be significant. No adjustments for multiple comparisons were made. All statistical analysis was performed using SAS (Cary, NC).

Results

Four hundred and seventy-two patients with low (10%), intermediate (59%), and high-risk (31%) prostate cancer were treated with mHFRT during the study period. Median age was 64 years (interquartile range [IQR] 60, 68). Ninety-three percent of patients received 70 Gy in 2.5 Gy fractions. Seventy-five percent received ADT. Median follow-up was 69 months (95% CI 65-75 months). Median prostate PTV was 108.1 cm^3 (IQR 86.9, 138.4). Therefore, LPTV was defined as >138.4 cm^3. Those with LPTV had a median PV of 76.1 cm^3 (IQR 65.4, 86.4) compared with those without who had a median PV of 39.5 cm^3 (IQR 31.6, 47.5; P <.001). There were no other significant differences in characteristics of patients with or without LPTV (Table 1).

Owing to differences in fractionation and as only a minority of patients were treated with 60 Gy in 3 Gy per fraction, dosimetric evaluation was limited to those who received 70 Gy in 2.5 Gy fractions (Table E1). Those with LPTV had a higher percent volume and absolute volume of bladder receiving 70 Gy (1.9% vs 1.4%, $P = .002$; 5.5 cm^3 vs 3.7 cm^3, $P < .001$), 50 Gy (15.2% vs 12.8%, $P < .001$; 41.9 cm^3 vs 31.2 cm^3, $P = .01$), and 31 Gy (29.9% vs 25.9%, $P = .01$; 83.5 cm^3 vs 63.7 cm^3, $P < .001$). The LPTV cohort also had higher percent volume and absolute volume rectal irradiation to 50 Gy (22.4% vs 19.6%, $P < .001$; 18.5 cm^3 vs 14.1 cm^3, $P < .001$) and 31 Gy (61.2% vs 55.3%, $P < .001$; 50.9 cm^3 vs 40.1 cm^3, $P < .001$).

Frequencies of acute and late grade 2 + GU/GI toxicity are presented in Table E2. A higher proportion of patients with LPTV had late grade 2 + GU compared with those without LPTV (59% vs 48%, $P = .03$). There were no differences in acute 2 + GU toxicity or acute/late 2 + GI toxicity between those with and without LPTV. Detailed frequencies of acute and late GI/GU toxicity, by grade, are listed in Table E3. Acute grade 3 GU toxicity was 3% for those with LPTV and 4% for those without. Late grade 3 GU toxicity was 7% for those with LPTV and 4% for those without.

Next, we looked at the timing of onset for late treatment-related GI/GU toxicity. The 2-year and 5-year freedom from late grade 2 + GU toxicity for all patients were 57% (95% CI, 52%-61%) and 49% (95% CI, 44%-54%), respectively. Patients with LPTV had a shorter time of onset of late grade 2 GU + toxicity at 2 years. The 2-year freedom from late grade 2 + GU toxicity was 46% (95% CI, 47%- 54%) for patients with LPTV versus 61% (95% CI, 55%-65%) for those without ($P = .041$; Fig. 1A). The 2-year and 5-year freedom from late grade 2 + GI toxicity for all patients were 93% (95% CI, 89%-94%) and 91% (95%, CI 88%-94%), respectively (Fig. 1B). There were no differences in time to development of late grade 2 + GI between patients with LPTV versus no LPTV.

Table E4 contains univariate results for factors associated with acute and late GU/GI toxicity. Associations between dosimetric variables and acute/late GU and GI toxicity are presented in Table E5. Bladder max dose (odds ratio [OR] 1.00; 95% CI, 1.00-1.00; $P = .047$) was associated with increased acute grade 2 + GU toxicity. Percent bladder V70 (OR 1.13; 95%, CI 0.99-1.29; $P = .06$) and absolute volume bladder V70 (OR 1.06; 95% CI, 1.00-1.12; $P = .051$) trended for associated increased acute grade 2 + GU toxicity. Percent bladder V31 trended for associated increased late grade 2 + GU toxicity (HR 1.01; 95% CI, 1.00-1.02; $P = .08$). Rectal max dose (OR 1.01; 95% CI, 1.00-1.02; $P = .002$), percent rectal V70 (OR 1.58; 95% CI, 1.18-2.21; $P = .002$), and absolute rectal V70 (OR 1.62; 95% CI, 1.10-2.37; $P = .01$) were associated with increased acute 2 + GI toxicity. Percent rectal V70 (HR 1.18; 95% CI, 1.01-1.37; $P = .04$) and absolute rectal V31 (HR 1.01; 95% CI, 1.00-1.02; $P = .048$) were associated with increased late GI 2 + toxicity.

