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Scientific Article

Ultrahypofractionated Radiation Therapy for Prostate Cancer Including Seminal Vesicles in the Target Volume: A Treatment-planning Study Based on the HYPO-RT-PC Fractionation Schedule

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Purpose: Ultrahypofractionated (UHF) radiation therapy (RT) has become a treatment alternative for patients with localized prostate cancer. In more advanced cases, seminal vesicles (SVs) are routinely included in the target volume. The Scandinavian HYPO-RT-PC trial, which compared 42.7 Gy in 7 fractions (fr) to conventional fractionation (CF), did not include SVs in the clinical target volume. The primary objective of the present work was to implement a ultrahypofractionated-simultaneous integrated boost (UHF-SIB) for prostate cancer RT, incorporating SVs into the target volume based on this fractionation schedule. A secondary objective was to analyze the unintentional dose coverage of SVs from state-of-the-art volumetric modulated arc therapy treatments to the prostate gland only.

Methods and Materials: Two different equieffective UHF-SIB treatment schedules to SVs were derived based on the CF clinical schedule (50.0 Gy/25 fr to elective SVs and 70.0 Gy/35 fr to verified SV-invasion (SVI)) using the linear quadric model with α/β = 2 Gy and 3 Gy. The dose to the prostate was 42.7 Gy/7 fr in both schedules, with 31.2 Gy/37.8 Gy (α/β = 2 Gy) and 32.7 Gy/40.1 Gy (α/β = 3 Gy) to elective SV/verified SVI. Volumetric modulated arc therapy plans to the proximal 10 mm and 20 mm were optimized, and dose-volume metrics for target volumes and organs at risk were evaluated.

Results: Dose metrics were overall lower for UHF-SIB compared with CF. QUANTEC-based volume criteria were 2% to 7% lower for the rectum and 2% to 4% lower for the bladder in the UHF-SIB. The $D_{98\%}$ to elective SV was 7 to 12 Gy_3 lower with UHF-SIB, and the corresponding data for verified SVI were approximately 2 to 3 Gy_3. The SV(10 mm) $V_{90\%/(29.5\ Gy)}$ for prostate-only treatments (42.7 Gy) were as follows: median (IQR), 99% (87-100) and 78% (58-99) for the clinical target volume and planning target volume, respectively.

Conclusions: UHF RT based on the HYPO-RT-PC fractionation schedule, with a SIB technique, to the prostate and the base of the SV can be planned with lower doses (EQD2) to organs at risk, compared with CF. The unintentional dose to the proximal parts of SVs in prostate-only treatment can be substantial.

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Introduction

Hypofractionation has become an integral part of prostate cancer radiation therapy (RT) owing to the proposed low α/β ratio.[1] There are a number of randomized trials, such as CHHiP,[2] HYPRO,[3] PROFIT,[4] and RTOG 0415,[5] reporting similar tumor control and toxicity rates between moderate hypofractionation (2.5-3.4 Gy per fraction [fr]) and conventional fractionation (CF) (1.8-2.0 Gy per fr) for low- to intermediate-risk localized prostate cancer.

There are two large randomized phase III studies on ultrahypofractionation (UHF). The Scandinavian HYPO-RT-PC-trial compared an intervention of 42.7 Gy in 7 fr over 2.5 weeks to the standard of care, 78 Gy in 39 fr over 8 weeks, for intermediate- to high-risk prostate cancer.[6] The 5-year outcome report concluded that UHF RT is noninferior to CF RT regarding failure-free survival, with similar late toxicity but with more pronounced acute side effects. The PACE-B trial compared 36.25 Gy in 5 fr over 1 to 2 weeks to CF or moderate hypofractionation (78 Gy in 39 fr over 8 weeks or 62 Gy in 20 fr over 4 weeks, respectively) for men with low- and favorable intermediate-risk prostate cancer. Two-year toxicity data from the PACE-B trial support the use of UHF RT from a safety perspective.[7] Recently, 5-year outcomes were presented, further supporting its efficacy in tumor control.[8] Therefore, UHF can now be considered a treatment alternative for patients with localized prostate cancer.

In more advanced cases (high Gleason score/high PSA/T3), seminal vesicles (SVs) are routinely included in the target volume. Histologic analysis of postprostatectomy specimens has shown that the risk of seminal vesicle tumor invasion (SVI) is correlated with common clinical factors used for prostate cancer risk group stratification.[9,10] Kestin et al demonstrated that tumor spread beyond 2 cm into the SVs is uncommon.[9] Therefore, current guidelines recommend that the proximal part of the SV be included in the clinical target volume (CTV) for patients with intermediate to high-risk cancer.[11] A risk assessment is generally performed, using, for example, nomograms,[12-14] and the robustness of these models can be increased with the addition of magnetic resonance imaging (MRI).[15,16]

As a reduced number of treatment fractions significantly increases the RT availability and is more convenient for the patients, it would be beneficial to extend the UHF on a larger scale to patients with prostate cancer for whom the SVs are included in the target volume.

