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CyberKnife Ultra-Hypofractionated SBRT for Localized Prostate Cancer with Dose Escalation to the Dominant Intraprostatic Lesion: In Silico Planning Study

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Abstract: The aim is to evaluate the feasibility of ultra-hypofractionated (UH) SBRT with CyberKnife® (CK) radiosurgery (Accuray Inc., Sunnyvale, California, USA) for localized prostate cancer (PCa) with a concomitant focal boost to the dominant intraprostatic lesion (DIL). Patients with intermediate/high-risk PCa, with at least one visible DIL on multi-parametric MRI, were included. For each, two CK-SBRT in silico plans were calculated using 95% and 85% isodose lines (CK-95%, CK-85%) and compared with the UH-DWA plan delivered with VERO®. All plans simulated a SIB prescription of 40 Gy to PTV-DIL and 36.25 Gy to the whole prostate (PTV-prostate) in five fractions every other day. Fifteen patients were considered. All plans reached the primary planning goal (D95% > 95%) and compliance with organs at risk (OARs) constraints. DVH metrics median values increased ($p < 0.05$) from UH-DWA to CK-85%. The conformity index of PTV-DIL was 1.00 for all techniques, while for PTV-prostate was 0.978, 0.984, and 0.991 for UH-DWA, CK-95%, and CK-85%, respectively. The CK-85% plans were able to reach a maximum dose of 47 Gy to the DIL while respecting OARs constraints. CK-SBRT plus a focal boost to the DIL for localized PCa appears to be feasible. These encouraging dosimetric results are to be confirmed in upcoming clinical trials such as the phase-II "PRO-SPEED" IEO trial.

Keywords: prostate cancer; CyberKnife; ultra-hypofractionated SBRT; in silico planning; feasibility study

1. Introduction

Prostate cancer (PCa) represents the second most common malignancy in men worldwide, with the highest prevalence in developed countries [1]. Patients affected by clinically

localized PCa with an intermediate- and high-risk disease, according to National Comprehensive Cancer Network (NCCN) guidelines, can be considered eligible for several local treatment modalities, including external-beam radiotherapy (EBRT) or brachytherapy ± androgen deprivation therapy (ADT) and surgery [2].

Exploiting the radiobiological rationale of the low PCa a/b ratio, resulting in enhanced sensitivity of PCa to higher doses per fraction [3], several trials and metanalysis reported comparable rates of biochemical control, progression-free survival (PFS), overall survival (OS), and toxicity of moderate hypofractionated radiation therapy (RT) respect to conventional fractionation [4–13].

Given these premises, two non-inferiority Randomized Controlled trials (RCTs) explored the role of ultra-hypofractionated RT (UH-RT) (defined as more or equal to 6.25 Gy/fraction) compared to conventional RT. The HYPO-RT-PC trial confirmed, with 5 years of follow-up, the same profiles of failure-free survival and genitourinary (GU)/gastrointestinal (GI) toxicity for both UH-RT and standard fractionation [14]. Recently published 12 months of GU and GI toxicity profile results from the PACE-B trial corroborate the non-inferiority of UH-RT with respect to conventional and moderate hypofractionated RT [15].

Considering these findings, UH-RT represents a well-established treatment option for localized PCa in high-expertise centers, as suggested by the NCCN guidelines in 2023 [2].

Because PCa local recurrences after RT often originates from the primary tumor site [16,17], a focal boost to the dominant intraprostatic lesion (DIL), identified through multi-parametric magnetic resonance imaging (mpMRI), has been proposed in order to increase biochemical disease-free survival (bDFS) in intermediate-to-high risk PCa patients.

This hypothesis has been confirmed by the results of the FLAME trial [18], which showed that, in conventional fractionation schemes, a focal boost on the DIL improves oncological outcomes without any relevant additional toxicity. Furthermore, as seen from the initial results of the SPARC Trial [19], dose-escalation to the DIL could increase the probability of an undetectable level of prostate-specific antigen (PSA) (<0.1 ng/mL) at least in the first 18 months after treatment in patients receiving ADT.

In our center at the European Institute of Oncology (IEO) IRCCS, Milan, Italy, a high level of expertise has been achieved in the setting of PCa UH-RT, counting more than one thousand patients treated with very low treatment-related toxicities reported [20]. In addition, data for patients receiving UH-RT and simultaneous integrated boost (SIB) on the DIL at IEO has already been published, demonstrating the safety and effectiveness of this treatment [20–22].

