

## Scientific Article

# Gantry-Mounted Linear Accelerator—Based Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer



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## Abstract

**Purpose:** To establish the safety and efficacy of gantry-mounted linear accelerator-based stereotactic body radiation therapy (SBRT) for low- and intermediate-risk prostate cancer.

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**Methods:** We pooled 921 patients enrolled on 7 single-institution prospective phase II trials of gantry-based SBRT from 2006 to 2017. The cumulative incidences of biochemical recurrence (defined by the Phoenix definition) and physician-scored genitourinary (GU) and gastrointestinal (GI) toxicities (defined per the original trials using Common Terminology Criteria for Adverse Events) were estimated using a competing risk framework. Multivariable logistic regression was used to evaluate the relationship between late toxicity and prespecified covariates: biologically effective dose, every other day versus weekly fractionation, intrafractional motion monitoring, and acute toxicity.

**Results:** Median follow-up was 3.1 years (range, 0.5-10.8 years). In addition, 505 (54.8%) patients had low-risk disease, 236 (25.6%) had favorable intermediate-risk disease, and 180 (19.5%) had unfavorable intermediate-risk disease. Intrafractional motion monitoring was performed in 78.0% of patients. The 3-year cumulative incidence of biochemical recurrence was 0.8% (95% confidence interval [CI], 0-1.7%), 2.2% (95% CI, 0-4.3%), and 5.1% (95% CI, 1.0-9.2%) for low-, favorable intermediate-, and unfavorable intermediate-risk disease. Acute grade  $\geq 2$  GU and GI toxicity occurred in 14.5% and 4.6% of patients, respectively. Three-year cumulative incidence estimates of late grade 2 GU and GI toxicity were 4.1% (95% CI, 2.6-5.5%) and 1.3% (95% CI, 0.5-2.1%), respectively, with late grade  $\geq 3$  GU and GI toxicity estimates of 0.7% (95% CI, 0.1-1.3%) and 0.4% (95% CI, 0-0.8%), respectively. The only identified significant predictors of late grade  $\geq 2$  toxicity were acute grade  $\geq 2$  toxicity ( $P < .001$ ) and weekly fractionation ( $P < .01$ ), although only 12.4% of patients were treated weekly.

**Conclusions:** Gantry-based SBRT for prostate cancer is associated with a favorable safety and efficacy profile, despite variable intrafractional motion management techniques. These findings suggest that multiple treatment platforms can be used to safely deliver prostate SBRT.

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## Introduction

Men presenting with low- or intermediate-risk prostate cancer (PCa) as defined by the National Comprehensive Cancer Network (NCCN)<sup>1</sup> have multiple management options available, including radical prostatectomy, definitive radiation therapy, and, in low- and select favorable intermediate-risk disease, active surveillance. Radiotherapeutic modalities include conventionally fractionated radiation therapy, brachytherapy, moderately hypofractionated radiation therapy, and stereotactic body radiation therapy (SBRT). In the latter 2 approaches, doses per fraction of 2.4 to 3.4 Gy or  $>5$  Gy, respectively, are delivered to take radiobiologic advantage of the presumed low  $\alpha/\beta$  ratio of PCa.<sup>2,3</sup>

The NCCN guidelines state that SBRT can be considered at clinics with “appropriate technology, physics, and clinical expertise.”<sup>1</sup> Although “appropriate technology” is not explicitly defined, the majority of large-scale prospective data for prostate SBRT comes predominantly from patients treated using robotic-arm linear accelerators (LINAC).<sup>4,5</sup> A theoretical advantage of this platform is the ability to perform real-time intrafractional motion monitoring.<sup>6</sup> However, other widely available treatment delivery platforms can be used to deliver extremely hypofractionated radiation therapy. Notably, all patients on the randomized HYPO-RT-PC trial, which demonstrated the non-inferiority of a 7-fraction extremely hypofractionated radiation therapy regimen versus conventionally fractionated radiation therapy, were treated on gantry-mounted LINACs.<sup>7</sup> Despite its noninferiority with

respect to conventionally fractionated radiation therapy, the 5-year, late grade  $\geq 3$  genitourinary (GU) and gastrointestinal (GI) toxicity rates on the extreme hypofractionation arm of HYPO-RT-PC are numerically higher than corresponding rates from the recent consortium study of modern SBRT reported by Kishan et al<sup>5</sup> (4.2% vs 1.8% for grade  $\geq 3$  GU and 1.5% vs 0.4% for grade  $\geq 3$  GI).