The CHHiP trial included SVs in the CTV with two dose levels in a simultaneous integrated boost (SIB) (CF: 59.2 Gy/71 Gy) to the proximal 2 cm and/or entire SV. The HYPRO trial adopted both a SIB and sequential boost with two dose levels (CF: 68 Gy/78 Gy) to the whole SV, while the PROFIT trial employed one dose level (CF: 78 Gy) to the proximal 10 mm of the SVs. The UHF PACE-B trial included the proximal 10 mm of the SVs to one dose level (CF: 78 Gy), whereas the HYPO-RT-PC trial did not include SVs in the CTV. Hence, the inclusion of SVs in the CTV varies considerably in terms of both volume extent and prescribed dose level. Because the addition of SV target volumes into UHF prostate cancer RT increases the irradiated volume, it is important to thoroughly explore its effect on doses to organs at risk (OARs) and target volumes.

The primary aim of the present work was therefore to assess the feasibility of implementing ultrahypofractionated-simultaneous integrated boost (UHF-SIB) for prostate cancer RT, including SVs, based on the HYPO-RT-PC fractionation schedule (7 fr over 2.5 weeks). A secondary objective was to analyze the unintentional dose coverage of SVs from state-of-the-art volumetric modulated arc therapy (VMAT) treatments of the prostate gland only in the CTV.

Methods Materials

Patients

The present study is based on 30 consecutive patients with prostate cancer treated at Skåne University Hospital, Lund, Sweden, between November 2013 and January 2015, who received UHF RT within the HYPO-RT-PC study (EPN Umeå: 03-513, 2003-12-23 and Lund: 2013/742). HYPO-RT-PC is an open-label, randomized, multicenter phase III study including men with verified localized intermediate-to-high risk prostate cancer.[6] Patients were randomized between UHF (42.7 Gy in 7 fr, 3 days per week for 2.5 weeks) and CF (78.0 Gy in 39 fr, 5 days per week for 8 weeks). The UHF fractionation schedule was based on near equal rectum late toxicity compared with the CF schedule, assuming an α/β ratio of 3 Gy. SVs were not included in the CTV, and no androgen deprivation therapy was allowed.

RT preparations and segmentation

The treatment planning computed tomography (CT) was performed in the supine position with a CT slice thickness of 3 mm. The CTV for the prostate was defined as the prostate gland (CTV_{pros}) on CT with MRI as guidance. An isotropic margin of 7 mm was added to the CTV_{pros} to obtain the planning target volume (PTV) for the prostate (PTV_{pros}). Guidelines for definition of the CTV for SVs vary, but typically recommend the proximal 10 to 20 mm of the SVs or the entire SVs[2,17]. Therefore, two CTVs for the proximal parts of the SVs were retrospectively defined CTV_{ves}(10 mm) and CTV_{ves}(20 mm), consisting of the proximal 10 and 20 mm of the SVs (long

axis measure), respectively. The corresponding PTVs PTV_{ves}(10mm) and PTV_{ves}(20 mm) were obtained by adding a 10 mm isotropic margin. This margin is routinely used in our clinic for CF SV treatment with image guided RT, based on fiducial markers in the prostate.

For the present work, the rectum and bladder were redefined and supplemented with the bladder trigone as a separate OAR. The urethra was not easily visible in the treatment planning images and hence not defined. The rectum and bladder were defined following the pelvic normal tissue contouring guidelines of RTOG.[18] The bladder trigone refers to the triangular subvolume of the 5 mm thick bladder wall located between the right and left ureteral orifice and the urethral orifice.

Prescribed doses to the SVs

In our present clinical CF schedule, the SVs are included in the target volume if the statistical risk for SVI is larger than 20% according to the Memorial Sloan Kettering Cancer Center nomogram.[14] The RT in this scheme is delivered as a sequential boost with 78.0 Gy in 39 fractions to the prostate and 50.0 Gy in 25 fractions to elective SVs and 70.0 Gy in 35 fractions in the definite setting to verified SVI.

The outcome of the HYPO-RT-PC study indicates an α/β ratio close to 3 Gy for both tumor response and normal tissue late toxicity.[6] In the meta-analysis by Vogelius and Bentzen, the best estimate of the α/β ratio was 1.6 Gy (95% CI, 1.3-2.0 Gy).[1] Based on these results, α/β ratios of 2.0 Gy and 3.0 Gy were used in the present work to design equieffective treatment schedules for the SVs using the linear quadratic model, $EQD2 = D\left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right)$, where D denotes the total prescribed dose, and d, the dose per fraction.

The prescribed UHF-SIB fractionation used in this study was 7 fr with 3 fr per week for 2.5 weeks. The prescribed dose to the prostate was 42.7 Gy with 37.8 Gy based on α/β = 2 Gy, or 40.1 Gy based on α/β = 3 Gy to verified SVI (corresponding to 70.0 Gy in 35 fr to the SVs), and elective SV RT of 31.2 Gy based on α/β = 2 Gy or 32.7 Gy based on α/β = 3 Gy (corresponding to 50.0 Gy in 25 fr to the SV). The UHF-SIBs corresponding to α/β = 2 Gy and 3 Gy are denoted UHF-SIB(α/β = 2) and UHF-SIB(α/β = 3), respectively.

RT planning and dose-volume analysis

The CT-based VMAT planning was performed in Eclipse version 15.6 (Varian Medical Systems, Palo Alto, CA, USA) with version 15.6.05 of the anisotropic analytical algorithm and photon optimization algorithm. Two full 10 MV arcs were used, with a collimator rotation of 5° (complementary collimator angle used). The optimization and anisotropic analytical algorithm calculation grid sizes were 2.5 mm. Target autocrop, manual normal tissue objective, aperture shape controller "very low", and intermediate dose were used during optimization.