Results of multivariable analyses for factors associated with acute/late 2 + GU and GI toxicity are presented in Table 2 and Table E6, respectively. ADT use (OR 1.70; 95% CI, 1.04-2.77; $P = .02$) and higher baseline AUA score (OR 1.05; 95% CI, 1.02-1.08; $P < .001$) were associated with increased acute 2 + GU toxicity. LPTV was significantly associated with increased risk of late 2 + GU toxicity (HR 1.36; 95% CI, 1.00-1.86; $P = .047$) along with the use of ADT (OR 1.60; 95% CI, 1.13-2.27; $P = .01$) and higher baseline AUA score (OR 1.03; 95% CI, 1.02-1.05; P <.001). For GI toxicity, percent rectum V70 was associated with both increased acute 2 + GI toxicity (OR 1.35; 95% CI, 1.06-1.72; $P = .02$), and with increased late 2 + GI toxicity (OR 1.25; 95% CI, 1.07-1.46; $P = .005$).

We assessed long term patient-reported urinary toxicity after mHFRT by analyzing AUA at the patient's last follow-up visit. Median post-RT AUA for all available patients (n = 213) was 17 (IQR 11, 23; Table E7). Post-

Table 1 Patient, tumor, and treatment characteristics: Overall and by LPTV

	LPTV		Total (N = 472)	*P* value
	Yes (N = 118)	No (N = 354)		
Age at diagnosis (y)				.41*
Median (Q1, Q3)	65 (61, 68)	64 (60, 68)	64 (60, 68)	
Race				.08†
Black	83 (70%)	218 (62%)	301 (64%)	
White	31 (26%)	130 (37%)	161 (34%)	
Others	4 (3%)	6 (2%)	10 (2%)	
ECOG				.69†
0	48 (41%)	134 (38%)	182 (39%)	
1	32 (27%)	102 (29%)	134 (28%)	
2	3 (3%)	18 (5%)	21 (4%)	
3	3 (3%)	5 (1%)	8 (2%)	
Unknown	32 (27%)	95 (27%)	127 (27%)	
Clinical T stage				.51†
T1	79 (67%)	223 (63%)	302 (64%)	
T2	31 (26%)	112 (32%)	143 (30%)	
T3-4	8 (7%)	19 (5%)	27 (6%)	
PSA (ng/dL)				.13*
Median (Q1, Q3)	9.0 (5.9, 15.3)	8.2 (5.9, 12.1)	8.4 (5.9, 12.9)	
Gleason grade				.05†
3 + 3	26 (22%)	51 (14%)	77 (16%)	
3 + 4	46 (39%)	146 (41%)	192 (41%)	
4 + 3	19 (16%)	76 (21%)	95 (20%)	
4 + 4	22 (19%)	47 (13%)	69 (15%)	
4 + 5	5 (4%)	34 (10%)	39 (8%)	
Risk group				.27†
Low	13 (11%)	32 (9%)	45 (10%)	
Favorable intermediate	36 (31%)	100 (28%)	136 (29%)	
Unfavorable intermediate	27 (23%)	118 (33%)	145 (31%)	
Favorable high	7 (6%)	22 (6%)	29 (6%)	
Unfavorable high	35 (30%)	82 (23%)	117 (25%)	
AUA score				.12*
Median (Q1, Q3)	13 (8, 19)	11 (6, 17)	12 (6, 18)	
Urinary medication				.69†
Yes	38 (32%)	107 (30%)	145 (31%)	
No	80 (68%)	247 (70%)	327 (69%)	
RT total dose				.23†
60 Gy	6 (5%)	30 (8%)	36 (7%)	
70 Gy	112 (95%)	324 (92%)	436 (93%)	
Duration of RT (d)				.74*
Median (Q1, Q3)	40 (38, 42)	40 (38, 42)	40 (38, 42)	
ADT				.18†
Yes	83 (70%)	271 (77%)	354 (75%)	
No	35 (30%)	83 (23%)	118 (25%)	
Prostate Volume (cm^3)				<.001*
Median (Q1, Q3)	76.1 (65.4, 86.4)	39.5 (31.6, 47.5)	44.8 (34.8, 59.6)	

