Received: 9 October 2023 | Accepted: 25 December 2023

DOI: 10.1002/cdt3.114

Chronic Diseases® and Translational Medicine

ORIGINAL ARTICLE

# Adaptive ultra-hypofractionated whole-pelvic radiotherapy in high-risk and very high-risk prostate cancer on 1.5-Tesla MR-Linac: Estimated delivered dose and early toxicity results

**Linrui Gao**[1] | **Ran Wei**[1] | **Shirui Qin**[1] | **Yuan Tian**[1] | **Wenlong Xia**[1] | **Yongwen Song**[1] | **Shulian Wang**[1] | **Hui Fang**[1] | **Yu Tang**[2] | **Hao Jing**[1] | **Yueping Liu**[1] | **Yuan Tang**[1] | **Shunan Qi**[1] | **Bo Chen**[1] | **Yexiong Li**[1] | **Nianzeng Xing**[3] | **Ningning Lu**[1]

[1]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2]GCP Center/Clinical Research Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[3]Department of Urology, State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**Correspondence**

Ningning Lu, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.
Email: Ning-Ning.Lu@hotmail.com

Nianzeng Xing, Department of Urology and State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.
Email: xingnianzeng@126.com

## Abstract

**Background:** Magnetic resonance (MR)-guided ultra-hypofractionated radiotherapy with whole-pelvic irradiation (UHF-WPRT) is a novel approach to radiotherapy for patients with high-risk (HR) and very high-risk (VHR) prostate cancer (PCa). However, the inherent complexity of adaptive UHF-WPRT might inevitably result in longer on-couch time. We aimed to estimate the delivered dose, study the feasibility and safety of adaptive UHF-WPRT on a 1.5-Tesla MR-Linac.

**Methods:** Ten patients with clinical stage T3a-4N0-1M0-1c PCa, who consecutively received UHF-WPRT, were enrolled prospectively. The contours of the target and organ-at-risks on the position verification-MR (PV-MR), beam-on 3D-MR(Bn-MR), and post-MR (after radiotherapy delivery) were derived from the pre-MR data by deformable image registration. The physician then manually adjusted them, and dose recalculation was performed accordingly. GraphPad Prism 9 (GraphPad Prism Software Inc.) was utilized for conducting statistical analyses.

**Results:** In total, we collected 188 MR scans (50 pre-MR, 50 PV-MR, 44 Bn-MR, and 44 post-MR scans). With median 59 min, the mean prostate clinical target volume (CTV)-$V_{100\%}$ was 98.59% ± 2.74%, and the mean pelvic CTVp-$V_{100\%}$ relative percentages of all scans was 99.60% ± 1.18%. The median $V_{29\ Gy}$ change in the rectal wall was −2% (−18% to 20%). With a median follow-up of 9 months, no patient had acute Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or more severe genitourinary (GU) or gastrointestinal (GI) toxicities (0%).

**Conclusion:** UHF-RT to the prostate and the whole pelvis with concomitant boost to positive nodes using an Adapt-To-Shape (ATS) workflow was technically feasible for patients with HR and VHR PCa, presenting only mild GU and GI toxicities. The estimated target dose

Linrui Gao and Ran Wei contributed equally to this study.

**Funding information**
Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences, Longevity and Health Project, Grant/Award Number: 2021-JKCS-003

during the beam-on phase was clinically acceptable based on the 3D-MR–based dosimetry analysis.
**Clinical trial registration:** Chinese Clinical Trial Registry ChiCTR2000033382.

**KEYWORDS**
dosimetry, hypofractionation, magnetic resonance imaging, prostate cancer, radiation dose, radiotherapy

**Highlights**

- Ultra-hypofractionated radiotherapy to the prostate and the whole pelvis with concomitant boost to positive nodes and bone oligo-metastases with Adapt-To-Shape workflow was technically feasible for prostate cancer patients, with only mild genitourinary and gastrointestinal toxicities.
- A slight decrease but reliable dose coverage of the prostate, pelvis, and metastatic lymph nodes during the beam-on period was observed.
- The 3-mm clinical target volume-planning target volume margin applied seemed to be sufficient for the prostate and pelvis but might be inadequate for seminal vesicles in a small percentage of patients.

## 1 | INTRODUCTION

External beam radiotherapy combined with androgen deprivation therapy is the recommended radical treatment for high-risk (HR) and very-high-risk (VHR) prostate cancer (PCa).[1–3] The inclusion of prophylactic radiotherapy (RT) of pelvic lymph nodes in patients without regional pelvic nodal involvement has been debated for decades due to lack of evidence of survival benefits. While whole-pelvic radiotherapy (WPRT) provides superior outcomes compared to prostate-only radiotherapy (PORT) for HR, locally advanced PCa RT was effective in treating regional PCa[4,5] or low metastatic burden, castration-sensitive diseases.[3,6]

Ultra-hypofractionated RT (UHF-RT), completed within 1–2 weeks, has been successful in patients with localized PCa.[7,8] In contrast, data on the role of UHF-RT in HR and VHR PCa are scarce. A recent study, which included 102 h PCa patients (81 patients had regional nodal involvement), showed a low overall incidence and clinical acceptability of severe adverse effects with pelvic UHF-RT (25 Gy in five fractions) compared to PORT.[9] These data demonstrate that UHF-RT with simultaneous WPRT provides a novel RT treatment schema for HR and VHR PCa; however, this also places higher demands on the precision and accuracy required during the clinical implementation of RT.

Poon et al.[10] conducted a study utilizing UHF-RT with simultaneous WPRT in HR PCa on a 1.5-T MR-Linac and observed infrequent RT-related toxicities and good patient-reported outcomes. However, the complexity of adaptive UHF-RT with WPRT will inevitably lead to longer on-couch time, highlighting the potential dose uncertainty raised by most researchers.[11,12] Currently, there is limited data available on the delivered dose of UHF-WPRT using adaptive magnetic resonance (MR)-guided radiotherapy (MRgRT). Hence, in the present study, we aimed to explore the feasibility and safety of patients with HR and very high-risk (VHR) PCa treated with adaptive UHF-WPRT on a 1.5-T MR-Linac, and to quantitatively analyze the dose metrics of targets and OARs based on 3D-MR acquisitions, including pre-, position verification (PV-), beam-on (Bn-), and post-3D-MR scans with high-resolution, of all adaptive RT fractions. Unlike the previous study on PORT,[13] the patients in this cohort received whole pelvis RT along with a concomitant boost to positive nodes. This approach not only increases the complexity of RT planning but also extends the on-couch time, which poses a significant challenge for the implementation of clinical precision RT on a 1.5-T MR-Linac.