For each patient, nine VMAT plans were made by the same experienced dose planner. These included a UHF prostate-only plan and proposed equieffective UHF-SIB treatment schedules based on α/β = 2 Gy and α/β = 3 Gy for both elective SV and verified SVI, as well as the clinical standard sequential boost technique for elective SV and verified SVI. The dose to the prostate was prescribed as median dose to PTV_{pros}. A homogenous dose distribution was strived for in the PTVs with no restrictions on the positions of doses above the prescribed dose, and the aim was to meet the same dose constraints in percentage units for all dose plans. Dose volume constraints applied for the treatment planning can be found in Table E1.

Dosimetric and statistical analysis

Defined structures and dose distributions were imported into the software package Medical Interactive Creative Environment, MICE toolkit v. 2022.4.9 (NONPI Medical AB, Sweden, https://www.micetoolkit.com/) for voxel-by-voxel conversion to 2 Gy per fraction equivalent doses (EQD2) and extraction of dose-volume descriptors in EQD2.

Structure volumes, near maximum doses ($D_{2\%}$), mean doses (D_{mean}), and volume criteria (V_{xGy}), as well as complete cumulative dose-volume histograms (DVHs), were derived for the rectum, bladder, and bladder trigone. For the target volumes, near maximum doses ($D_{2\%}$, only PTV) and near minimum doses ($D_{98\%}$) were extracted.

The normal tissue complication probability (NTCP) for rectum based on the Quantitative Analyses of Normal Tissue Effects in the Clinic collaboration (QUANTEC) Lyman-Kucher-Burman model parameters for grade ≥2 late toxicity or rectal bleeding (n = 0.09, m = 0.13, and TD_{50} = 78.5 Gy)[19] was calculated using the biologic evaluation module in Eclipse v15.6 (Varian Medical Systems, Palo Alto, CA, USA).

Comparisons of dose data between groups were performed with the Wilcoxon signed-rank test, and the difference was estimated with the Hodges-Lehmann median difference. Statistical analyses were carried out using the MedCalc Statistical Software version 22.002 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

Results

Evaluation of all DVH metrics both for OARs and target volumes were performed on EQD2 (α/β = 3 Gy) corrected dose distributions. The analyzed DVH metrics were derived from the physical dose-volume objectives/constraints used in our clinic for CF (78.0 Gy in 39 fractions),

which are based on the QUANTEC criteria.[19,20] Specifically, for the rectum, the criteria are $V_{75\ Gy} < 10\%$ (15% in QUANTEC), $V_{70\ Gy} < 17\%$ (20% in QUANTEC), and $V_{60\ Gy} < 35\%$. For the bladder, the criteria are $V_{65\ Gy} < 50\%$ and $D_{mean} < 62$ Gy. Since we could not find any consensus regarding dose-volume criteria for the bladder trigone, the same metrics as those for the bladder were used.

The results for the rectum, bladder, and bladder trigone, as well as for the CTV and PTV from the UHF-SIB and CF sequential boost plans are shown in Tables 1 and 2 for elective SV and verified SVI treatment, respectively. The large variation in the DVH metrics for the bladder is primarily due to the wide range of bladder filling among patients. The median volume (IQR) for the bladder is 81.9 cm^3 (64.8-130.1). The higher $D_{98\%}$ for the SV target volumes in the CF sequential boost plans compared with that in the UHF-SIB plans is due to the dose contribution to the SV from the prostate-only dose plans. The coverage in Gy_3 for the prostate target volumes is slightly lower in the UHF-SIB dose plans compared with that in the CF dose plans, since the same coverage in percentage units was aimed for during treatment planning. The median (IQR) $D_{98\%}$ for PTV_{pros} in the EQD2 70 Gy dose plans are 97.6% (97.4-97.8), 97.4% (97.2-97.6), and 97.3% (97.0-97.4) for CF, UHF-SIB(α/β = 3), and UHF-SIB(α/β = 2), respectively. The corresponding numbers for the EQD2 50 Gy dose plans are 97.4% (97.2-97.6), 96.2% (95.8-96.7), and 96.1% (95.8-96.4). All OAR dose metrics, except near maximum doses, were statistically significantly lower for UHF-SIB than for CF sequential boost for both elective and definite SV treatment. Average DVHs in EQD2 for the rectum, bladder, and bladder trigone for the UHF-SIB(α/β = 3), CF sequential boost, and UHF prostate-only plans are shown in Fig. 1a-c (corresponding figures for UHF-SIB(α/β = 2) are presented in Fig. E1a-c). The EQD2 values corresponding to the QUANTEC criteria are indicated with squares. The large standard error observed for the bladder is primarily due to the variation in patient-to-patient anatomy, as mentioned above.

The estimated NTCP for rectal grade ≥2 late toxicity is presented in Table 3. The results indicate that the NTCP is lower with UHF-SIB than with CF sequential boost.

For the UHF prostate-only dose plans, the median volume (range) of the CTV_{ves}(10 mm) and CTV_{ves}(20 mm) that receives 90% of the UFH-SIB(α/β = 3) dose (32.7 Gy/40.1 Gy) was 99% (87-100) and 71% (42-97), respectively. The corresponding figures for PTV_{ves}(10 mm) and PTV_{ves}(20 mm) were 78% (58-99) and 52% (35-82) of the PTV volume, respectively.