Abbreviations: AUA = American Urologic Association; ECOG = Eastern Cooperative Oncology Group; LPTV = large prostate planning target volume; PSA = prostate specific antigen; RT = radiation therapy.

* Wilcoxon rank-sum test.

† χ^2 test.

RT AUA was not significantly different between patients with LPTV or without LPTV (median AUA 20 vs 17, $P = .32$). Median change in AUA from baseline to last follow-up was + 4 (IQR −1, 10) for all patients, and not significantly different between patients with or without LPTV (median difference + 3 vs + 4, $P = .89$).

Survival outcomes for all patients are presented in Table E8. The overall 5-year OS, BRFS, PCCS, and

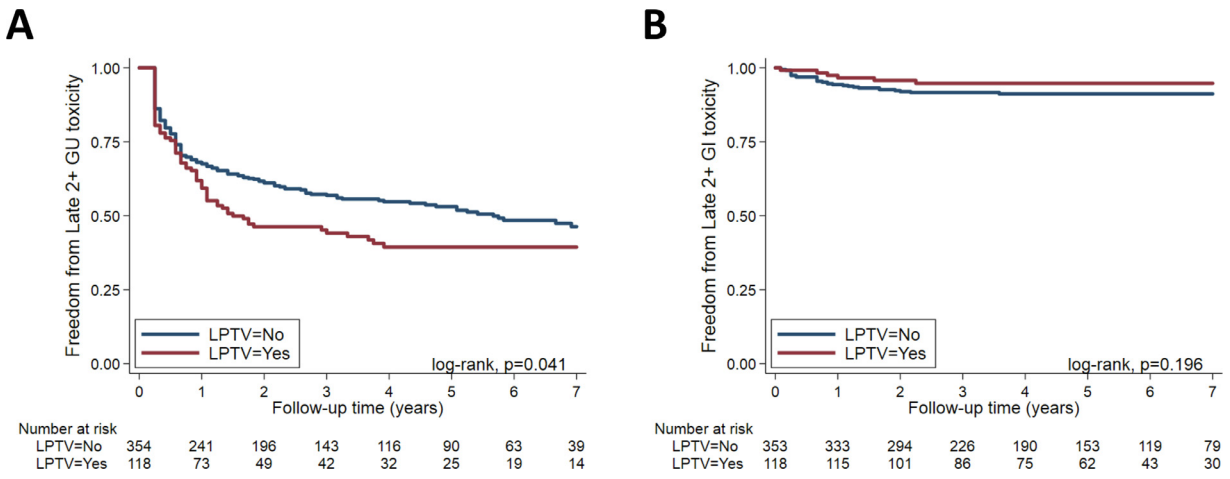

Figure 1 Freedom from (A) late 2 + genitourinary (GU) and (B) late 2 + gastrointestinal (GI) toxicity, for patients with and without large prostate planning target volume (LPTV).

DMFS was 82% (95% CI, 78%-86%), 86% (95% CI, 82%-89%), 94% (95% CI, 92%-96%), and 94% (95% CI, 91%-96%), respectively. There were no differences in OS, BRFS, prostate cancer specific survival, DMFS between patients with LPTV versus no LPTV (Fig. E1).

To determine whether LPTV was an acceptable surrogate for prostate volume, we conducted a secondary analysis comparing patients with or without LPV, defined as the highest quartile (PV >59.8 cm^3). This secondary analysis was consistent with the aforementioned findings of the LPTV cohort, with a trend for higher risk of 2 + GU toxicity (HR 1.30; 95% CI, 0.98-1.72; P = .07) and for shorter time to development of late GU toxicity (2 year freedom from late 2 + GU toxicity, 48% (95% CI, 39%-57%) in patients with LPV versus 60% (54%-65%) for those without (P = .07).