## 2 | METHODS

### 2.1 | Patient eligibility

A prospective research study has been conducted to examine the viability, tolerance, and profiles of toxicity in patients with pathologically confirmed localized or oligo-metastatic PCa who received UHF-RT on a 1.5-T MR-Linac since 2019. The research protocol has received approval from the Independent Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, registered as NCT05183074/ChiCTR2000033382. MRI, chest-abdomen-pelvis CT scan, and/or prostate-specific membrane antigen positron emission tomography scans were used to define nodal or distant metastases. The risk groups were classified according to the National Comprehensive Cancer Network v.1.2019 edition. Data pertaining to clinical characteristics and dosimetry were gathered

from a cohort of 10 patients with HR and VHR PCa w/o positive pelvic node or bone oligo-metastases. The oligo-metastases were defined as fewer than four bone metastases in the whole body without visceral or distant lymph node metastases.[14]

## 2.2 | Target volume delineation and reference plan

Patient preparation and simulation images acquired for contouring were consistent with a published study.[13] The definition of clinical target volume (CTV), PTV, and CTV 40 were defined according to the outlined criteria.[13] The pelvic nodal CTV (CTVp) was contoured starting at L4–5 junction to include bilateral common iliac, external iliac, internal iliac, presacral, and obturator nodes as per guidelines by Radiation Therapy Oncology Group.[15] The PTVp was uniformly expanded by CTVp plus 3 mm. Positive regional lymph nodes were contoured as gross tumor volume (GTV)-N. The primary gross tumor volume (PGTV)-N was determined as PGTV-N plus isotropic 3 mm margin. The 3-mm–inner rings of the bladder and rectum were designated as the boundaries for the bladder and rectal walls, respectively.

The PTV received a dose of every-other-day 7.25 Gy per fraction for five fractions in total, with a simultaneous boost of total 40 Gy to the whole prostate. Additionally, a dose of 25 Gy was administered to PTVp, with a concurrent boost of 35 Gy to metastatic regional nodes, throughout a treatment period spanning 10–12 days. If mandatory bowel dose constraints were not met, 95% PTVp receiving 23.75 Gy (95% prescription dose) and 95% PGTV-N receiving 33.25 Gy (95% prescription dose) were also accepted.

Supporting Information: Table S1 presents the dose prescriptions of target volume and constraints for OARs in this study. A reference plan was optimized as per these constraints by the Monaco planning system (v5.40; Elekta AB).

## 2.3 | Patient follow-up and toxicity evaluation

Patients were followed up regularly since enrollment, at the beginning date of MRgRT; at 1 and 2 weeks during the RT; and 2, 4, 6, 8, and 12 weeks and every 3 months afterwards. Gastrointestinal (GI) and genitourinary (GU) symptoms were scored using the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. per study protocol, and patients would continue to be followed up until 5 years after treatment to assess treatment-related adverse effects. Biochemical recurrence, local recurrence, and distant metastases were also assessed.

Before the referral for MRgRT, one patient had received tamsulosin, and another patient had received solifenacin succinate (Vesicare®, Astellas); no prophylactic tamsulosin or Vesicare® was prescribed. Prophylactic rectal lavage was performed with mucosal protector every other day during radiotherapy (Supporting Information: Table S2).

## 2.4 | Online ATS workflow, image acquisition, fusion, and re-planning on each MR scan for dose calculation

The image acquisition procedure and online ATS workflow were the same as introduced in a published study, including pre-, PV-, Bn-, and post-MR scans of every adaptive fraction.[13] In each treatment session, an initial T2-weighted 3D (pre-MR) scan was obtained after patient setup. The pre-MR data were then aligned with the simulation CT or pre-MR image of the last session using rigid registration techniques. Subsequently, the contours on the pre-MR image underwent automatic deformation to align with the anatomical structures, then manual adjustments were made by the physician if necessary.

The online adaptive plan was then re-optimized using the Monaco system. Before finalizing the plan re-optimization, a PV-MR scan was conducted. The ATS plan was deemed acceptable only if the CTV stayed inside the PTV on the PV scan and there was no ventral movement of the rectum. Otherwise, another Adapt-To-Position (ATP) or ATS workflow should be started. During beam-on period, real-time 2D cine MR was collected continuously. In cases where all the organs maintained a stable position, the monitoring with 2D cine MR was discontinued, and a Bn-MR T2-weighted 3D sequence scan was collected. Immediately after the completion of RT delivery, a post-MR scan with same sequence was conducted. The process of image registration and propagation of anatomical contours formed the basis of image fusion and re-planning methods employed for dose calculation on each MR scan. This facilitated the transfer of the specified targets and organs at risk (OARs) from the initial ATS plan to the corresponding PV-, Bn-, and post-MR scans. Subsequently, plan re-optimization was conducted, and the dosimetry assessment was done for all adapted regions of interest (ROIs). To ensure the accuracy and consistency of ROIs delineation and RT re-planning on each scan, a senior radiation oncologist and a physicist verified these processes.

## 2.5 | Statistical analysis

GraphPad Prism 9 (GraphPad Prism Software Inc.) was utilized for conducting statistical analyses. We calculated the mean ± standard deviation (SD), median (range), 95% confidence interval (CI) for continuous variables, or frequency with percentage based on their distribution.

## 3 | RESULTS

Patients' ($N = 10$) baseline characteristics are shown in Supporting Information: Table S2. The median follow-up was 9 (3–15) months, and all patients were followed up for more than 3 months. Early toxicities scored by clinicians according to the CTCAE criteria are shown in Table 1. No patient had acute CTCAE grade 2 or more severe GU or GI toxicities (0%).

A total of 188 high-resolution 1.5-T MRIs were included in the dosimetry analysis, derived from 50 fractions of 10 consecutive patients. This data set comprised 50 pre-, 50 PV-, 44 Bn-, and 44 post-MR scans. Because of the observation of rectal gas bubbles, the continuous 2D cine MR was adopted in four sessions, thus four Beam-on 3D-MR scans were missing involving four patients. Owing to a system breakdown, two Bn-scans and two post-scans were lost; these were changed to ATP workflow. For two fractions of two patients, no post-MR scans were collected due to excessively full bladders. Additionally, the remaining two post-scans were not successfully transmitted to the Monaco system. In Figure 1, an illustrative example presents the isodose lines on different MR scans after re-planning.

The median time duration of all fractions was 59 (43–77) min, with time for contour adaptation and plan re-optimization around 10 min and 20 min, respectively (Supporting Information: Figure S1). The reference ATS plans had 12 (9–15) beams, with 88 (77–100) segments and 3777.05 (2766.70–6034.90) monitor units for the 10 patients (Supporting Information: Table S3). Supporting Information: Table S4 provides the volumes of the target and OARs, along with the volume differences compared with the corresponding ATS plan delivered clinically. The volume differences between prostate and CTV were all below 3.0 cc, suggesting consistent and accurate contouring of the targets across each fraction.