Although 69% of patients in the Kishan et al consortium study were treated on robotic-arm linear accelerators, between that study and HYPO-RT-PC include the use of narrower planning margins, uniform use of intensity modulated radiation therapy, and much higher rates of intrafractional motion management in the SBRT consortium study. Thus, the lower severe toxicity rates in the consortium study may simply reflect more modern planning and treatment delivery principles. However, as this study pooled patients treated with both gantry-mounted and robotic arm-mounted LINACs, the true toxicity profile of gantry-based prostate SBRT using modern treatment delivery techniques is not as clearly established.

When considering broader scale implementation of modern prostate SBRT, particularly in clinics serving large numbers of diverse patient groups or with limited resources, it is important to identify whether the highly favorable safety and efficacy profile of modern SBRT can be generalized to SBRT delivered with gantry-mounted LINACs as well. We thus evaluated the safety and efficacy of gantry-mounted LINAC SBRT for PCa in a multi-institutional consortium of prospective trials.

## Methods

### Study design and participants

The present study constitutes an institutional review—board approved consortium study with the pre-defined goals of evaluating toxicity and efficacy for prostate SBRT delivered on gantry-mounted LINACs. To generate the consortium, a single author (AUK) performed a systematic literature review by interrogating multiple electronic databases (MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials) as well as the [clinicaltrials.gov](https://clinicaltrials.gov) to identify prospective trials investigating gantry-mounted LINAC-based SBRT. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, and the diagram is included as Fig E1 (available online at <https://doi.org/10.1016/j.adro.2019.09.010>). Invitations to join the consortium were sent to the corresponding authors or principal investigators for these trials. Ultimately, we obtained individual patient-level data from 7 single-institution prospective phase II trials of gantry-based prostate SBRT from 2006 to 2017.<sup>5,8-13</sup>

The site-specific distribution of patients and their treatment characteristics, including dose and prescription specifications, fractionation schedule, margin expansions, image guidance modalities, and toxicity scoring version are displayed in Table 1. Additional details on specific treatment planning parameters and treatment delivery platforms can be found in Table E1 (available online at <https://doi.org/10.1016/j.adro.2019.09.010>).

Data from all 7 trials have been published in some capacity before. Four of the included trials have been previously published with no updated data in the current consortium,<sup>9,10,12,13</sup> although 2 others have been previously published, but the present consortium includes update data from these studies.<sup>8,11</sup> The seventh study contributed patient data to the Kishan et al consortium analysis as well, but the present analysis includes additional patients with prolonged follow-up, and individual patient outcomes from this trial have not been previously reported.<sup>5</sup> Six of the included studies were NCT-registered; the one exception was the prospective study conducted by D'Agostino et al,<sup>13</sup> which was initiated in 2012, at which point it was uncommon for trials from that institution to be registered with [clinicaltrials.gov](https://clinicaltrials.gov).

Patients were stratified into low-, favorable intermediate-, and unfavorable intermediate-risk cohorts, as defined by the NCCN.<sup>1</sup> Deidentified data were shared in concordance with the Health Insurance Portability and Accountability Act, with each institutional review board

approving contribution of its data to the coordinating data center (University of California, Los Angeles).

Details of the treatment planning methods are described in Table E1 (available online at <https://doi.org/10.1016/j.adro.2019.09.010>).