Several SBRT techniques for UH-RT administration have been explored in order to increase patients' compliance and safety. Interestingly, the recently published update at 2 years of the PACE-B trial [23] showed that CyberKnife (CK)-SBRT has significantly reduced Common Terminology Criteria for Adverse Events (CTCAE) GU toxicity than SBRT with conventional linacs. CK-SBRT radiosurgery has been successfully used to treat the whole prostate up to 40 Gy, with excellent rates of bDFS while maintaining low rectal and genitourinary toxicities [24–29].

Given the above, CK-SBRT could represent the "winning horse" in the race for the best ablative treatment for localized PCa, considering both patient compliance and treatment effectiveness.

Dose escalation to the DIL with CK LINAC starting from these promising toxicity results is expected to further improve oncological outcomes even in UH schedules. These improvements are particularly needed from intermediate-unfavorable to high-risk localized PCas, which are the risk categories more prone to develop an early systemic disease progression [30].

Nevertheless, robust data on focal dose escalation in this setting should be yet generated. The ongoing HYPO-FLAME trial [31] is likely to shed light on the effectiveness of the DIL boost in this setting.

The present in silico study has evaluated the feasibility of ultra-hypofractionated (UH)-SBRT with CK radiosurgery system (Accuray Inc., Sunnyvale, California, USA) for

localized PCa with a concomitant focal boost to the DIL. Two different isodose prescription levels were tested, and dose distributions were compared to delivered UH-dynamic wave arc (DWA) plans in the intermediate-unfavorable/high-risk PCa setting.

2. Materials and Methods

2.1. Study Design

The plans of UH-DWA and CK were compared in a series of 15 patients treated with UH-DWA. For the purpose of the study, new CK plans were generated using available simulation-CT and contours.

2.2. Patients' Cohort

Patients with localized PCa who underwent UH-DWA at our institution from October 2021 to March 2022 were considered for study inclusion. The eligibility criteria were the following:

(i) Histologically confirmed adenocarcinoma of the prostate;
(ii) Availability of a previous diagnostic multi-parametric magnetic resonance imaging (mpMRI);
(iii) At least one visible intraprostatic lesion classified with a PI-RADS 4 score [32];
(iv) A maximum of 2 total DILs and a prostate gland volume < 100 cm^3 of intermediate and high-risk categories, according to the NCCN version 01.2023 and the cN0 and cM0 TNM classifications.

This retrospective study was approved by the ethical committee with UID number IEO 1872.

2.3. Region of Interest Definition

Contouring of region of interest was performed by an expert radiation oncologist using RayStation® TPS (RaySearch Laboratories, Stockholm, Sweden) after rigid registration of simulation CT (CTsim) with mpMRI-T2W imaging.

The clinical target volume (CTV) of the prostate (CTV-p) included the whole prostate and proximal 1 cm of seminal vesicles; CTV of the DIL (CTV-d) included the DIL visible volume on the diagnostic mpMRI. According to institutional guidelines, prostate PTV (PTV-p) was created by the expansion of CTV-p by 5 mm in all directions except 3 mm posteriorly; for the DIL PTV (PTV-d), an expansion of 3 mm in all directions was added to CTV-d [33].

2.4. Treatment Characteristics

Patients were treated with UH-RT delivered with the VERO® system (Vero, BrainLab AG, Feldkirchen, Germany, and Mitsubishi Heavy Industries, Ltd., Tokyo, Japan) and DWA technique. The dose prescription was 36.25 Gy to the PTV-p and 40 Gy to the PTV-d with a simultaneous integrated boost (SIB) technique in 5 fractions every other day. The dose prescription scheme is reported in Figure 1. Dose distribution was calculated with Collapsed Cone Convolution (CCC) calculation algorithm in Raystation (RaySearch Laboratories, Stockholm, Sweden) treatment planning system (TPS). The primary planning goal was to achieve, both for PTV-p and PTV-d, the dose of 95% of volume $\geq$ 95% of the prescription dose (D95% > 95%) and to reach organs at risk (OARs) constraint compliance according to Folkert and Timmerman [34] (Table 1). Secondary planning goals were D0.03 cm^3 < 108% for PTV-d and D0.03 cm^3 < 111% for PTV-p.