Supporting Information: Figure S2 displays the target dose metrics of all fractions which were evaluated by analyzing the daily ATS plan dose on scans of different phases. A minor underdosing of SVs (Figure 2 C1) was the primary cause for the lower CTV-$V_{100\%}$ ($V_{36.25Gy}$). Figure 2 illustrates the $V_{95\%}$ of CTV, prostate, and the SVs (Figure 2 A2–C2). The prostate-$V_{95\%}$ ($V_{34.4Gy}$) was lower than 95% on only one scan (94% of PV-MRI). Among the eight scans (six fractions of four patients) on which the SV-$V_{34.4Gy}$ (SVs-$V_{95\%}$) was lower than 95%, the

**TABLE 1** Clinician-reported early toxicity.

| | | Radiotherapy | | After radiotherapy | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Toxicities** | **Baseline** | **1-Week** | **2-Week** | **2-Week** | **4-Week** | **6-Week** | **8-Week** | **12-Week** | **6-Month** | **9-Month** | **12-Month** |
| ***Grade 1**** | | | | | | | | | | | |
| Fatigue | 1 | 2 | 4 | 5 | 2 | 1 | 2 | 3 | 1 | 0 | 0 |
| Urinary frequency | 2 | 3 | 4 | 3 | 5 | 2 | 2 | 2 | 1 | 0 | 0 |
| Urinary urgency | 1 | 4 | 5 | 3 | 3 | 0 | 0 | 0 | 1 | 1 | 1 |
| Urinary pain | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hematuresis | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Uracratia | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Uroschesis | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cystitis | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea/Proctitis/ Rectal Pain | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Radiodermatitis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Weight loss | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Leukopenia | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neutropenia | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemoglobin | 2 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Thrombocytopenia | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Elevated bilirubin | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Elevated creatinine | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

*Note*: No patient was observed with acute CTCAE grade 2 or more severe GU or GI toxicities.

*The toxicities were classified according to Common Terminology Criteria for Adverse Events criteria (NCI-CTCAE 5.0).

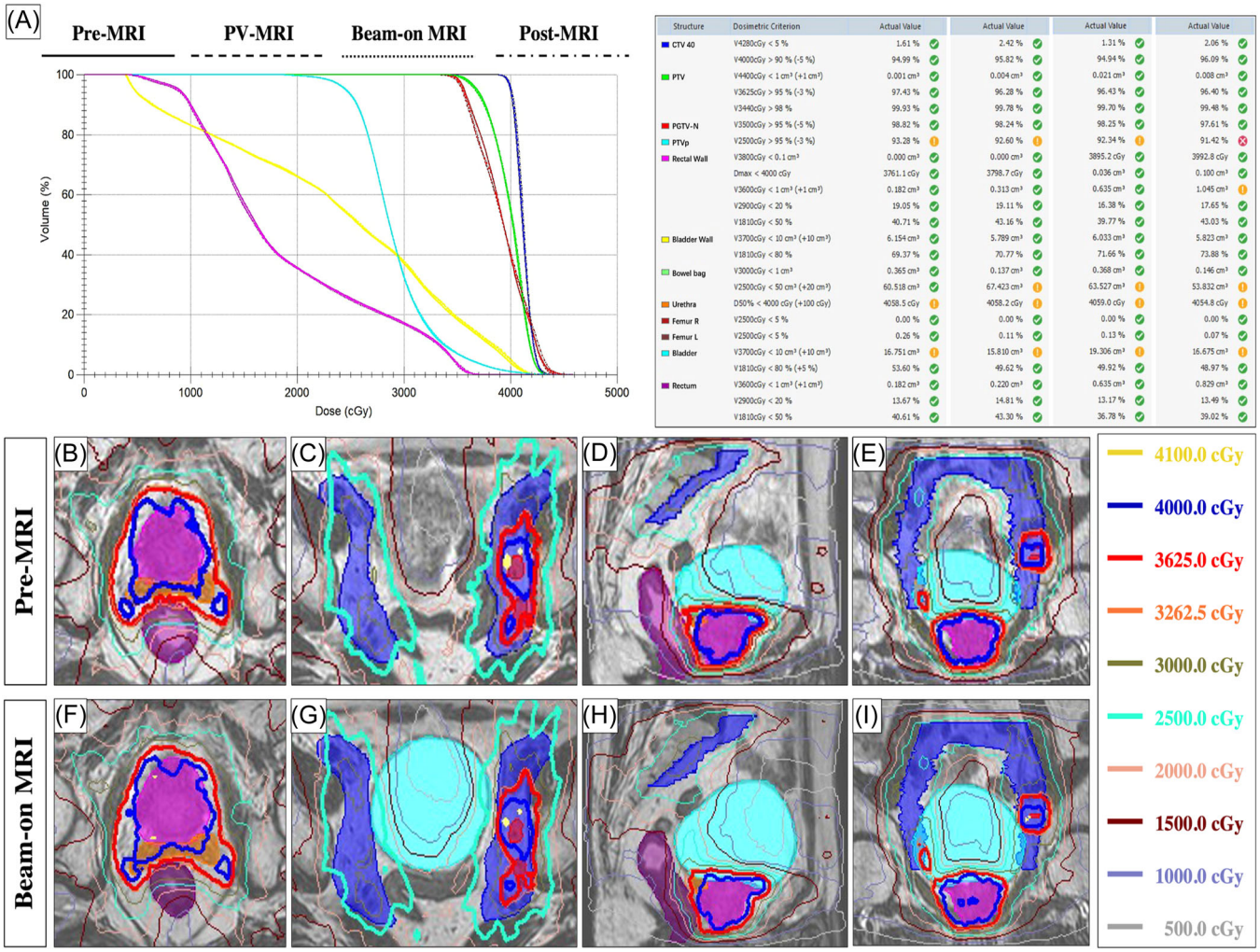


**FIGURE 1** The dose distributions on each MRI scan. (A) A representative DVH plot with four plans and dose metrics on each MRI scan after re-planning in one fraction. (B–I) Representative dose distributions of the prostate and pelvic of the ATS plan on Pre-MR (B–E) and Beam-on MR scan (F–I). ATS, Adapt-To-Shape; MRI, magnetic resonance imaging.

SV-$V_{34.4Gy}$ was less than 90% on four scans (PV-MRI: 1, Bn-MRI: 1, post-MRI: 2).