Discussion

In this large retrospective analysis of patients with prostate cancer treated with mHFRT in a consistent manner, we describe efficacy and toxicity outcomes for patients with and without large prostate planning target volumes (defined as prostate PTV >138.4 cm^3). Oncologic outcomes did not differ by prostate PTV, with rates similar to those reported by RCTs of mHFRT.[1,4] However, we did find that a greater proportion of LPTV

Table 2 Multivariate analysis of acute/late G2 + genitourinary toxicity

	Acute grade 2 + GU toxicity		Late grade 2 + GU toxicity	
	OR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (y)	0.99 (0.96-1.03)	.72	1.00 (0.98-1.02)	.93
Risk group		.64		.55
LR/FIR	ref		ref	
UIR/FHR/UHR	1.12 (0.70-1.81)		0.91 (0.65-1.26)	
ADT		.02		.01
No	ref		ref	
Yes	1.70 (1.04-2.77)		1.60 (1.13-2.27)	
Pre-RT AUA score	1.05 (1.02-1.08)	<.001	1.03 (1.02-1.05)	<.001
LPTV		.96		.047
No	ref		ref	
Yes	1.01 (0.64-1.61)		1.36 (1.00-1.86)	
Bladder V70 (% volume)	1.01 (0.88-1.17)	.85	1.01 (0.92-1.10)	.89
RT total dose (Gy)		.70		.34
60	ref		ref	
70	0.87 (0.42-1.81)		0.78 (0.46-1.30)	

Abbreviations: ADT = androgen deprivation therapy; AUA = American Urologic Association; CI = confidence intervals; FHR = favorable high-risk; FIR = favorable intermediate risk; GU = genitourinary; HR = hazard ratio; LPTV = large planning target volume; LR = low risk; OR = odds ratio; RT = radiation therapy; UHR = unfavorable high-risk; UIR = unfavorable intermediate risk.

patients experienced late 2 + GU toxicity at 2 years. To our knowledge, this is the first analysis which reports on outcomes after mHFRT for patients with large prostate planning target volumes. These results are also the first to suggest that late urinary toxicity after mHFRT may differ by prostate gland size.

We found that LPTV, baseline AUA, and receipt of ADT were significantly associated with increased late GU 2 + toxicity on univariate and multivariable analysis. Additionally, patients with LPTV developed onset of late 2 + GU toxicity sooner than those without LPTV. Of note, there were not significant differences in pretreatment AUA score or use of urinary medication between those with or without LPTV, indicating that baseline urinary function was comparable between cohorts. In addition, LPTV remained a risk factor for late GU toxicity on multivariate analysis when controlling for baseline AUA. Together, this suggests that the increased GU toxicity observed in the LPTV cohort is the result of the radiation therapy, and not a manifestation of underlying urinary function. Patients with LPTV did have higher volumes of bladder irradiation to 31 Gy, 50 Gy and 70 Gy, but we did not identify any dosimetric bladder parameters which were independently associated with increased GU toxicity.

Previously, large prostate volume has been implicated as a risk factor for increased urinary toxicity after brachytherapy.[6-8,11] and conventionally fractionated radiation therapy.[9,10] However, only 1 of the 4 major RCTs of mHFRT has reported the effect of prostate size on outcomes. In the HYPRO trial, 45% of those receiving mHFRT had prostate volume $\leq$50 cm^3 and 51% of men had prostate volume >50 cm^3. In post hoc multivariate analyses of those who received mHFRT, prostate volume >50 cm^3 was not associated with relapse-free survival or GU/GI toxicity.[4,10] A threshold of >50 cm^3 in this study may not have identified the individuals of highest risk of GU toxicity after mHFRT. Although a prostate size >50 cm^3 has generally been adopted as the size cutoff for large PV for modalities such as brachytherapy and stereotactic body radiation therapy, our LPTV cohort had a higher median PV of 76 cm^3 (IQR 65.40, 86.40). For mHFRT, our data suggests that the prostate size cutoff which portends increased GU toxicity may be higher than 50 cm^3. Consistent with this observation, one retrospective study of mHFRT reported that prostate volume >80 cm^3 was a predictor for acute G2 GU toxicity.[12]