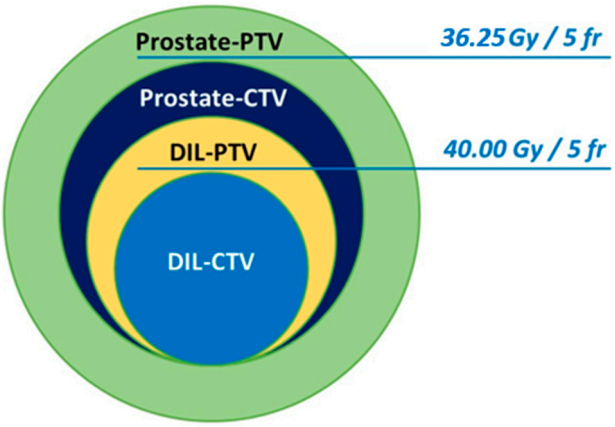

Figure 1. Ultra-hypofractionated stereotactic body radiation therapy dose prescription scheme.

Table 1. Summary of the OARs dose constraint objectives [34].

Organ at Risks	Objective
Rectum	
V18 Gy	<50%
V29 Gy	<20%
V33 Gy	<10%
V36.25 Gy	<5%
Rectum Posterior Wall	
D1cc	<17 Gy
Anal Canal	
Dmean	<15 Gy
Bladder	
V36.25 Gy	<5%
V36.25 Gy	<5 cc
V18 Gy	<40%
Femoral Heads	
V15 Gy	<5%
Bowel Cavity	
V30 Gy	<1 cc
Dmean	<5.4 Gy
V17 Gy	<195 cc
Penile Bulb	
V29 Gy	<50%
Penis	
V13 Gy	<1 cc
Testis	
D20%	<2 Gy

2.5. Data Analysis

For the purpose of the study, for each patient, two CK-SBRT plans with virtual fiducials tracking were generated in silico using Accuray Precision® TPS (Accuray Inc., Sunnyvale, California, USA). Two different isodose prescriptions lines were tested, 95% and 85% (CK-85% and CK-95). More in detail, the prescription isodose line can be defined as the ratio of prescription dose and maximum dose (i.e., prescribing to the 85% or 95% isodose lines means normalizing the prescription dose to the 85% or 95% isodose surface, respectively, that includes the target volume).

CTsim and contours, including PTV-p and PTV-d with the same margins, were imported from UH-DWA plans, and the same dose prescription was used for both CK plans.

Comparison between the three treatment approaches focused on the following: (i) PTV coverage metrics, (ii) homogeneity index (HI), (iii) conformity index (CI), and (iv) OARs dosimetric parameters. HI was calculated as (D2%–D98%)/D50%, while CI was calculated

as V95%/volume. Beam on time was considered, as well. Median dose values across all patients and their respective interquartile ranges (IQR) were reported. Statistical analyses were performed using the Friedman test and the Wilcoxon signed-rank test to assess statistical differences between the techniques. The significance level of multiple comparisons was set as $p < 0.05/3$, determined by Bonferroni correction for the Friedman test, and as $p < 0.05$ for the Wilcoxon signed-rank test.

3. Results

A total of 15 patients with a median age of 75 years (IQR 72–77) are included in the present analysis. The median mpMRI prostate volume is 38 cm^3 (IQR 30–52), and the median DIL volume is 1.4 cm^3 (IQR 1–1.6). Only one patient has two visible DILs. Characteristics of the patients are summarized in Table 2.

Table 2. Summary of patients' characteristics.