In contrast with the ATS plan, the mean CTVp-$V_{100\%}$ relative percentage of all scans was 98.56% ± 2.41%, and those of the PV-MR, Bn-MR, and post-MR phases were 99.13% ± 1.54%, 98.70% ± 2.55%, and 97.76% ± 2.88%, respectively (Figure 2 D1). Among the 14 scans on which the CTVp-$V_{100\%}$ relative percentage was less than 95%, the relative CTVp-$V_{100\%}$ was between 90% and 95% on 7.1% (12/168) scans and 85% and 90% on 1.2% (2/168) scans (Figure 2 D1). The relative CTVp-$V_{95\%}$ of two scans was 94%, which was less than 95% (Figure 2 D2). In addition, the mean PGTV-N-$V_{95\%}$ (56 scans) for nodal diseases was 99.05% ± 2.41% (Figure S2B).

The $D_{95\%}$ values of CTV, prostate, SVs, CTVp, and GTV-N (Figure 3A–E) were summed up for each patient across five fractions. This summation was performed separately for scans in different phases. Only one patient's sum of CTV-$D_{95\%}$ of the Beam-on period (36.17 Gy) was slightly lower than the prescribed dose (36.25 Gy; Figure 3A). The sum of prostate-$D_{95\%}$ values for each MR scan exceeded the prescribed dose of 36.25 Gy for all 10 patients (Figure 3B). Though the sum of SVs-$D_{95\%}$, CTVp-$D_{95\%}$, and GTV-N $D_{95\%}$ on each MR scan varied above or below the 100% prescription dose, all of them reached the 95% prescription dose. The sum of $D_{99\%}$ of targets was also evaluated (Supporting Information: Figure S3). Compared to the ATS plan, there was a decrease of 1.0 Gy ± 1.5 Gy (2.2% ± 3.4%) in prostate-$D_{99\%}$ and a decrease of 0.9 Gy ± 1.7 Gy (3.1% ± 4.6%) in CTVp-$D_{99\%}$.

The rectum volumes displayed variations throughout the entire workflow. The mean variations were 1.04, 1.76, and 0.53 cc on the PV-MR, Bn-MR, and post-MR scans, respectively (Supporting Information: Table S4). Additionally, the estimated delivered dose to the rectum wall exhibited variations throughout treatment, with a mean

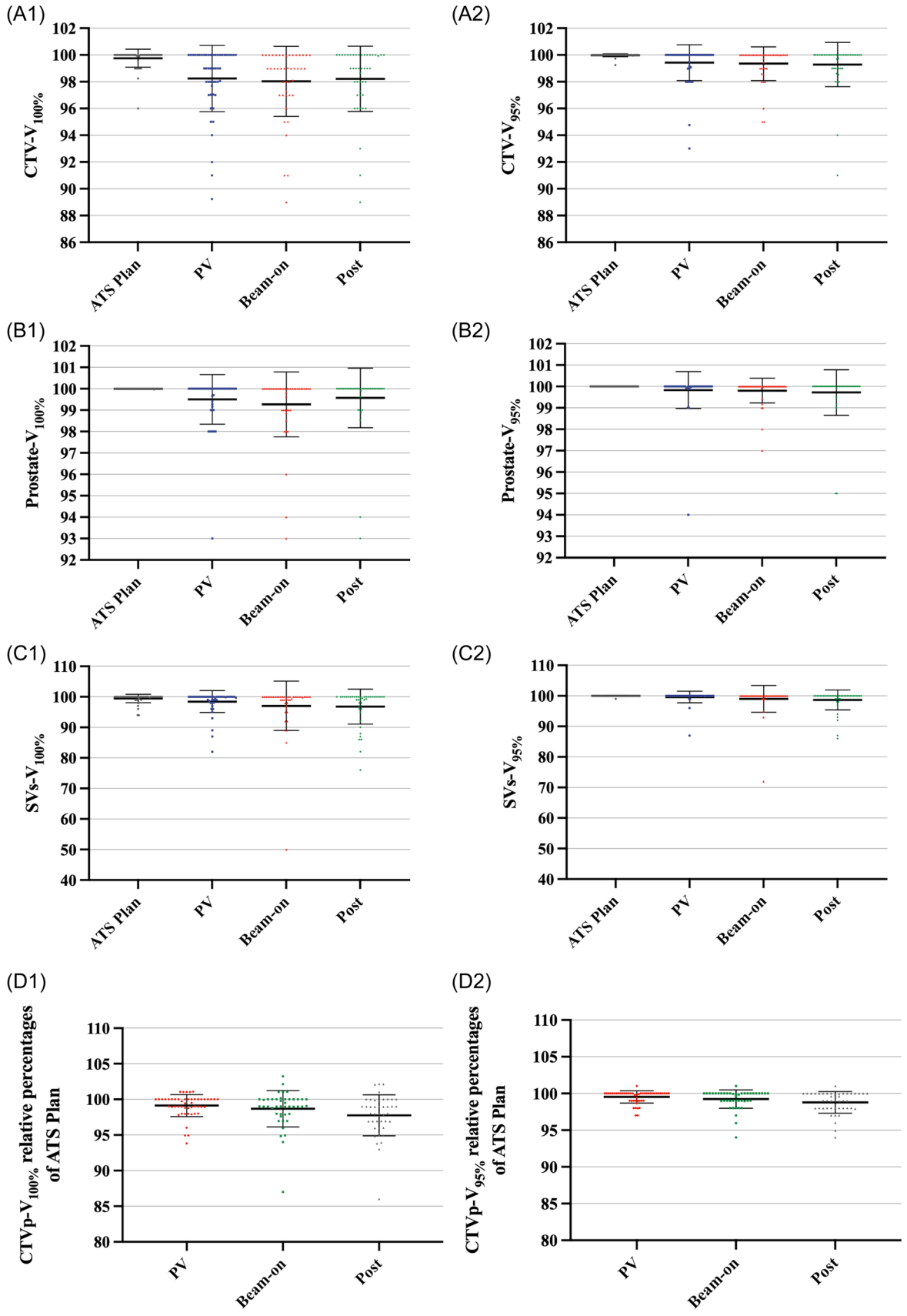


**FIGURE 2** Boxplot of $V_{100\%}$ and $V_{95\%}$ values to the CTV (A1, A2), Prostate (B1, B2), and SVs (C1, C2) calculated by the daily ATS plan dose on the PV-, Bn- and post-MR scan for each session and patient. The $V_{100\%}$ relative percentage of ATS plan for CTVp (D1, D2) on the PV-, Bn- and post-MR scan. Individual data points are shown as dots. The mean ± SD values are shown as error bars. ATS, Adapt-To-Shape; CTV, clinical target volume; MRI, magnetic resonance imaging; SD, standard deviation.