Discussion

In this treatment planning study, we demonstrated that UHF RT delivering 42.7 Gy in 7 fractions to the prostate according to the HYPO-RT-PC fractionation schedule and 31.2 Gy (α/β = 2)/32.7 Gy (α/β = 3) (elective) or 37.8 Gy (α/β = 2)/40.1 Gy (α/β = 3) (verified SVI) to the base of the SV (10-20 mm) using a SIB technique can be planned with acceptable doses to OARs. UHF-SIB compared favorably to dose plans with the CF sequential boost technique, with overall lower dose metrics for the OARs. In most cases, dose constraints based on QUANTEC criteria could be fulfilled, both for elective treatment of the proximal 1 cm of the SV (EQD2 50 Gy) and for the verified SVI case with an EQD2 of 70.0 Gy to the proximal 2 cm of the SV. In cases where the OAR criteria could not be fully met, the OAR doses were generally lower in the UHF-SIB plans than in the CF sequential boost plans. The unintentional SV dose from the prostate-only treatment in the CF sequential boost setting resulted in a significantly higher $D_{98\%}$ than prescribed. The SV coverage in the UHF-SIB plans with respect to the prescribed dose in EQD2, ie, 50/70 Gy, was excellent. The prescribed dose in the elective setting for prostate cancer is generally 46 to 50 Gy, and hence, the lower dose in the UHF-SIB should be adequate.[21,22] However, for the definite setting, the unintentional SV dose from the CF sequential boost might be clinically significant, potentially resulting in a lower target dose in the UHF-SIB. This should be carefully considered when designing treatment schedules for UHF-SIB, where a higher prescribed SV dose in EQD2 might be needed. Note, though, that the EQD2 results strongly depend on the α/β ratio adopted.

In this study, α/β ratios of 2 and 3 Gy have been used to derive equieffective treatment schedules for UHF-SIB to the prostate/SVs. Data from the HYPO-RT-PC study indicate an α/β ratio close to 3 Gy for tumor response.[6] This is higher than the estimate of 1.6 Gy (95% CI, 1.3-2.0 Gy) in the meta-analysis by Vogelius and Bentzen.[1] However, the meta-analysis included only one UHF study (HYPO-RT-PC), and it is hypothesized that that the α/β ratio can be dose per fraction-dependent, with an estimated increase in the α/β ratio of 0.6 Gy per Gy increase in dose per fraction.

The guidelines for definition of the SV CTV vary, but the stated volume is generally the proximal 10 to 20 mm of the SVs or entire SVs.[11] In some studies, the definition depends on the indication for SV RT, ie, prostate cancer risk level and verified/statistical risk for SVI.[2,17] Kestin et al found that 41% of the SVI extended beyond the proximal 10 mm of the SV, and the corresponding values for the proximal 20 mm and 30 mm were 6% and 1%, respectively.[9] They concluded that only the proximal 20 to 25 mm (approximately 60%) of the SVs needs to be included within the CTV. This is in line with the 20 mm, which is one of the two CTV volumes for SVs investigated in this study.

The motion of the SVs is primarily caused by variations in bladder and rectum volume, and the motion is largely uncorrelated with the prostate gland motion.[23,24] Greater SV motion has been observed with increasing

Table 1 Dose-volume metrics (median and IQR; 95% CI) evaluated based on the EQD2 (α/β = 3 Gy) corrected dose distribution in the elective setting with prescribed physical doses of 31.2 Gy (α/β = 2) / 32.7 Gy (α/β = 3) in 7 fractions to the SV in the UHF-SIB and 50.0 Gy / 25 fractions in the CF sequential boost