Characteristic	Value (IQR)
Median Age (years)	75 (72–77)
Median iPSA (ng/mL)	6.37 (5.04–8.45)
Gleason Score	
3 + 4	7
4 + 3	6
4 + 4	2
Median ISUP Score	3 (2–4)
NCCN Risk Category	
Intermedium Favorable	7
Intermedium Unfavorable	5
High	3
AJCC Stage	
T1c N0	6
T2 N0	8
T3a N0	1
ADT Prescription	
LHRHa	7
Bicalutamide 150 mg	1
Radiological Data	
Median mpRMN Prostate Volume (cm^3)	38 (30–52)
Median DIL Max Dimension (mm)	11 (7–14)
PIRADS 4 Score	12
PIRADS 5 Score	4
ECE+	1
DIL Location	
Peripheral	15
Transitional	1
Volumes (cc) and Distances (mm)	
Median DIL Distance to the Bladder Wall	12.00 (10.90–16.35)
Median DIL Distance to the Rectum	3.90 (3.05–6.40)
Median DIL Clinical Volume (CTV-d)	1.40 (1.01–1.65)
Median Prostate Clinical Volume (CTV-p)	51.30 (43.26–61.35)
Median DIL-Prostate Clinical Volume Ratio (%)	2.27 (1.66–3.76)
Median DIL Planning Volume (PTV-d)	4.67 (3.65–5.49)
Median Prostate Planning Volume (PTV-p)	101.93 (81.40–115.39)
Median DIL-Prostate Planning Volume Ratio (%)	4.58 (3.30–6.90)

When considering treatment time, beam-on time for in silico CK plans is considerably higher with a median of 27.0 min (IQR 26.0–29.5), as opposed to 6.8 min (IQR 5.6–7.3) median treatment time for UH-DWA.

3.1. Target Coverage

The results of the planning study for target coverage of the three selected techniques are shown in Table 3. All target volumes (DIL and PTV) could achieve the planning goals as expected. A visual representation of the target coverage for different parameters among the three techniques is depicted in Figure 2a,b.