### Endpoints

The cumulative incidence of biochemical recurrence (BCR) was the primary measure of efficacy. Biochemical relapse was defined as PSA rise  $>2$  ng/mL above the nadir value per the Phoenix definition.<sup>14</sup> Secondary efficacy measures included the cumulative incidence of distant metastases (DM), biochemical recurrence-free survival (BCRFS), and overall survival (OS). Physician-scored toxicities were defined per the original trial criteria, focusing on genitourinary (GU) and gastrointestinal (GI) toxicity. Toxicity scoring criteria were based on common terminology criteria for adverse events (CTCAE) version 3.0<sup>15</sup> or version 4.0<sup>16</sup> (Table E2, available online at <https://doi.org/10.1016/j.adro.2019.09.010>). Initiation of medical therapy for urinary symptoms such as urinary hesitancy was considered a grade 2 toxicity per CTCAE version 3.0 and version 4.0. Acute toxicity was defined as an adverse event occurring within the first 90 days after completion of SBRT.

### Statistical analyses

Kaplan-Meier methods were used to obtain 3-year survival estimates of BCRFS and OS, with time to event measured from the final day of SBRT. Kaplan-Meier curves were truncated when there were fewer than 10 subjects at risk. Three-year cumulative incidence estimates of BCR and DM were obtained using a competing risk framework (with death as a competing risk).<sup>17</sup> Due to a low rate of BCR across risk groups, eligible fits from Fine-Gray and Cox proportional hazards models could not be obtained to assess for predictive covariates. Multivariable logistic regression models using predictive variables specified a priori were used to analyze the association between late grade  $\geq 2$  GU and GI toxicity and biologically effective dose (BED), fractionation (every other day vs weekly), intrafractional motion monitoring, and acute composite grade  $\geq 2$  toxicity. Multivariable predictive modeling was conducted in accordance with the guidelines for Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis.<sup>18</sup> To minimize residual ecological bias, the within-trial correlations were addressed via random effects in the logistic regression models. Analyses were completed using R version 3.5.2<sup>19</sup> using significance level 0.05.

**Table 1** Individual prospective study characteristics

NCT identifier	Institution or trial	No. of patients	Dose/fraction	Margins	Prescription specification	Intrafraction motion monitoring?	Image guidance	Fractionation	Original toxicity scoring
NCT02339948	21st Century Oncology <sup>8</sup>	413	8 Gy × 5	2 mm isotropic expansion from prostate	100% of rx to cover 98% of PTV	Yes	Real-time tracking of implanted electromagnetic beacons	Every other day	CTCAE v3.0
NCT01578902	Sunnybrook pHART 3 <sup>9</sup>	84	7 Gy × 5	4 mm isotropic expansion from prostate	95% of rx to cover 99% of PTV	No	Orthogonal imaging to implanted fiducial markers before treatment	Once a week	CTCAE v3.0
NCT01146340	Sunnybrook pHART 6 <sup>10</sup>	30	8 Gy × 5	5 mm isotropic expansion from prostate	95% of rx to cover 99% of PTV	No	Orthogonal imaging to implanted fiducial markers before treatment	Once a week	CTCAE v3.0
NCT01059513	University of California, Los Angeles <sup>5</sup>	245	8 Gy × 5	5 mm expansion from prostate, except 3 mm posteriorly	100% of rx to cover 95% of PTV	Yes	Cone beam CT before treatment; Orthogonal imaging to implanted fiducial markers before and 3 times during treatment.	Every other day	CTCAE v4.0
NCT01664130	Cleveland Clinic Foundation <sup>11</sup>	35	7.25 Gy × 5*	3 mm expansion from prostate, except 0 mm posteriorly	100% of rx to cover 95% of PTV*	Yes	Triggered imaging every 30° with a 2 mm threshold	Every other day	CTCAE v3.0
NCT01581749	Lankenau <sup>12</sup>	25	7.25 Gy × 5	3 mm isotropic expansion from prostate	100% of rx to cover 95% of PTV	Yes	Cone beam CT to align to fiducials with Brainlab monitoring every 15 seconds	Every other day	CTCAE v3.0
PMID 27389021 <sup>†</sup>	Humanitas <sup>13</sup>	89	7 Gy × 5	3-5 mm isotropic expansion from prostate, including proximal 1/3 seminal vesicles in some cases	95% of rx to cover 95% of PTV	No	Cone beam CT before treatment, with alignment to implanted fiducial markers	Every other day	CTCAE v4.0
<b>Total</b>		<b>921</b>							

Abbreviations: CTCAE v3.0 or v4.0, common terminology criteria for adverse events; NCT, national clinical trial; PMID, PubMed Identification; PTV, planning target volume; rx, prescription dose.