	CF seq. boost 50.0 Gy 10 mm ves Median (IQR)	UHF-SIB(α/β = 2) 31.2 Gy 10 mm ves Median (IQR)	Median diff (α/β = 2) Median (95% CI)	*P* (α/β = 2)	UHF-SIB(α/β = 3) 32.7 Gy 10 mm ves Median (IQR)	Median diff (α/β = 3) Median (95% CI)	*P* (α/β = 3)
Rectum Vol: 72.7 cc (64.7-81.2)							
D2% [Gy_3]	77.7 (77.4-78.0)	77.2 (76.7-77.7)	−0.5 (−0.6 to −0.3)	< .0001	77.2 (76.7-77.5)	−0.6 (−0.7 to −0.5)	< .0001
V54.5 Gy_3 [%]	22.8 (20.1-28.1)	16.8 (13.2-19.3)	−7.5 (−9.0 to −5.9)	< .0001	16.8 (13.3-20.9)	−6.5 (−7.8 to −4.8)	< .0001
V67.1 Gy_3 [%]	14.4 (11.5-17.5)	11.5 (8.1-13.3)	−3.1 (−3.9 to −2.4)	< .0001	11.1 (8.3-14.8)	−2.8 (−3.5 to −2.1)	< .0001
V73.8 Gy_3 [%]	8.9 (7.1-11.7)	7.7 (5.2-9.9)	−1.7 (−2.2 to −1.3)	< .0001	7.5 (5.0-10.3)	−1.8 (−2.2 to −1.4)	< .0001
Bladder Vol: 81.9 cc (64.8-130.1)							
Dmean [Gy_3]	34.0 (25.0-42.2)	28.3 (21.2-38.5)	−4.2 (−4.6 to −3.6)	< .0001	28.0 (22.3-40.3)	−3.9 (−4.7 to −3.3)	< .0001
D2% [Gy_3]	79.3 (78.9-79.6)	79.6 (79.2-80.1)	0.3 (0.1 to 0.6)	.007	79,6 (78.9-80.4)	0.4 (0.1 to 0.6)	.008
V60.7 Gy_3 [%]	21.0 (14.5-29.8)	17.6 (13.1-28.3)	−2.5 (−3.0 to −2.0)	< .0001	17.5 (13.3-29.1)	−2.4 (−3.1 to −1.9)	< .0001
Bladder Trigone Vol: 10.5 cc (8.3-12.6)							
Dmean [Gy_3]	67.9 (60.3-71.6)	63.6 (54.7-68.6)	−3.4 (−4.0 to −2.9)	< .0001	64.6 (54.9-69.0)	−2.7 (−3.3 to −2.2)	< .0001
D2% [Gy_3]	80.0 (79.7-80.4)	80.9 (80.0-82.0)	1.2 (0.6 to 1.8)	< .0001	81.0 (80.0-81.5)	1.0 (0.6 to 1.3)	< .0001
V60.7 Gy_3 [%]	76.8 (62.3-88.1)	71.4 (55.0-84.0)	−6.1 (−7.6 to −4.5)	< .0001	73.1 (56.7-84.1)	−4.9 (−6.3 to −3.5)	< .0001
CTV_{ves}(10 mm) Vol: 7.4 cc (6.8-8.9)							
D98% [Gy_3]	63.9 (62.5-65.7)	46.7 (46.2-48.5)	−16.6 (−17.5 to −15.4)	< .0001	51.4 (50.2-52.6)	−12.5 (−13.3 to −11.6)	< .0001
PTV_{ves}(10 mm) Vol: 67.4 cc (60.6-74.2)							
D98% [Gy_3]	55.3 (51.7-57.8)	43.6 (43.2-43.7)	−11.5 (−13.0 to −10.1)	< .0001	47.5 (47.0-47.7)	−7.6 (−9.2 to −6.4)	< .0001
D2% [Gy_3]	79.1 (79.0-79.3)	80.5 (80.4-80.9)	1.5 (1.3 to 1.7)	< .0001	80.0 (79.9-80.3)	1.0 (0.8 to 1.1)	< .0001
CTV_{prost} Vol: 62.0 cc (48.0-76.4)							
D98% [Gy_3]	76.5 (76.5-76.6)	76.1 (76.0-76.2)	−0.5 (−0.5 to −0.4)	< .0001	76.1 (76.1-76.2)	−0.4 (−0.5 to −0.4)	< .0001
PTV_{prost} Vol: 138.3 cc (118.1-163.9)							
D98% [Gy_3]	75.2 (75.0-75.5)	73.0 (72.4-73.5)	−2.2 (−2.5 to −1.9)	< .0001	72.9 (72.6-73.2)	−2.4 (−2.6 to −2.1)	< .0001
D2% [Gy_3]	80.0 (79.9-80.2)	80.8 (80.4-81.2)	0.8 (0.6 to 1.0)	< .0001	80.5 (80.3-80.7)	0.5 (0.3 to 0.6)	< .0001

The prescribed physical dose to the prostate was 42.7 Gy in 7 fractions for the UHF regimen and 78 Gy in 39 fractions for the CF regimen. Structure volumes are reported as the median and IQR.
Abbreviations: CF = conventional fractionation; CTV_{prost} = prostate clinical target volume; CTV_{ves} = seminal vesicle clinical target volume; EQD2 = 2 Gy per fraction equivalent dose; PTV_{prost} = prostate planning target volume; PTV_{ves} = seminal vesicle planning target volume; SV = seminal vesicle; UHF = ultrahypofractionated; UHF-SIB = ultrahypofractionated simultaneous integrated boost; ves = vesicle.

Table 2 Dose-volume metrics (median and IQR; 95% CI) evaluated based on the EQD2 (α/β = 3 Gy) corrected dose distribution in the verified SVI setting with prescribed physical doses of 37.8 Gy (α/β = 2) / 40.1 Gy (α/β = 3) in 7 fractions to the SV in the UHF-SIB and 70.0 Gy / 35 fractions in the CF sequential boost