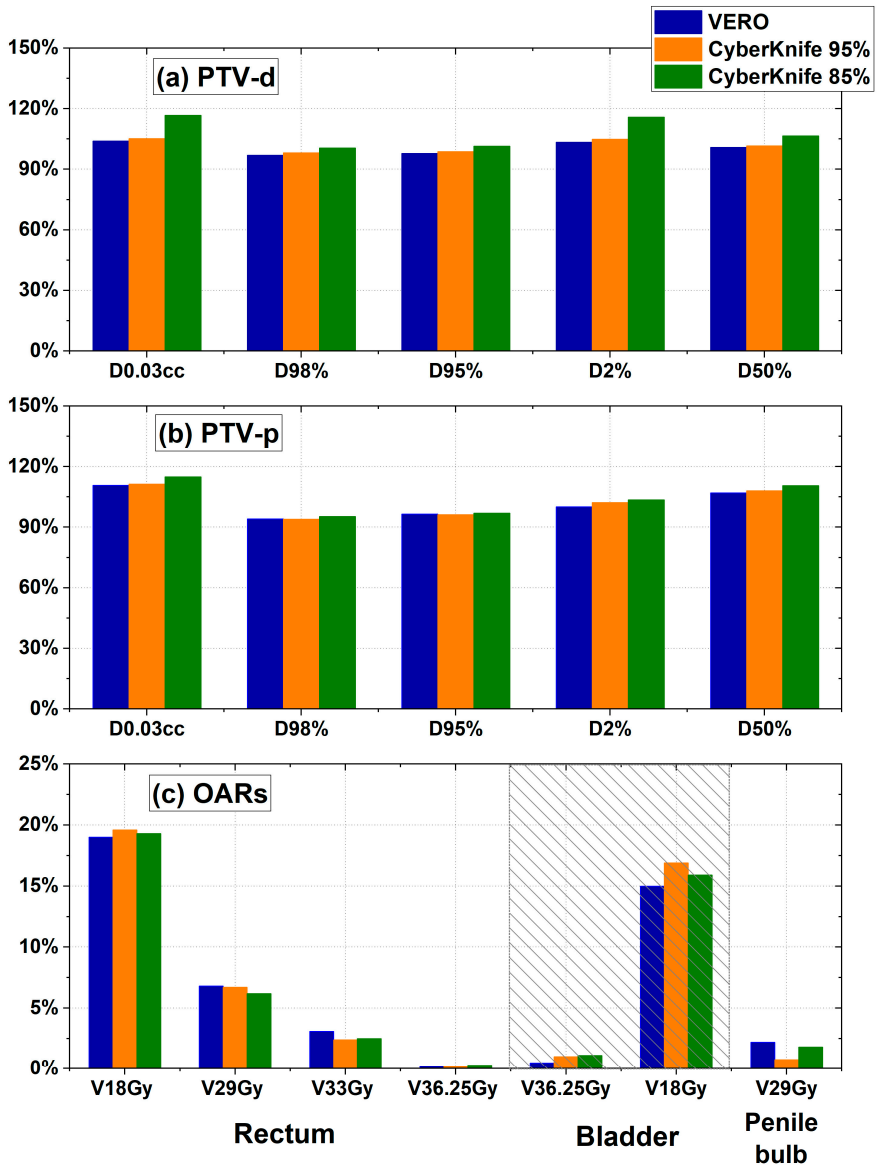

Figure 2. Graphics comparison of median target coverage parameters for PTV-DIL (PTV-d) (Panel **a**), PTV-prostate (PTV-p) (Panel **b**), and organ at risks (OARs) for the three considered techniques (Panel **c**). The greyed-out part in Panel **c** denotes the histograms for the bladder.

Table 3. Comparison of median values of dose-volume histogram parameters for PTV of the prostate (PTV-p) and PTV of the DIL (PTV-d).

PTV-d (40 Gy)	**UH-DWA**	**CyberKnife 95%**	**CyberKnife 85%**	**Overall (*p*-Value from Friedman Test) ***	**UH-DWA vs. CK95%**	**UH-DWA vs. CK85%**	**CK95% vs. CK85%**
D 0.03 cm^3	104.00%	105.25%	116.65%	<0.00001	$p < 0.05$	$p < 0.05$	$p < 0.05$
D98%	97.00%	98.20%	100.57%	0.00007	$p < 0.05$	$p < 0.05$	$p < 0.05$
D95%	97.80%	98.77%	101.45%	0.00012	$p < 0.05$	$p < 0.05$	$p < 0.05$
D2%	103.40%	104.82%	115.77%	<0.00001	$p < 0.05$	$p < 0.05$	$p < 0.05$
D50% (Median)	100.80%	101.62%	106.57%	<0.00001	$p < 0.05$	$p < 0.05$	$p < 0.05$
V100%	68.50%	78.70%	98.50%	0.00003	$p < 0.05$	$p < 0.05$	$p < 0.05$
V110%	0.00%	0.00%	26.10%	0.00001	$p < 0.05$	$p < 0.05$	$p < 0.05$
CI	1.00	1.00	1.00	0.8052	ns	ns	**
HI	0.06	0.06	0.15	0.00001	ns	$p < 0.05$	$p < 0.05$
PTV-p (36.25 Gy)	UH-DWA	CyberKnife 95%	CyberKnife 85%	Overall (*p*-value from Friedman Test) *	UH-DWA vs. CK95%	UH-DWA vs. CK85%	CK95% vs. CK85%
D 0.03 cm^3	110.70%	111.39%	114.86%	0.00005	$p < 0.05$	$p < 0.05$	$p < 0.05$
D98%	94.10%	93.93%	95.36%	0.00019	$p < 0.05$	$p < 0.05$	$p < 0.05$
D95%	96.55%	96.16%	96.99%	0.00516	$p < 0.05$	$p < 0.05$	ns
D2%	100.10%	102.12%	103.53%	0.00061	$p < 0.05$	$p < 0.05$	$p < 0.05$
D50% (Median)	107.00%	108.08%	110.59%	0.00003	$p < 0.05$	$p < 0.05$	$p < 0.05$
V100%	58.00%	74.60%	81.60%	0.00041	$p < 0.05$	$p < 0.05$	$p < 0.05$
V110%	0.30%	0.20%	3.40%	0.00232	$p < 0.05$	$p < 0.05$	$p < 0.05$
CI	0.98	0.98	0.99	0.00129	ns	$p < 0.05$	$p < 0.05$
HI	0.13	0.14	0.14	0.03122	$p < 0.05$	$p < 0.05$	ns

* Significant *p*-value if <0.016 (Bonferroni correction). ** comparison was not possible because of tied values. List of abbreviations: CK = CyberKnife; UH-DWA = ultra-hypofractionated dynamic wave arc; ns = not significant.

Regarding PTV parameters, the comparison of median values of DVH metrics both for PTV-p and PTV-d show an increase ($p < 0.05$, Table 3) from UH-DWA to CK-95% to CK-85% in almost all considered indexes. The median CI of PTV-p is 1.00 for the three considered techniques, while a statistically significant increase ($p < 0.05$) is observed for PTV-p in CK-85% if compared with both CK-95% and UH-DWA (0.991, 0.984, and 0.978). An example of dose distribution can be found in Figure 3; the maximum dose points are all located in the DIL.