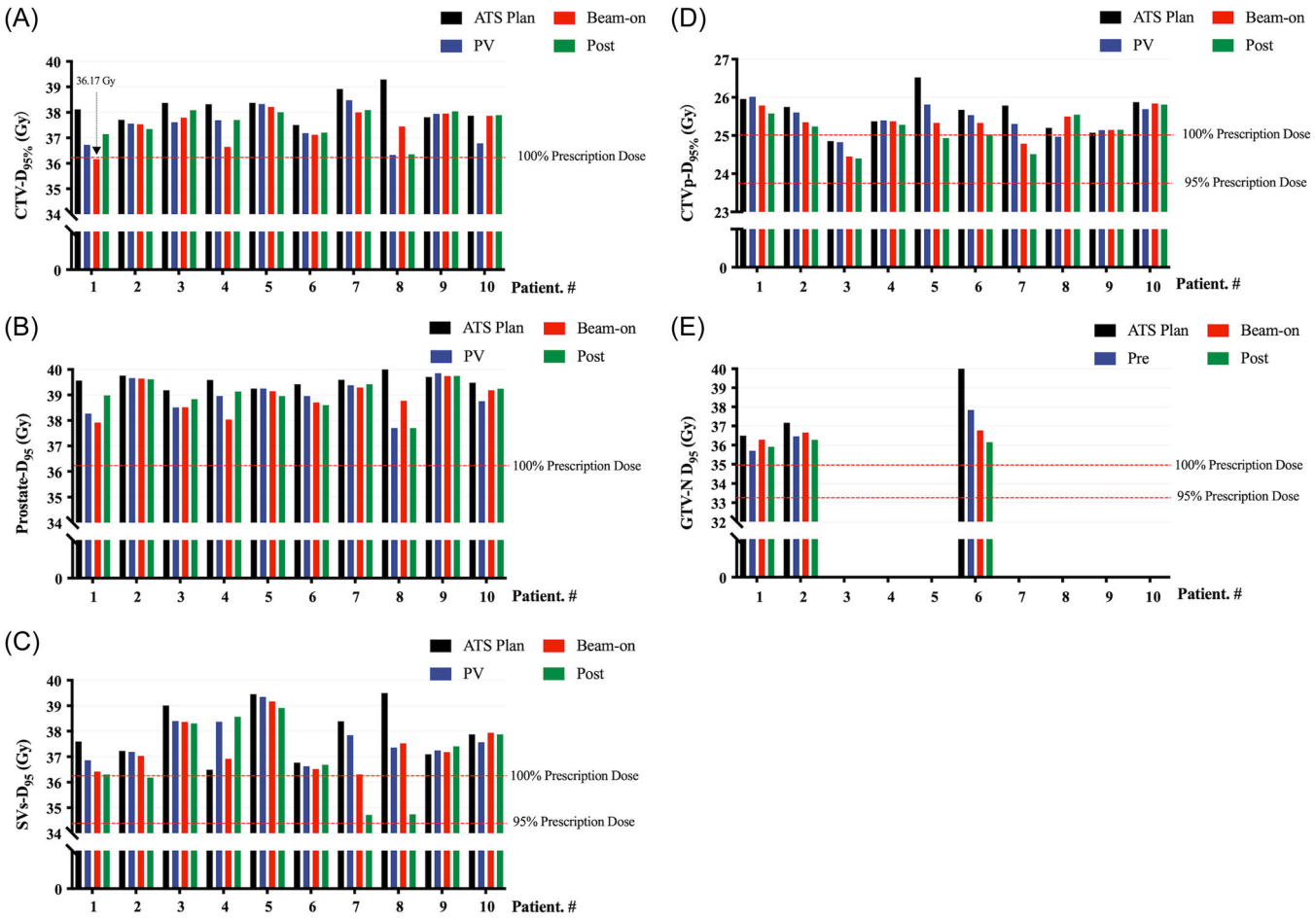


**FIGURE 3** Per-patient $D_{95\%}$ values to the CTV (A), Prostate (B), SVs (C), CTVp (D), GTV-N, and (E), summed by five fractions of pre- (ATS plan), PV-, Bn- and post-MR scans. No lymph nodes irradiation for Patients #3 to #5 and #7 to #10. ATS, Adapt-To-Shape; CTV, clinical target volume; GTV, gross tumor volume; MRI, magnetic resonance imaging; SV, seminal vesicle.

difference $V_{38Gy}$ of 0.12 ± 0.44 cc on PV-MR, 0.30 ± 0.69 cc on Bn-MR, and 0.44 ± 0.78 cc on post-MR, and a mean variation $V_{36Gy}$ of −0.07 ± 0.96 cc on PV-MR, 0.13 ± 1.19 cc on Bn-MR, and 0.56 ± 1.26 cc on post-MR, respectively. Figure 4A and B present the changes in $V_{29Gy}$ and $V_{18.1Gy}$ of the rectum wall compared with the ATS plans. The median changes for $V_{29Gy}$ and $V_{18.1Gy}$ were −2% (−18% to 20%) and 1% (−14% to 22%), respectively. Only one scan showed an increase of >15% in $V_{29Gy}$ of the rectal wall (1/188, 0.5%). While an increase of >15% in $V_{18.1Gy}$ was observed in 0 of the PV-MR, 2.3% (1/44) of the Bn-MR, and 6.8% (3/44) of the post-MR (Figure 4B).

With volume increases as time passes, the mean variations in bladder volume in different phases was 88.82, 132.82, and 161.98 cc. Hence, the high dose that delivered to the bladder volume gradually increased. The mean $V_{37Gy}$ was 3.86 ± 1.63 cc in the ATS plan, 4.51 ± 2.24 cc in PV-MR, 4.71 ± 2.31 cc in Bn-MR, and 4.90 ± 2.67 cc in post-MR phases. A $V_{18.1Gy}$ increase of 10% was observed in eight scans (8/168, 4.8%), while an increase of >5% was only observed in 10.0% (5/50), 11.4% (5/44), and 11.4% (5/44) of the PV-, Bn- and post-MR scans, respectively. No larger increase of bladder wall V18.1 Gy was observed on any scan (Figure 4C). Furthermore, the dose metrics of bowel bags and other OARs are summarized in Table 2.

## 4 | DISCUSSION

The current study represents the initial evaluation on the delivered dose to targets and OARs in adaptive UHF-WPRT for HR and VHR PCa, utilizing high-resolution 3D MRIs on a 1.5 T MR-Linac. Although an extended on-couch time was observed, we noted technical feasibility, as well as very mild GU and GI toxicities. The dosimetry analysis indicated clinically favorable estimated dose coverages of almost all the targets except the SVs during the beam-on period. Again, the application of a 3-mm uniform CTV-PTV margin appeared to be inadequate for some SVs, but can meet clinical requirements for both the prostate and pelvis.