	CF seq. boost 70.0 Gy 20 mm ves Median (IQR)	UHF-SIB(α/β = 2) 37.8 Gy 20 mm ves Median (IQR)	Median diff (α/β = 2) Median (95% CI)	*P* (α/β = 2)	UHF-SIB(α/β = 3) 40.1 Gy 20 mm ves Median (IQR)	Median diff (α/β = 3) Median (95% CI)	*P* (α/β = 3)
Rectum Vol: 72.7 cc (64.7-81.2)							
D2% [Gy_3]	77.8 (77.6-78.1)	77.2 (76.8-77.5)	−0.5 (−0.7 to −0.4)	< .0001	77.3 (76.9-77.6)	−0.6 (−0.7 to −0.4)	< .0001
V54.5 Gy_3 [%]	31.2 (25.6-36.3)	23.7 (18.8-28.1)	−7.0 (−8.3 to −5.7)	< .0001	27.2 (22.4-31.2)	−3.8 (−4.6 to −2.8)	< .0001
V67.1 Gy_3 [%]	21.6 (15.8-25.3)	12.5 (10.3-15.4)	−7.6 (−9.6 to −5.7)	< .0001	16.8 (13.3-21.1)	−3.5 (−4.0 to −2.9)	< .0001
V73.8 Gy_3 [%]	11.6 (9.2-14.2)	8.4 (5.6-10.5)	−3.8 (−4.7 to −2.8)	< .0001	8.0 (6.3-11.0)	−3.3 (−4.0 to −2.5)	< .0001
Bladder Vol: 81.9 cc (64.8-130.1)							
Dmean [Gy_3]	41.1 (32.9-48.8)	36.0 (28.9-43.1)	−4.9 (−5.7 to −4.3)	< .0001	35.7 (29.7-45.1)	−4.3 (−4.8 to −3.5)	< .0001
D2% [Gy_3]	79.0 (78.7-79.6)	79.1 (78.8-79.4)	−0.1 (−0.2 to 0.1)	.558	79.2 (78.6-79.8)	0.1 (−0.1 to 0.3)	.280
V60.7 Gy_3 [%]	27.4 (18.8-38.8)	22.5 (15.8-34.7)	−4.0 (−5.0 to −3.2)	< .0001	24.5 (16.9-37.3)	−2.1 (−2.8 to −1.5)	< .0001
Bladder Trigone Vol: 10.5 cc (8.3-12.6)							
Dmean [Gy_3]	73.9 (70.6-75.3)	71.2 (66.2-73.3)	−3.1 (−3.6 to −2.7)	< .0001	73.0 (68.8-74.6)	−1.2 (−1.4 to −0.9)	< .0001
D2% [Gy_3]	79.9 (79.5-80.4)	79.8 (79.4-80.3)	−0.2 (−0.5 to 0.2)	.299	80.0 (79.5-80.6)	0.1 (−0.1 to 0.3)	.417
V60.7 Gy_3 [%]	94.7 (87.4-97.1)	88.5 (80.6-93.7)	−5.1 (−6.7 to −3.7)	< .0001	93.1 (86.7-95.7)	−1.5 (−2.1 to −1.0)	< .0001
CTV_{ves}(20 mm) Vol: 14.8 cc (12.5-16.6)							
D98% [Gy_3]	71.4 (70.7-72.3)	62.2 (61.7-62.7)	−9.2 (−9.7 to −8.7)	< .0001	68.9 (68.2-69.2)	−2.7 (−3.3 to −2.1)	< .0001
CTV_{ves}(10 mm) Vol: 7.4 cc (6.8-8.9)							
D98% [Gy_3]	73.6 (73.2-74.4)	63.9 (62.8-64.5)	−9.7 (−10.1 to −9.2)	< .0001	70.2 (69.2-70.9)	−3.8 (−4.1 to −3.4)	< .0001
PTV_{ves}(20 mm) Vol: 93.7 cc (87.1-105.8)							
D98% [Gy_3]	68.7 (68.6-69.3)	60.0 (59.6-60.7)	−9.0 (−9.5 to −8.5)	< .0001	66.8 (66.3-67.1)	−2.2 (−2.7 to −1.9)	< .0001
D2% [Gy_3]	79.2 (79.0-79.3)	78.9 (78.8-79.2)	−0.2 (−0.4 to −0.1)	.0007	78.9 (78.7-79.0)	−0.3 (−0.4 to −0.2)	< .0001
CTV_{prost} Vol: 62.0 cc (48.0-76.4)							
D98% [Gy_3]	76.3 (76.2-76.4)	76.2 (76.1-76.5)	0.0 (−0.1 to 0.0)	.206	76.2 (76.1-76.3)	−0.1 (−0.1 to 0.0)	.063
PTV_{prost} Vol: 138.3 cc (118.1-163.9)							
D98% [Gy_3]	75.5 (75.3-75.7)	74.1 (73.8-74.4)	−1.4 (−1.6 to −1.2)	< .0001	74.3 (74.1-74.8)	−1.2 (−1.4 to −1.0)	< .0001
D2% [Gy_3]	80.2 (80.1-80.4)	80.1 (79.8-80.3)	−0.2 (−0.3 to 0.0)	.032	80.0 (79.8-80.2)	−0.2 (−0.3 to −0.1)	.0007

The prescribed physical dose to the prostate was 42.7 Gy in 7 fractions for the UHF regimen and 78 Gy in 39 fractions for the CF regimen. Structure volumes are reported as the median and IQR.

Abbreviations: CF = conventional fractionation; CTV_{prost} = prostate clinical target volume; CTV_{ves} = seminal vesicle clinical target volume; EQD2 = 2 Gy per fraction equivalent dose; PTV_{prost} = prostate planning target volume; PTV_{ves} = seminal vesicle planning target volume; SV = seminal vesicle; SVI = seminal vesicle invasion; UHF = ultrahypofractionated; UHF-SIB = ultrahypofractionated-simultaneous integrated boost; ves = vesicle.