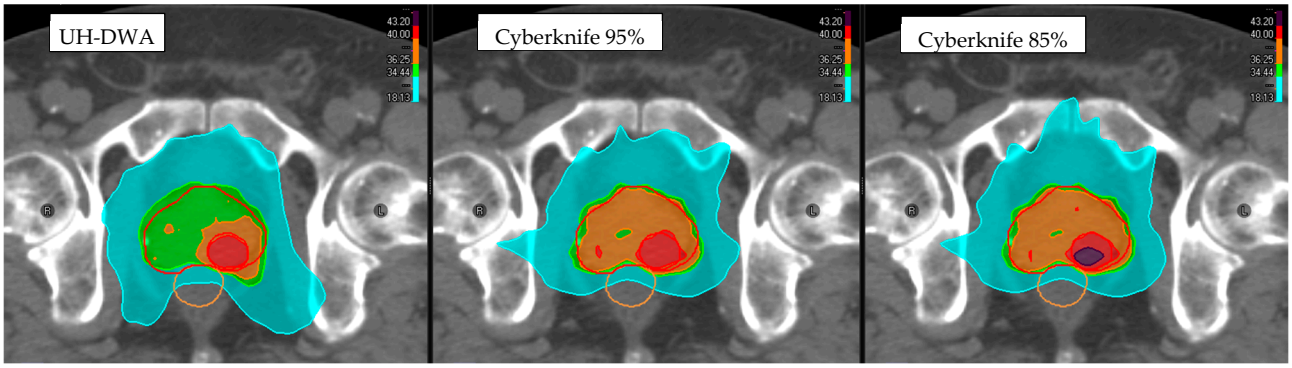

Figure 3. Dose distribution in a 78-year-old man with a dominant lesion in the left peripheral-apex side of the prostate for the three different techniques. Light Blue: 50% of PTV-p prescription dose [PD]; green: 95% of PTV-p PD; orange: 100% of PTV-p PD; red: 100% of PTV-d PD; and purple: 108% of PTV-d PD); R: right; L: left.

3.2. Organs at Risk

Dose escalation to the DIL does not significantly impact the dose received by the OARs (Table 4). In fact, although borderline statistically significant differences between the three planning techniques exist for the rectum, bladder, testis, and bowel cavity, all the considered parameters remain well below the constraints. A visual representation of the dose received by the considered OARs among the three techniques is depicted in Figure 2c.

Table 4. Comparison of median values of dose-volume histogram parameters for considered OARs.

Organs at Risk	Results (Median Value)			Overall (*p*-Value from Friedman Test) *	UH-DWA vs. CK95%	UH-DWA vs. CK85%	CK95% vs. CK85%
Rectum	**UH-DWA**	**CyberKnife 95%**	**CyberKnife 85%**				
V18 Gy	19.00%	19.60%	19.30%	0.0043	$p < 0.05$	$p < 0.05$	ns
V29 Gy	6.80%	6.70%	6.20%	0.86071	ns	ns	ns
V33 Gy	3.10%	2.40%	2.50%	0.08073	$p < 0.05$	ns	$p < 0.05$
V36.25 Gy	0.18%	0.20%	0.30%	0.02431	ns	ns	$p < 0.05$
Rectum Posterior Wall							
D1 cm^3	15.10	16.30	15.56	0.05689	$p < 0.05$	ns	ns
Bladder							
V36.25 Gy	0.50%	1.00%	1.10%	0.0043	$p < 0.05$	$p < 0.05$	$p < 0.05$
V18 Gy	15.00%	16.90%	15.90%	0.21944	$p < 0.05$	$p < 0.05$	ns
Femoral Heads							
V15 Gy (Right)	0.01%	0.80%	0.30%	0.53974	ns	ns	ns
V15 Gy (Left)	0.00%	0.00%	0.00%	0.38674	ns	**	**
Penile Bulb							
V29 Gy	2.20%	0.75%	1.80%	0.95123	ns	ns	ns
Testis							
D20%	0.30	0.74	0.57	0.00004	$p < 0.05$	$p < 0.05$	ns
Bowel Cavity							
Dmean	0.40	1.10	0.95	0.00004	$p < 0.05$	$p < 0.05$	ns
Penis							
V13 Gy	0.30	0.67	0.68	0.08487	ns	ns	ns

* Significant *p*-value if < 0.016 (Bonferroni correction). ** comparison is not possible due to tied values. List of abbreviations: CK = CyberKnife; UH-DWA = ultra-hypofractionated dynamic wave arc; ns = not significant.