The first study on MR-guided UHF-RT with concomitant WPRT showed encouraging results of feasible

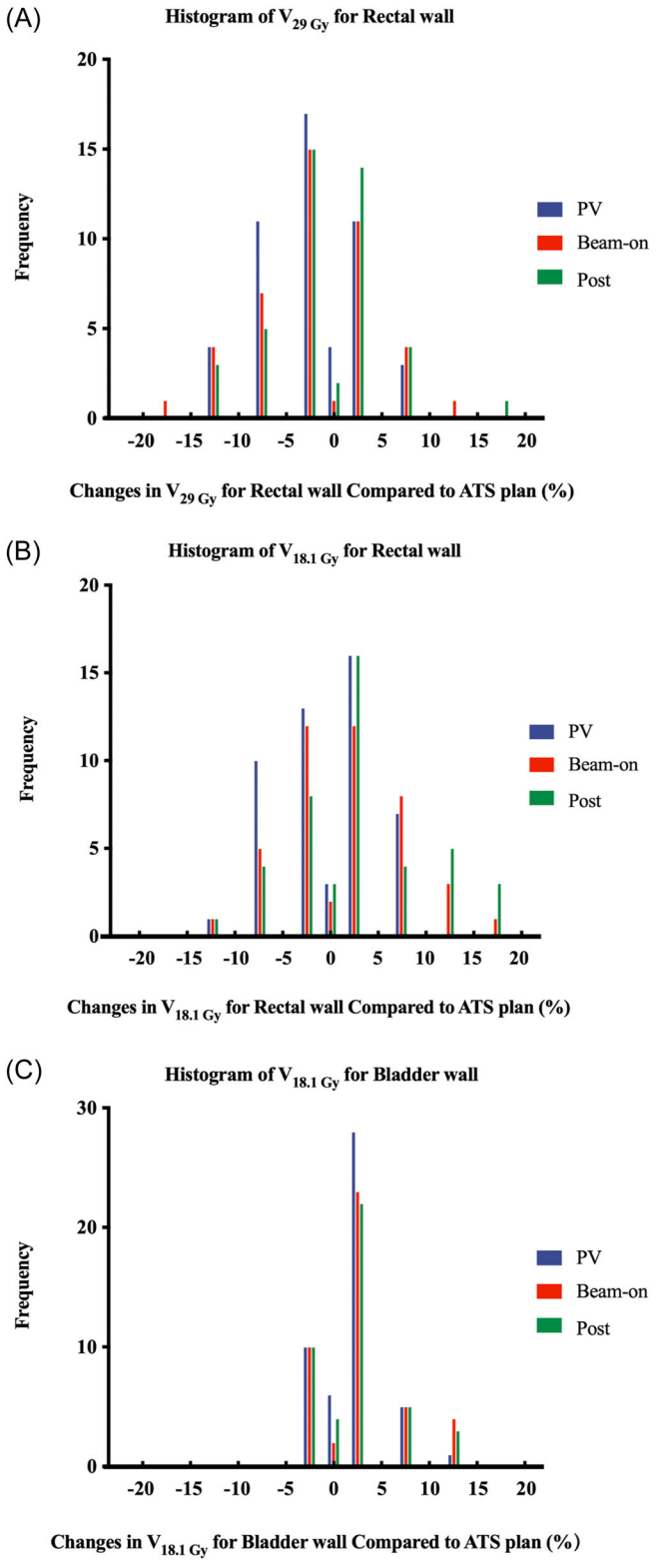


**FIGURE 4** Histogram of changes in volume receiving 29 Gy (A, $V_{29\ Gy}$) or 18.1 Gy (B, $V_{18.1\ Gy}$) dose for the rectal wall and 18.1 Gy (C) dose ($V_{18.1\ Gy}$) for the bladder wall among PV-, Bn- and post-MR scans compared to ATS plans. ATS, Adapt-To-Shape; PV, position verification.

clinical implementation and favorable treatment-related toxicities.[10] However, this study solely included HR-PCa patients with N0M0 stage.[10] In contrast, our study explored the feasibility of MRgRT in more complex patients with positive nodes ($N = 3$). Although the contouring and planning are more complicated with a larger field, more ROIs, and plenty of optimization parameters, which consequently lead to longer on-couch time, our cohort demonstrated technical feasibility of implementing this workflow.

Since adaptive RT with MR-Linac was introduced in clinical use, dose inaccuracy owing to long on-couch time has remained a concern. Compared with a median of 49 min for patients treated with PORT,[13] the on-couch time for patients with WPRT was longer, with a median of 59 (48–77) minutes. We also observed a slight CTV dose reduction with time (a 2.2% ± 3.4% decrease in CTV-$D_{99\%}$). This result was not worse than other studies using beam-on 2D-cine MR (a 1.1 ± 1.6 Gy decrease of CTV-$D_{98\%}$)[16] or cine MR dynamics (a 2.2% ± 2.9% decrease of CTV-$D_{99\%}$),[17] indicating that the prostate motion reached plateau after approximately 30 min.[12] Furthermore, we also first evaluated the estimated dose at the pelvis and positive nodes. Striking a balance between planning coverage, organ-at-risk (OAR) protection, and plan optimization time during online adaptation can indeed be challenging, especially when dealing with complex targets and varying boost doses. Nevertheless, the estimated CTVp-$V_{95\%}$ (98.56% ± 2.41%) on each scan in our study was clinical feasibility.

Though a 3-mm margin for PTV appears to provide adequate coverage for the prostate, with $V_{36.25Gy} \geq 95\%$ observed in 97.3% (183/188) scans (Figure 2 B1), this margin is not applicable for SVs. Similar to the results in the PORT-only study,[13] intra-fractional SV motion is a general problem and the main reason for CTV underdose. We expanded the margin from 3 mm to 5 mm for the latter three patients but found better dose coverage of SVs in only one for two patients. Further data and analysis are needed to verify the appropriate margin for optimal SVs' coverage.