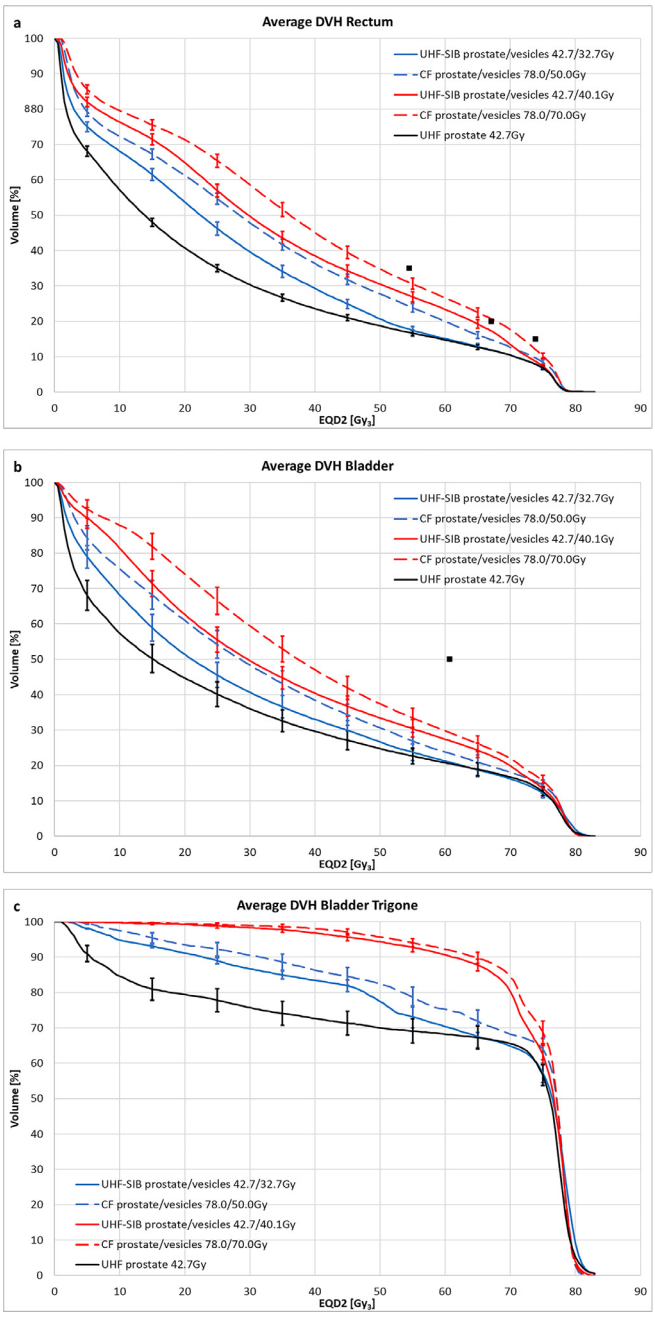

Figure 1 Average dose-volume histograms and standard error in EQD2 (α/β = 3) for the UHF-SIB(α/β = 3), CF sequential boost, and UHF prostate-only dose plans for the rectum (a), bladder (b), and bladder trigone (c). Squares indicate evaluated QUANTEC dose-volume criteria for the rectum and bladder.

Abbreviations: CF = conventional fractionation; EQD2 = 2 Gy per fraction equivalent dose; QUANTEC = quantitative analyses of normal tissue effects in the clinic collaboration; UHF = ultrahypofractionated; UHF-SIB = ultrahypofractionated-simultaneous integrated boost.

distance from the prostate, indicating that different CTV to PTV margins may be needed for partial and full SV treatment.[25] In this study, the CTV to PTV margin of 10 mm for SV used in our clinical CF schedule was also adopted for the present UHF treatment planning study. This margin is slightly larger than the approximately 8 mm margin needed for SV with image guided RT based on fiducials in the prostate, as reported in the review by Brand et al.[23] The margins presented in Brand et al are based on CF, and the safety of reducing margins for target structures in the UHF-SIB setting needs further investigation.

The unintentional dose to the SVs in state-of-the-art VMAT dose plans for prostate-only treatments is still substantial, especially for the proximal 10 mm of the SVs. In our study, the median volume (range) of CTV_{ves}(10 mm) and PTV_{ves}(10 mm) that receives 90% of the UFH-

Table 3 Estimated NTCP in percent for rectal grade ≥2 late toxicity based on EQD2 (α/β = 3 Gy) corrected dose distributions

	Estimated NTCP for rectal grade ≥2 late toxicity [%]						
	CF seq. boost Median (IQR)	UHF-SIB(α/β = 2) Median (IQR)	Median diff (α/β = 2) Median (95% CI)	*P* (α/β = 2)	UHF-SIB(α/β = 3) Median (IQR)	Median diff (α/β = 3) Median (95% CI)	*P* (α/β= 3)
Elective SV (1 cm)	6.9 (5.3-8.7)	5.4 (3.7-7.0)	−1.8 (−2.2 to −1.4)	< .0001	5.2 (3.6-7.0)	−1.8 (−2.1 to −1.5)	< .0001
Verified SVI (2 cm)	9.1 (7.6-11.4)	5.9 (4.5-7.5)	−3.3 (−3.9 to −2.6)	< .0001	6.8 (5.2-9.1)	−2.2 (−2.6 to −1.9)	< .0001

Prescribed physical doses of 31.2 Gy (α/β = 2) / 32.7 Gy (α/β = 3) in 7 fractions to the elective SV in the UHF-SIB and 50.0 Gy/25 fractions in the CF sequential boost, and 37.8 Gy (α/β = 2) / 40.1 Gy (α/β = 3) to verified SVI in the UHF-SIB and 70.0 Gy/35 fractions in the CF sequential boost. The prescribed physical dose to the prostate was 42.7 Gy in 7 fractions for the UHF regimen and 78 Gy in 39 fractions for the CF regimen.