Irrespective of LPTV, the rate of G2 + late GU toxicity is higher in this study that what has been reported previously in RCTs of mHFRT.[1,3,13] RTOG 0415 first reported outcomes for mHFRT using 70 Gy in 2.5 Gy fractions, with a late G2 + urinary toxicity of 29.7% in the mHFRT arm. We speculate that the higher late G2 + GU toxicity observed in our study may be due, in part, to the different toxicity grading schema used. RTOG 0415 used CTCAEv3 which defines grade 2 urinary frequency/urgency as "increase >2 × normal but <hourly"; our study used CTCAE, which defines grade 2 urinary frequency as "limiting instrumental ADL; medical management indicated." Therefore, patients who required medications to manage lower urinary tract symptoms (LUTS) were graded as having a grade 2 GU toxicity.

Reassuringly, patient-reported AUA at last follow-up was not significantly different between patients with or without LPTV. This suggests that although patients with LPTV may require urinary medications at higher rates or sooner than those without LPTV, they are still able to achieve comparable rates of long-term LUTS satisfaction. Irrespective of LPTV, the rates of grade 3 + GU toxicity requiring invasive intervention/hospitalization were low.

Conclusions

In our study, we found that patients with LPTV had higher volumes of rectal irradiation; however, LPTV was not associated with an increased risk of acute or late GI toxicity. Volume of rectal irradiation to 70 Gy in all patients was an independent risk factor for both acute and late GI toxicity. This observation is concordant with prior reports which have reported that higher doses of rectal irradiation (>60-70 Gy) are consistently associated with increased risk of late rectal toxicity.[14-16] LPTV patients had higher apparent volumes of bladder irradiation based on dosimetric evaluation at CT simulation. However, as in prior studies, we did not identify any bladder dosimetric metrics which were significantly associated with late GU toxicity. This may be due to variations in bladder filling or positioning during treatment which alter actual bladder irradiation. Additionally, some have suggested that chronic urinary toxicity may be more reflective of prostatic urethral toxicity than bladder toxicity.[17]

One limitation of this study is that prostate to PTV expansion varied over time. As these variations could affect oncologic and toxicity outcomes and confound the effect of prostate volume, we selected prostate PTV as our proxy for prostate volume/anatomic differences in our analysis. To help justify that prostate PTV is an appropriate surrogate for prostate volume, we conducted a secondary analysis of patients with or without LPV, which was consistent with the aforementioned findings of the LPTV cohort. Our institutional practice shifted from using the hypofractionation scheme of 70 Gy/2.5 Gy to 60 Gy/3 Gy in 2018. Therefore, a second limitation of the study is that, although 60 Gy/3 Gy is commonly used and our current institutional practice, only patients who received 70 Gy were included in this study's dosimetric analysis. The clinical effect of SV irradiation was not accounted for in this study and may influence acute and late toxicity after mHFRT. Finally, the use of anticoagulation, a known risk factor for GI toxicity after radiation

therapy, was not available for analysis. The strengths of this VA study include the large numbers of patients, diverse patient population, consistent radiation, long follow-up, and rigorous toxicity documentation.

Future investigations should focus on specifically identifying which groups of patients are at highest risk for toxicity after mHFRT. First, the precise cutoff for "large" prostate PTV or prostate volume which portends inferior toxicity after mHFRT is unknown and should be defined in future studies. Second, it is uncertain whether the higher rates of late GU toxicity observed in the LPTV cohort are in excess over that which would be experienced after conventional radiation therapy in the same population. Secondary analyses of previously completed RCTs, using a higher prostate volume cutoff to define "large prostate," may be valuable in identifying whether patients with large prostates are likely to experience differential toxicity with mHFRT compared with CFRT. Finally, strategies to mitigate urinary toxicity after mHFRT are needed for patients with large volume prostates. For example, optimal sequencing/timing of neoadjuvant ADT may allow for effective downsizing in this population and should be the subject of additional investigation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2021.100805.

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