\* Sixty-five percent of patients treated at this institution received a simultaneous integrated boost plan wherein tissues within the prostate but >5 mm away from rectum, bladder, and urethra received 50 Gy in 5 fractions, although the rest of the prostate received 7.25 Gy × 5. For the remaining 35% of patients, the 90% isodose line for 36.25 Gy covered the prostate PTV.

<sup>†</sup> At the time this study was initiated, it was uncommon for trials from that institution to be registered with [clinicaltrials.gov](http://clinicaltrials.gov).

**Table 2** Patient and treatment characteristics

Characteristic	Value (N = 921)
Follow-up, mean (median) [range], y	3.6 (3.1) [0.5-10.8]
Age, mean (median) [range], y	67.6 (68) [41-87]
Risk group	
Low risk	505 (54.8%)
Favorable intermediate risk	236 (25.6%)
Unfavorable intermediate risk*	180 (19.5%)
Gleason Grade Group	
I	571 (62.0%)
II	263 (28.6%)
III	87 (9.4%)
Clinical T stage	
T1c	614 (66.7%)
T2a	247 (26.8%)
T2b	58 (6.30%)
T2c	2 (0.2%)
Initial PSA, mean (median) [range], ng/mL	6.6 (6) [0.3-19.9]
BED	
≥200 Gy	748 (81.2%)
<200 Gy	173 (18.8%)
Fractionation	
Every other day	807 (87.6%)
Weekly	114 (12.4%)
Intrafractional motion monitoring	
Yes	718 (78.0%)
No	203 (22.0%)
Method of intrafractional motion monitoring	
Orthogonal imaging to gold fiducials	305 (42.5%)
Electromagnetic beacons	413 (57.5%)
Androgen deprivation therapy use	
Total	20 (2.2%)
Low risk	1 (5.0%)
Favorable intermediate risk	6 (30.0%)
Unfavorable intermediate risk	13 (65.0%)
Duration of androgen deprivation therapy, mean (median) [range], months	8.8 (6) [3-30.5]

Abbreviations: BED, biologically effective dose; PSA, prostate specific antigen.

\* Percentage of positive cores was not available for 127 of the patients currently classified as having favorable intermediate-risk disease (53.5%); these patients were classified conservatively as having favorable intermediate-risk disease.

## Results

A total of 921 patients were included. Patient and treatment characteristics are presented in Table 2. In the study, 505 (54.8%) patients had low-risk disease, 236 (25.6%) had favorable intermediate-risk disease, and 180 (19.5%) had unfavorable intermediate-risk disease. Overall, 20 (2.2%) men received concurrent ADT.

Assuming an  $\alpha/\beta$  ratio of 1.5 Gy,<sup>2,3</sup> 81.2% of patients received a biologically effective dose of  $\geq 200$ , and 87.6% received treatment every other day. All patients were treated with image guidance, either solely interfractional imaging at initial set-up (22.0%) or with additional intrafractional motion monitoring (78.0%).