4. Discussion

The present study showed that in silico 85% isodose CK treatment plans could generate a higher boost dose to the DIL (PTV-d median D95% = 40.58 Gy and D0.03 cm^3 = 46.66 Gy) while maintaining a lower dose prescription to the prostate volume (PTV-p median D95% = 35.16 Gy and D0.03 cm^3 = 41.63 Gy) with homogeneous dose distribution and respecting all the OARs constraints applied.

Technical advances in the field of RT in recent years have enabled the progressive implementation of UH-RT in various scenarios of localized PCa treatment. As a matter of fact, the use of hypofractionated schedules in PCa has provided sufficient evidence in terms of tumor control results, QoL, toxicity, and reduced treatment time and costs for the patient, and the recent publication of two randomized trials comparing the use of UH-RT versus conventional fractionation (HYPO-RT-PC [14] and PACE-B trials [15]) has been crucial in supporting its use. This in silico planning comparison study showed that UH-RT for localized PCa with a SIB to the macroscopic lesion with CK radiosurgery SBRT-based system, both with 95% and 85% isodose prescriptions is feasible. Dose-volume histograms for the 85% isodose prescription reported better dose coverage up to a maximum of 47 Gy to the DIL PTV while respecting all the OARs constraints previously applied in UH-DWA plans delivered with the VERO system.

The rationale of the present study is based on the recently published data of Tree et al. [23] in the update at 2 years of the PACE-B trial, which reported lower levels of GU and GI Radiation Therapy Oncology Group (RTOG) toxicity for CK vs. standard linac SBRT treatments (significantly lower for GU: 5.8% vs. 16.5%).

Also, in the "FLAME" trial, Kerkmeijer et al. [18] proved that focal boosting the DIL up to 95 Gy in a conventional radiotherapy scheme for 264 patients (vs. 271 patients in the arm without focal boost) improved bDFS and PFS without any relevant additional toxicity. In addition, the preliminary results reported by Marvaso et al. [20] in the "GIVE ME FIVE" trial reported very low acute RTOG GU and GI toxic (G2 4.69% and 1.56%, respectively, and only one patient with GU G3 at 6 months) when a dose escalation to 37.5 Gy in 5 fractions was applied as a SIB to the DIL with the VERO® system.

In this context, a high focal boost strategy to the DIL with SBRT delivery technique is required to improve tumor control while respecting organ at-risk dose constraints. The pattern of failure analysis by Groen et al. [35] demonstrated that a focal boost to the DIL decreased the rates of local failure (7 vs. 21 events) and the development of regional-distant metastasis (32 vs. 56 events).

Similar to our study, Tree et al. [36] confronted two methods of SBRT delivery, CK and VMAT. The dosing scheme applied was a higher prescription dose of 47.5 Gy while maintaining a 36.25 Gy to the whole prostate in five fractions with different PTV margins. Both CK and VMAT planning produced clinically acceptable plans, but certain OARs constraints have not been met for all plans. More violations (43 out of 75) were observed in VMAT planning with larger prostate margins (5 mm).

With the experience derived from the above-mentioned planning study, Nicholls et al. [19] reported in the "SPARC" trial the longest follow-up (56 months) of the first eight patients treated with CK SBRT (at 70% isodose prescription) with focal boost for intermediate and high-risk PCa. No biochemical recurrence was detected at the follow-up time, and early results suggest a 2-year bDFS between 95% and 100%, but grade 2+ acute GU and GI toxicities were 37.5%, while grade 2+ late GU and GI toxicities were 12.5% and 0%, respectively.

A previous study from Aluwini et al. [37] reported the early results of CK SBRT with a focal boost to the DIL in low- and intermediate-risk PCa. Fifty patients received 38 Gy to the prostate and 44 Gy to the MRI-visible tumor in four daily fractions. At a median follow-up of 23 months, the 2-year bDFS was 100%, similar to the oncological results achieved in the "SPARC" trial, but grade 2 acute GU and GI toxicities were 15% and 12%, respectively, while grade 2 late GU and GI toxicities were 10% and 3%, respectively. The acute G2 toxicity reported was slightly lower than those found in the SPARC trial, but probably because only 14 patients out of 50 in this cohort received the boost to the DIL. A summary of the published literature for PCa CK-SBRT plus DIL boost can be found in Table 5.