Abbreviations: CF = conventional fractionation; EQD2 = 2 Gy per fraction equivalent dose; NTCP = normal tissue complication probability; SV = seminal vesicle; SVI = seminal vesicle invasion; UHF = ultrahypofractionated; UHF-SIB = ultrahypofractionated-simultaneous integrated boost.

SIB (α/β = 3) dose (32.7 Gy) were 99% (87-100%) and 78% (58-99%), respectively. This can be compared with data for prostate-only 3D-conformal RT, where $V_{50\ Gy}$ of the proximal 6 mm of the SVs ranged from 47% to 100% (incorporating a correction for organ motion).[26]

A limitation of the present study is the restricted number of patients included in the analysis. On the other hand, all patients were selected from a prospective phase III trial, which enhances the quality and homogeneity of the cohort. Another limitation in UHF treatment planning studies is the uncertainty in the α/β ratio, and hence, the EQD2 distributions to target volumes.

Conclusion

UHF RT based on the HYPO-RT-PC fractionation schedule with a SIB technique to the prostate and SVs can be planned with generally lower doses (EQD2) to OARs, compared with CF RT based on a sequential boost technique. The unintentional dose to the proximal parts of SVs in prostate-only treatment can be substantial and should be considered when designing UHF-SIB schedules, especially in the definite setting.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101531.

References

1. Vogelius IR, Bentzen SM. Diminishing returns from ultrahypofractionated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2020;107:299-304.
2. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*. 2016;17:1047-1060.
3. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with

localised prostate cancer (HYPRO): Final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2016;17:1061-1069.
4. Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol*. 2017;35:1884-1890.
5. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol*. 2016;34:2325-2332.
6. 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.
7. Tree AC, Ostler P, van der Voet H, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2022;23:1308-1320.
8. van As N, Tree A, Patel J, et al. 5-Year outcomes from PACE B: An international phase III randomized controlled trial comparing stereotactic body radiotherapy (SBRT) versus conventionally fractionated or moderately hypo fractionated external beam radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2023;117:e2-e3.
9. Kestin L, Goldstein N, Vicini F, et al. Treatment of prostate cancer with radiotherapy: Should the entire seminal vesicles be included in the clinical target volume? *Int J Radiat Oncol Biol Phys*. 2002;54:686-697.
10. Pierorazio PM, Ross AE, Schaeffer EM, et al. A contemporary analysis of outcomes of adenocarcinoma of the prostate with seminal vesicle invasion (pT3b) after radical prostatectomy. *J Urol*. 2011;185:1691-1697.
11. Salembier C, Villeirs G, De Bari B, et al. ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. *Radiother Oncol*. 2018;127:49-61.
12. Eifler JB, Feng Z, Lin BM, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int*. 2013;111:22-29.
13. Ohori M, Kattan MW, Koh H, et al. Predicting the presence and side of extracapsular extension: A nomogram for staging prostate cancer. *J Urol*. 2004;171:1844-1849.
14. Sloan Kettering Cancer Center. Memorial. Accessed December 27, 2023. https://www.mskcc.org/nomograms.
15. Feng TS, Sharif-Afshar AR, Wu J, et al. Multiparametric MRI improves accuracy of clinical nomograms for predicting extracapsular extension of prostate cancer. *Urology*. 2015;86:332-337.
16. Wibmer AG, Kattan MW, Alessandrino F, et al. International multisite initiative to develop an MRI-inclusive nomogram for side-specific prediction of extraprostatic extension of prostate cancer. *Cancers (Basel)*. 2021;13.
17. Boehmer D, Maingon P, Poortmans P, et al. Guidelines for primary radiotherapy of patients with prostate cancer. *Radiother Oncol*. 2006;79:259-269.
18. Gay HA, Barthold HJ, O'Meara E, et al. Pelvic normal tissue contouring guidelines for radiation therapy: A Radiation Therapy Oncology Group consensus panel atlas. *Int J Radiat Oncol Biol Phys*. 2012;83:e353-e362.
19. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys*. 2010;76:S123-S129.
20. Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys*. 2010;76:S116-S122.
21. 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;39:1234-1242.
22. Pollack A, Karrison TG, Balogh AG, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): An international, multicentre, randomised phase 3 trial. *Lancet*. 2022;399:1886-1901.
23. Brand VJ, Milder MTW, Christianen M, Hoogeman MS, Incrocci L. Seminal vesicle inter- and intra-fraction motion during radiotherapy for prostate cancer: A review. *Radiother Oncol*. 2022;169:15-24.
24. Lim Joon D, Chao M, Piccolo A, et al. Proximal seminal vesicle displacement and margins for prostate cancer radiotherapy. *J Med Radiat Sci*. 2021;68:289-297.
25. Stenmark MH, Vineberg K, Ten Haken RK, Hamstra DA, Feng M. Dosimetric implications of residual seminal vesicle motion in fiducial-guided intensity-modulated radiotherapy for prostate cancer. *Med Dosim*. 2012;37:240-244.
26. Parker C, Haycocks T, Bayley A, Alasti H, Warde P, Catton C. A dose-volume histogram analysis of the seminal vesicles in men treated with conformal radiotherapy to "prostate alone". *Clin Oncol (R Coll Radiol)*. 2002;14:298-302.