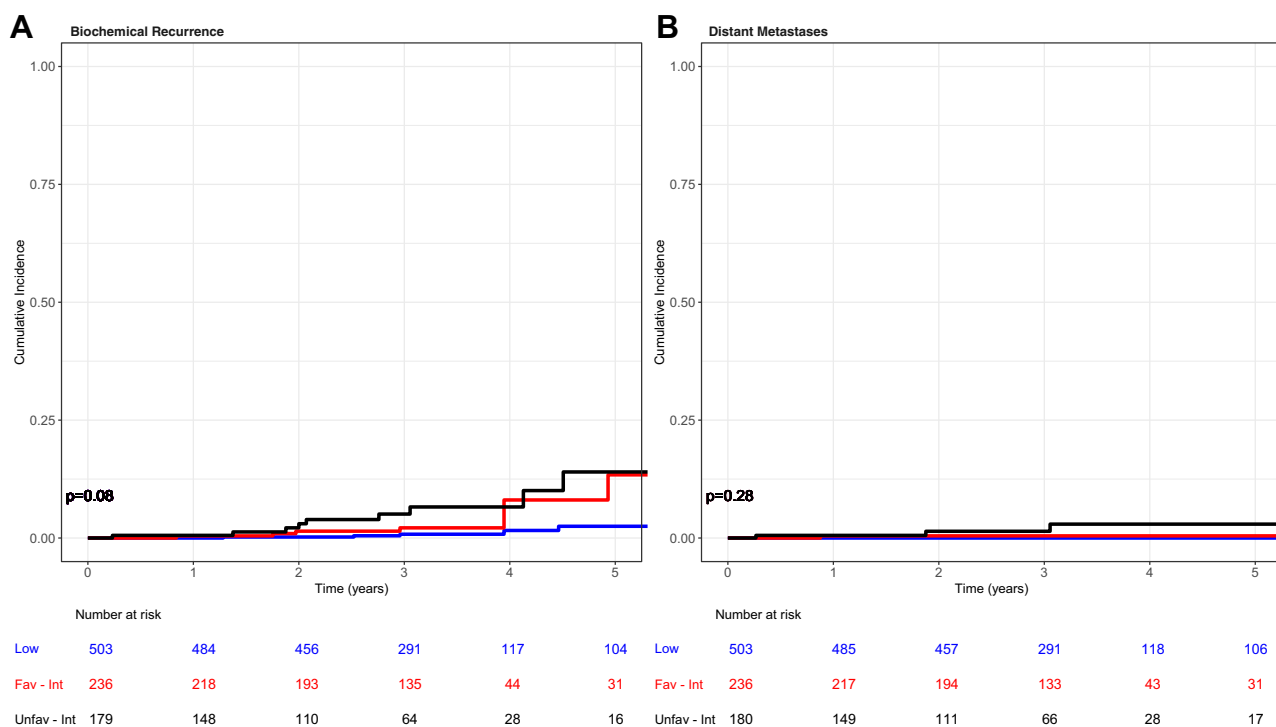
## Efficacy

The median follow-up period was 3.1 years (range, 0.5-10.8 years). Cumulative incidence plots of BCR and DM are shown in Fig 1. Corresponding survival and rate estimates are presented in Table E3 (available online at <https://doi.org/10.1016/j.adro.2019.09.010>). A total of 14 patients with low-risk disease developed BCR, with a 3-year cumulative incidence of 0.8% (95% confidence interval [CI], 0-1.7%). One patient with low-risk disease developed DM. Among patients with favorable intermediate-risk disease, 9 developed BCR and 1 developed DM, with 3-year cumulative incidence rates of 2.2% (95% CI, 0-4.3%) and 0.5% (95% CI, 0%-1.3%), respectively. Among patients with unfavorable intermediate-risk disease, 10 developed BCR and 3 developed DM, with 3-year cumulative incidence rates of 5.1% (95% CI, 1.0-9.2%) and 1.4% (95% CI, 0-3.4%), respectively. At the time of analysis, there were 154, 89, and 24 patients available for analysis at 5, 7, and 10 years, respectively.

## Acute and late toxicity

Crude rates and cumulative incidence estimates of acute and late grade 2 and grade  $\geq 3$  GU and GI toxicities are shown in Tables 3 and 4. Narrative descriptions of grade  $\geq 3$  toxicities are provided in Table E4 (available online at <https://doi.org/10.1016/j.adro.2019.09.010>).