Finally, when considering the median beam-on time for CK plans was, as expected, considerably higher respect UH-DWA. It should, however, be considered that our median beam-on time for in silico CK plans was 27 min, greatly reduced in comparison with the median of 46 min reported by Tree and colleagues [36] For our cohort of patients treated with the VERO system, the use of a Foley catheter is not required and was not taken into consideration in this in silico planning study.

The primary limit of this dosimetric study is relative to its intrinsic nature of the study and consists of the lack of clinical outcomes. Nevertheless, the experience acquired thanks to this in silico planning study will be applied to the upcoming PRO-SPEED trial in our Institute. This trial aims to evaluate the effectiveness of CK-SBRT treatment on the whole prostate gland plus SIB to the DIL(s) in intermediate-unfavorable to high-risk PCa patients, both in terms of toxicity and oncological outcomes, compared with UH-DWA treatments in a real-world setting. Another relevant limit in the dosimetric analysis was the absence of the prostatic urethra contours. However, the prostatic urethra constraints used by Draulans et al. [25] (D0.035 cm^3 < 42 Gy) or by Nicholls et al. [19] (V42 Gy < 40% and V45.6 Gy < 10%) could probably be respected in the majority of the plans analyzed with the three different

techniques for the dosing scheme taken in consideration by our study. In most of the cases, the location of the DIL would be peripheral and far enough from the central position of the prostatic urethra, and, as a surrogate result, the higher median near-maximum D0.03 cm^3 of the prostate volume was 41.64 Gy for the in silico CK 85% isodose prescription plans, which is lower enough to meet the prostatic urethra constraints previously reported.

Table 5. Overview of published literature of CyberKnife UH-SBRT with or without concomitant DIL boost.

Authors	Risk Group	Patient Cohort	Dose per Fraction (Gy)		Total Fraction	Follow-Up (Months)	bRFS	Acute G2+ Toxicity		Late G2+ Toxicity	
			Prostate	SIB				GU	GI	GU	GI
Nicholls et al. [19], 2020	Int., High	8	7.25	9.5	5	56	100%	37.5%	37.5%	12.5%	0%
Meier et al. [24], 2018	Low, Int.	309	8	-	5	61	97.2%	26%	8.1%	13.3%	2%
Vuolukka et al. [25], 2020	Low, Int., High	213	7.25	-	5	64	100% (L) 87.5% (I) 80% (H)	NA	NA	NA	NA
King et al. [26], 2012	Low	304	7.25	-	5	32	94%	NA	NA	8.5%	2%
Freeman et al. [27], 2011	Low	41	7/7.25	-	5	60	93%	7%	NA	7%	2.5%
Katz et al. [28], 2013	Low, Int., High	304	7/7.25	-	5	60	97% (L) 90% (I) 74% (H)	4.6%	3.6%	9.9%	4.5%
Fuller et al. [29], 2014	Low, Int.	79	9.5	-	4	60	100% (L) 92% (I)	10%	0%	15%	1%
Aluwini et al. [37], 2013	Low, Int.	50	9.5	11	4	23	100%	23%	14%	16%	3%
Herrera et al. [38], 2018	Int., High	9	7.25	9–9.5–10	5	3	100%	25%	5%	NA	NA
Zhao et al. [39], 2021	Low, Int., High	133	7.5	-	5	60	83.6%	1.5%	0.8%	2.3%	0%

5. Conclusions

This in silico planning comparison study showed that UH-SBRT with CK radiosurgery system plus a high focal boost to the DIL is feasible, both prescribing to 95% and 85% isodose lines. Few clinical trials with similar radiosurgery SBRT techniques have been published, and others are ongoing with promising results in terms of oncological outcome and treatment toxicity profile. These encouraging dosimetric results need to be confirmed by oncological outcomes and toxicity data in the upcoming mono-institution phase 2 "PRO-SPEED" IEO trial.

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Data Availability Statement: The data presented in this study are available upon reasonable request from the corresponding author.

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