The extended radiotherapy field in UHF-WPRT inevitably leads to a larger area under irradiation; hence, the estimated delivered dose to the rectal and bladder walls was higher than PORT. Compared with the data of PORT-only study,[13] which reported no fraction of the rectal wall $V_{18.1Gy}$ increased by >15%, UHF-WPRT resulted in $V_{18.1Gy}$ increase of >15% ($V_{18.1Gy}$ range between 65% and 75%) on four scans of three fractions for two patients (Bn-MRI: 1 and post-MRI: 3; Figure 4A,B). In addition, the estimated delivered dose to the bladder wall, including $V_{37Gy}$ and $V_{18.1Gy}$ also gradually increased with time, but remained clinically acceptable. The lower RT-related GI or GU toxicities

**TABLE 2** Dosimetry parameters for the delivered ATS plan and re-computed plans on PV-MR, beam-on MR, and post-MR scans.

| Dose metrics<br>Target coverage | | ATS plan | PV | Beam-on | Post |
|---|---|---|---|---|---|
| CTV4000 | | | | | |
| | $V_{100\%\ (40\ Gy)}$ | 93.16 ± 3.50 | 89.36 ± 6.30 | 88.92 ± 7.36 | 90.02 ± 5.47 |
| | $V_{95\%\ (38\ Gy)}$ | 100.00 ± 0 | 98.76 ± 2.60 | 98.70 ± 3.02 | 99.25 ± 1.54 |
| PTV | | | | | |
| | $V_{100\%\ (36.25Gy)}$ | 94.92 ± 2.04 | 90.84 ± 4.46 | 90.13 ± 4.68 | 90.06 ± 4.40 |
| | $V_{95\%\ (34.4\ Gy)}$ | 98.98 ± 1.11 | 96.01 ± 3.72 | 95.50 ± 3.77 | 95.41 ± 3.68 |
| PTVp | | | | | |
| | $V_{100\%\ (25\ Gy)}$ | 93.33 ± 4.98 | 91.88 ± 4.80 | 91.32 ± 5.31 | 90.30 ± 5.74 |
| | $V_{95\%\ (23.75\ Gy)}$ | 97.94 ± 2.02 | 96.85 ± 2.36 | 96.37 ± 2.76 | 95.71 ± 3.18 |
| PGTV-N* | | | | | |
| | $V_{100\%}$ | 98.67 ± 1.91 | 95.53 ± 4.12 | 93.38 ± 4.82 | 91.62 ± 7.93 |
| | $V_{95\%}$ | 100.00 ± 0 | 98.93 ± 2.60 | 99.23 ± 1.17 | 97.92 ± 3.84 |
| **OAR metrics** | | | | | |
| Rectal wall | | | | | |
| | $D_{max}$ | 38.92 ± 0.87 | 38.25 ± 2.11 | 38.91 ± 2.10 | 39.42 ± 2.16 |
| | $V_{38\ Gy}$ (cc) | 0.07 ± 0.08 | 0.19 ± 0.45 | 0.38 ± 0.72 | 0.51 ± 0.79 |
| | $V_{36\ Gy}$ (cc) | 0.81 ± 0.45 | 0.76 ± 0.98 | 0.98 ± 1.17 | 1.36 ± 1.27 |
| | $V_{29\ Gy}$ | 17.28 ± 3.57 | 14.49 ± 6.72 | 14.85 ± 7.05 | 16.40 ± 7.72 |
| | $V_{18.1\ Gy}$ | 44.59 ± 9.45 | 44.37 ± 12.62 | 45.42 ± 12.64 | 47.63 ± 13.95 |
| Bladder wall | | | | | |
| | $V_{37Gy}$ (cc) | 3.86 ± 1.63 | 4.51 ± 2.24 | 4.71 ± 2.31 | 4.90 ± 2.67 |
| | $V_{18.1\ Gy}$ | 63.60 ± 8.25 | 65.51 ± 8.64 | 66.67 ± 8.58 | 66.41 ± 8.80 |
| Bowel bag | $D_{max}$ | 30.22 ± 1.41 | 30.78 ± 1.50 | 30.91 ± 1.64 | 30.92 ± 1.60 |
| | $V_{30\ Gy}$ (cc) | 0.36 ± 0.48 | 0.38 ± 0.49 | 0.36 ± 0.49 | 0.32 ± 0.47 |
| | $V_{25\ Gy}$ (cc) | 32.06 ± 17.18 | 33.56 ± 19.07 | 34.28 ± 19.23 | 33.48 ± 19.15 |
| Femur L | $V_{25\ Gy}$ | 2.32 ± 6.56 | 2.28 ± 6.56 | 1.59 ± 5.58 | 1.64 ± 5.79 |
| Femur R | $V_{25\ Gy}$ | 0.06 ± 0.24 | 0.02 ± 0.14 | 0.05 ± 0.21 | 0 |

Abbreviations: ATS, Adapt-To-Shape; CTV, clinical target volume; OAR, organs at risk; PGTV primary gross tumor volume; PTV, planning target volume; PV, position verification.

*There were three patients with positive lymph nodes. Data are presented as mean ± standard deviation.

with online adaptive UHF-RT further support the notion that a slightly increased dose at the rectal and bladder walls will not cause clinically significant toxicities.

In contrast to the results of UHF-WPRT studies with X-ray-based image-guidance (Grade ≥2 GI: 0–29.4%; Grade ≥2 GU: 3.0%–46.7%),[18–21] in our study, no patients had grade ≥ 2 GU or GI toxicities. The main reason for this finding could be the small sample size. Second, online plan adaptation may also have contributed to this favorable toxicity profile, as another preliminary outcome that used 1.5 Tesla MR Linac also reported low adverse events (Grade 2 GI: 2.4%; Grade 2 GU: 7.1%).[10] Finally, all patients were recommended to take Vesicare®[22] when Grade 1 toxicity occurred, and since RT initiation to completion, prophylactic rectal lavage with Recombinant Human SOD was recommended, both of which could have relieved patients' symptoms.

This study has some limitations. The relatively long acquisition time of 3D-MR images, coupled with low temporal resolution of MR datasets and data collection at specific time points could potentially introduce dose inaccuracy and reduce temporal accuracy compared to continuous cine-MR dynamics.[12,17] Nevertheless, we attempted to mitigate these limitations by collecting

dosimetric data from different phases' scans, providing comprehensive information on dose changes in various organs, including the prostate, seminal vesicles (SVs), lymph nodes, and pelvis. The utilization of high-resolution, large-field-of-view 3D MR images offers notable advantages in this regard. Furthermore, we only enrolled 10 patients and the follow-up time was not sufficiently long to report toxicities, which may affect the generalizability of the findings. In addition, the complexity of the workflow required higher demands on physicians and physicists and caused longer on-couch time. Consequently, this radiotherapy paradigm may be more suitable for patients with good performance status and better urinary continence, as they can better tolerate the extended treatment sessions.

## 5 | CONCLUSION

This prospective study demonstrated the technical feasibility of UHF-RT to the prostate and pelvis with simultaneous boost to positive pelvic nodes with ATS workflow for patients with HR and VHR PCa, with only mild GU and GI toxicities. Despite a much longer on-couch time, the estimated target dose coverage was clinically satisfactory during radiotherapy delivery. It is important to note that probably 5-mm CTV-PTV margin also could not provide satisfying coverage for a small subset of SVs. These findings warrant further multicenter clinical trials with larger patient cohorts.

### AUTHOR CONTRIBUTIONS

Ningning Lu, Nianzeng Xing, Yexiong Li, Linrui Gao, and Ran Wei designed the study. Linrui Gao and Ran Wei analyzed the data and made the figures. Ningning Lu and Linrui Gao wrote the manuscript. Ningning Lu, Yexiong Li, and Nianzeng Xing contributed to the study coordination; all authors contributed to data collection and interpretation, and finally approved the manuscript.