Acute grade 2 GU and GI toxicity occurred in 123 (13.3%) and 39 (4.2%) patients, respectively. Eleven patients (1.2%) experienced acute grade  $\geq 3$  GU toxicity, and 3 patients (0.3%) experienced acute grade  $\geq 3$  GI toxicity. The 3-year cumulative incidence rates of late grade 2 GU and GI toxicity were 4.1% (95% CI, 2.6-5.5%) and 1.3% (95% CI, 0.5-2.1%), respectively. Seven patients (0.8%) experienced late grade 3 GU toxicity and 3 patients (0.3%) experienced late grade 3 GI toxicities. A patient with a history of diverticulitis had late grade 4 GI toxicity due to a spontaneous fistula in ano 9 months after SBRT. One patient experienced late grade 4 GU and GI toxicities; this patient had a 290 mL prostate and developed a necrotizing soft tissue infection requiring prostatectomy, colostomy, and placement of a suprapubic catheter 25 months after SBRT. Overall, 3-year cumulative incidence estimates of late grade  $\geq 3$  GU and GI toxicities were 0.7% (95% CI, 0.1-1.3%) and 0.4% (95% CI, 0-0.8%), respectively.



**Figure 1** Cumulative incidence plots for risk of (A) biochemical recurrence and (B) distant metastasis for low-risk, intermediate-risk, and unfavorable intermediate-risk prostate cancer treated with gantry-mounted linear accelerator–based prostate stereotactic body radiation therapy.

The crude rate of late grade  $\geq 2$  GU or GI toxicity among those not receiving intrafractional motion monitoring was 19% (38 out of 203), versus 8% (57 out of 718) among those receiving intrafractional motion monitoring (2-tailed  $\chi^2$  test  $P < .0001$ ). However, on multivariable logistic regression, omitting intrafractional motion monitoring was not associated with late severe toxicity (OR 1.87, 95% CI 0.3-10.3,  $P = .47$ ; Table 5).

On multivariable logistic regression, the only significant predictors for late composite GI or GU grade  $\geq 2$  toxicity were prior acute grade  $\geq 2$  GI or GU toxicity (odds ratio [OR] 4.53, 95% CI, 2.7-7.6,  $P < .001$ ) and weekly fractionation, which was associated with higher late grade  $\geq 2$  toxicity compared with every other day fractionation (OR 0.1; 95% CI, 0.03-0.6), although

substantially fewer patients (12.4%) were treated weekly (Table 5).

### Discussion

In this multi-institutional pooled analysis of 7 prospective phase II trials of gantry-mounted LINAC-based SBRT for low- and intermediate-risk PCa, gantry-based treatment demonstrated excellent safety and efficacy outcomes. Three-year BCR rates were less than 1% for low-risk disease and approximated 5% for unfavorable intermediate-risk disease. Acute and late severe toxicities were rare, with 3-year cumulative incidence rates of 0.7% or less for late grade  $\geq 3$  GU or GI toxicities, and omission of intrafractional motion monitoring was not

**Table 3** Crude incidence of acute and late composite CTCAE v3.0 to 4.0\* toxicity

	Grade 2	Grade 3	Grade 4
Acute GU	123 (13.3%)	10 (1.1%)	1 (0.1%)
Acute GI	39 (4.2%)	2 (0.2%)	1 (0.1%)
Late GU	63 (6.8%)	7 (0.8%)	1 (0.1%)
Late GI	28 (3.0%)	3 (0.3%)	2 (0.2%)

Abbreviations: CTCAE v3.0 or v4.0, common terminology criteria for adverse events; GI, gastrointestinal; GU, genitourinary.

\* Toxicity scoring derived per institutional or clinical trial protocol, as described in the Methods.

**Table 4** Cumulative incidence estimates of late gastrointestinal and genitourinary toxicity

	3-year rate (95% CI)
Late grade 2 GI	1.3% (0.5-2.1%)
Late grade 2 GU	4.1% (2.6-5.5%)
Late grade $\geq 3$ GI	0.4% (0-0.8%)
Late grade $\geq 3$ GU	0.7% (0.1-1.3%)

Abbreviations: CI, confidence interval; GI, gastrointestinal; GU, genitourinary.

**Table 5** Multivariable logistic regression for predictors of late composite CTCAE grade  $\geq 2$  toxicity

Parameter	Odds ratio (95% CI)	P value
BED	1.01 (0.99-1.03)	.30
Fractionation (every other day vs weekly)	0.12 (0.03-0.56)	<.01
Acute composite CTCAE grade $\geq 2$ toxicity	4.53 (2.70-7.60)	<.001
Intrafractional motion monitoring	1.87 (0.34-10.27)	.47

Abbreviations: BED, biologically effective dose; CTCAE, common terminology criteria for adverse events.

predictive of late severe toxicity. These findings are important because much of the published evidence for prostate SBRT draws from patients treated with robotic-arm LINACs, which offer real-time intrafractional motion monitoring to help offset the expected 3- to 5-mm prostatic motion during treatment.<sup>4,5,20</sup> However, anchoring prostate SBRT to a single highly specialized platform could cause significant logistical impediments to widespread adoption of this treatment modality. This is particularly true in multipurpose clinics and resource-poor settings, an important consideration given the global burden imposed by PCa.<sup>20</sup> Thus, the ability to safely and effectively deliver prostate SBRT using gantry-based techniques may have significant effect on utilization rates.

The present results compare favorably with prior reports on prostate SBRT, including those in a recent consortium study by Kishan et al that included 2142 patients, 69% of whom were treated with a robotic-arm LINAC,<sup>5</sup> and a recent meta-analysis of 6116 patients, many of whom were treated on modern prospective trials.<sup>21</sup> In these studies, the cumulative incidences of late grade  $\geq 3$  GU and GI toxicity were 1.7% and 0.4%,<sup>5</sup> and 2.0 and 1.1%,<sup>21</sup> respectively. These studies, as well as the present analysis, all report quantitatively lower severe toxicity rates than the recently published HYPO-RT-PC randomized trial, which studied a 7-fraction regimen (6.1 Gy  $\times$  7).<sup>7</sup> In that study, only 20% of patients had IMRT plans, margins were as large as 7 mm isotropically in 90% of patients, and no intrafractional monitoring was performed; late grade  $\geq 3$  GU and GI toxicity rates were 4.2% and 1.5%. When comparing the SBRT consortium studies (the present study and the Kishan study) and meta-analysis with HYPO-RT-PC, the results suggest that modern planning may allow substantially lower rates of serious adverse toxicity with extreme hypofractionation. Specifically comparing the 2 SBRT consortium studies with each other suggests that real-time intrafractional

monitoring is not required to produce low rates of serious toxicity, provided that modern planning practices are used.

An unexpected finding in our study was the relationship between weekly fractionation and increased late grade  $\geq 2$  toxicity, which contrasts with a recent phase II trial reporting lower toxicity rates with weekly treatment. In that study, fractionation was only significantly associated with acute, but not late, GU and GI toxicity.<sup>22</sup> Within our consortium, the 2 trials that used weekly fractionation were 2 of the relatively older studies, and although the differences in treatment planning and delivery were small, they did not necessarily use the same margins, motion monitoring, planning parameters, and quality assurance protocols that have been used in the more recent studies. It is possible that the summation of these factors contributed to the finding. Additionally, the number of patients treated weekly was proportionally quite small.

This report has several limitations. Although this is a consortium of prospective studies, all were single arm, and therefore susceptible to selection bias. Although we attempted to control for ecologic bias by including the specific trial in our logistic regression analysis as a random effect, this method of adjustment would likely not have entirely accounted for differences in treatment planning and delivery that might otherwise confound analyses related to use of intrafraction monitoring and toxicity. Although our results suggest that variable intrafractional motion management may not be critical for successful prostate SBRT and acceptable outcomes can be obtained even with just interfractional motion management, this conclusion is limited by short follow-up and an overall low number of patients treated without any intrafractional motion management. Specifically, only 203 patients did not have intrafraction monitoring, and in this subgroup, only 38 patients experienced this degree of toxicity. The relatively small difference (11%) in the crude incidence of late grade  $\geq 2$  toxicity between patients who did versus did not receive intrafractional monitoring, relative to our sample size of patients, could explain our finding. Thus, although on multivariable logistic regression we did not identify an association between the use of intrafractional monitoring and grade  $\geq 2$  toxicity, the analyses simply may not have been powered to do so. Given the low numbers of failures and toxic events, we were also not able to evaluate predictors of BCR or the relationship between margins and outcomes. Finally, patient-reported outcomes were not available.