### ACKNOWLEDGMENTS

This work was supported by the Non-profit Central Research Institute Fund of the Chinese Academy of Medical Sciences, Longevity and Health Project, 2021-JKCS-003. The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of this manuscript.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Professor Nianzeng Xing and Ningning Lu are members of Chronic Diseases and Translational Medicine editorial board and are not involved in the peer review and decision process of this article. Part of this work was selected to be presented as poster discussion at the ASTRO meeting, San Diego, California, USA, October 1–4, 2023.

### DATA AVAILABILITY STATEMENT

The corresponding author has full access to all the data in the study and final responsibility for the decision to submit for publication. The data that support the findings of this study are available from H6WORLD platform (https://h6world.cn/signin) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of H6WORLD platform.

### ETHICS STATEMENT

The research protocol has received approval from the Independent Ethics Committee of the Chinese Academy of Medical Sciences, registered as NCT05183074/ChiCTR2000033382.

### ORCID

*Linrui Gao* https://orcid.org/0000-0003-2730-7910

### REFERENCES

1. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*. 2011;378(9809):2104-2111. doi:10.1016/S0140-6736(11)61095-7
2. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010;11(11):1066-1073. doi:10.1016/S1470-2045(10)70223-0
3. Network NCC. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer, Version 1, 2023.
4. Murthy V, Maitre P, Kannan S, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. *J Clin Oncol*. 2021;39(11):1234-1242. doi:10.1200/JCO.20.03282
5. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018;392(10162):2353-2366. doi:10.1016/S0140-6736(18)32486-3
6. Kishan AU, Ma TM, Lamb JM, et al. Magnetic resonance imaging-guided vs computed tomography-guided stereotactic body radiotherapy for prostate cancer: the MIRAGE randomized clinical trial. *JAMA Oncol*. 2023;9(3):365-373. doi:10.1001/jamaoncol.2022.6558
7. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531-1543. doi:10.1016/S1470-2045(19)30569-8
8. 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(10196):385-395. doi:10.1016/S0140-6736(19)31131-6
9. Murthy V, Adsul K, Maitre P, et al. Acute and late adverse effects of prostate-only or pelvic stereotactic radiation therapy in prostate cancer: a comparative study. *Int J Radiat Oncol Biol Phys*. 2022;114(2):275-282. doi:10.1016/j.ijrobp.2022.05.050

10. Poon DMC, Yuan J, Yang B, et al. A prospective study of stereotactic body radiotherapy (SBRT) with concomitant whole-pelvic radiotherapy (WPRT) for high-risk localized prostate cancer patients using 1.5 tesla magnetic resonance guidance: the preliminary clinical outcome. *Cancers*. 2022;14(14):3484. doi:10.3390/cancers14143484
11. Murray J, Tree AC. Prostate cancer - advantages and disadvantages of MR-guided RT. *Clin Transl Radiat Oncol*. 2019;18:68-73. doi:10.1016/j.ctro.2019.03.006
12. de Muinck Keizer DM, Kerkmeijer LGW, Willigenburg T, et al. Prostate intrafraction motion during the preparation and delivery of MR-guided radiotherapy sessions on a 1.5T MR-Linac. *Radiother Oncol*. 2020;151:88-94. doi:10.1016/j.radonc.2020.06.044
13. Gao LR, Tian Y, Wang MS, et al. Assessment of delivered dose in prostate cancer patients treated with ultra-hypofractionated radiotherapy on 1.5-Tesla MR-Linac. *Front Oncol*. 2023;13:1039901. doi:10.3389/fonc.2023.1039901
14. Stevens DJ, Sooriakumaran P. Oligometastatic prostate cancer. *Curr Treat Options Oncol*. 2016;17(12):62. doi:10.1007/s11864-016-0439-8
15. Lawton CAF, Michalski J, El-Naqa I, et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2009;74(2):383-387. doi:10.1016/j.ijrobp.2008.08.002
16. Menten MJ, Mohajer JK, Nilawar R, et al. Automatic reconstruction of the delivered dose of the day using MR-linac treatment log files and online MR imaging. *Radiother Oncol*. 2020;145:88-94. doi:10.1016/j.radonc.2019.12.010
17. Kontaxis C, de Muinck Keizer DM, Kerkmeijer LGW, et al. Delivered dose quantification in prostate radiotherapy using online 3D cine imaging and treatment log files on a combined 1.5T magnetic resonance imaging and linear accelerator system. *Phys Imag Radiat Oncol*. 2020;15:23-29. doi:10.1016/j.phro.2020.06.005
18. Bauman G, Ferguson M, Lock M, et al. A phase 1/2 trial of brief androgen suppression and stereotactic radiation therapy (FASTR) for high-risk prostate cancer. *Int J Rad Oncol Biol Phys*. 2015;92(4):856-862. doi:10.1016/j.ijrobp.2015.02.046
19. Murthy V, Gupta M, Mulye G, et al. Early results of extreme hypofractionation using stereotactic body radiation therapy for high-risk, very high-risk and node-positive prostate cancer. *Clin Oncol*. 2018;30(7):442-447. doi:10.1016/j.clon.2018.03.004
20. Musunuru HB, D'Alimonte L, Davidson M, et al. Phase 1-2 study of stereotactic ablative radiotherapy including regional lymph node irradiation in patients with High-Risk prostate cancer (Saturn): early toxicity and quality of life. *Int J Radiat Oncol Biol Phys*. 2018;102(5):1438-1447. doi:10.1016/j.ijrobp.2018.07.2005
21. Pinitpatcharalert A, Happersett L, Kollmeier M, et al. Early tolerance outcomes of stereotactic hypofractionated accelerated radiation therapy concomitant with pelvic node irradiation in high-risk prostate cancer. *Adv Radiat Oncol*. 2019;4(2):337-344. doi:10.1016/j.adro.2018.12.001
22. Ohtake A, Sato S, Sasamata M, Miyata K. The forefront for novel therapeutic agents based on the pathophysiology of lower urinary tract dysfunction: ameliorative effect of solifenacin succinate (Vesicare), a bladder-selective antimuscarinic agent, on overactive bladder symptoms, especially urgency episodes. *J Pharmacol Sci*. 2010;112(2):135-141. doi:10.1254/jphs.09r13fm

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Gao L, Wei R, Qin S, et al. Adaptive ultra-hypofractionated whole-pelvic radiotherapy in high-risk and very high-risk prostate cancer on 1.5-Tesla MR-Linac: estimated delivered dose and early toxicity results. *Chronic Dis Transl Med*. 2024;10:51-61. doi:10.1002/cdt3.114