In summary, gantry-mounted prostate SBRT seems to be safe and effective in a multi-institutional setting. Thus, prostate SBRT need not be anchored to any particular treatment platform.

## Supplementary Data

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2019.09.010>.

## References

- Mohler JL, Hurwitz M, Richey S. Prostate Cancer version 3.2019. *J Natl Compr Canc Netw*. 2019;1:1-164.
- Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys*. 1999;43:1095-1101.
- Dasu A, Toma-Dasu I. Prostate alpha/beta revisited—An analysis of clinical results from 14 168 patients. *Acta Oncol Stockh Swed*. 2012; 51:963-974.
- King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol*. 2013;109:217-221.
- Kishan AU, Dang A, Katz AJ, et al. Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. *JAMA Netw Open*. 2019;2. e188006-e188006.
- Avkshtol V, Dong Y, Hayes SB, et al. A comparison of robotic arm versus gantry linear accelerator stereotactic body radiation therapy for prostate cancer. *Res Rep Urol*. 2016;8:145-158.
- Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet*. 2019;394:385-395.
- Mantz C. A phase II trial of stereotactic ablative body radiotherapy for low-risk prostate cancer using a non-robotic linear accelerator and real-time target tracking: Report of toxicity, quality of life, and disease control outcomes with 5-year minimum follow-up. *Front Oncol*. 2014;4:279.
- Loblaw A, Cheung P, D'Alimonte L, et al. Prostate stereotactic ablative body radiotherapy using a standard linear accelerator: Toxicity, biochemical, and pathological outcomes. *Radiother Oncol*. 2013;107:153-158.
- Quon HC, Musunuru HB, Cheung P, et al. Dose-escalated stereotactic body radiation therapy for prostate cancer: Quality-of-life comparison of two prospective trials. *Front Oncol*. 2016;6.
- Kotecha R, Djemil T, Tendulkar RD, et al. Dose-escalated stereotactic body radiation therapy for patients with intermediate- and high-risk prostate cancer: Initial dosimetry analysis and patient outcomes. *Int J Radiat Oncol Biol Phys*. 2016;95:960-964.
- DeNittis A, Wang Y, Orisamolu A, Ravella S, Gasalberti D, Wang D. A phase II experience evaluating quality of life and survival in Linac-based SBRT for prostate cancer. *J Radiat Oncol*. 2016;5:445-451.
- D'Agostino G, Franzese C, De Rose F, et al. High-quality Linac-based stereotactic body radiation therapy with flattening filter free beams and volumetric modulated arc therapy for low-intermediate risk prostate cancer. A mono-institutional experience with 90 patients. *Clin Oncol*. 2016;28:e173-e178.
- Roach M, Hanks G, Thames H, 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.
- National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Published August 9, 2006. Available at: [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf). Accessed April 18, 2019.
- National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Published May 28, 2009 (v4.03: June 14, 2010). Available at: [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03/CTCAE\\_4.03\\_2010-06-14\\_Quick\\_Reference\\_5x7.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_Quick_Reference_5x7.pdf). Accessed April 18, 2019.
- Dignam JJ, Kochevsky MN. Choice and interpretation of statistical tests used when competing risks are present. *J Clin Oncol*. 2008;26:4027-4034.
- Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD statement. *Ann Intern Med*. 2015;162:55-63.
- R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.
- Koike Y, Sumida I, Mizuno H, et al. Dosimetric impact of intra-fraction prostate motion under a tumour-tracking system in hypofractionated robotic radiosurgery. *PLoS ONE*. 2018;13:e0195296.
- Soerjomataram I, Lortet-tieulent J, Parkin DM, et al. Global burden of cancer in 2008: A systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet*. 2012;380:1840-1850.
- Jackson WC, Silva J, Hartman HE, et al. Stereotactic body radiation therapy for localized prostate cancer: A systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *Int J Radiat Oncol Biol Phys*. 2019;104:778-789.