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Dosimetric evaluation of ultrafractionated dose escalation with simultaneous integrated boost to intraprostatic lesion using 1.5-Tesla MR-Linac in localized prostate cancer

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ABSTRACT

Background: We analyzed a dose escalation of 36.25 Gy to the entire prostate and a dose increment up to 40 Gy with 1.25 Gy increments to intraprostatic lesion (IPL) using simultaneous integrated boost (SIB) in five fractions.

Materials and methods: Eighteen low- and intermediate-risk prostate cancer patients treated with 1.5T MR-Linac were retrospectively evaluated. The same planning computed tomography (CT) images generated four plans: no SIB, 37.5 Gy SIB, 38.75 Gy SIB, and 40 Gy SIB. In four plans, planning target volume (PTV) doses, organ at risk (OAR) doses, and PTV-SIB homogeneity index (HI), gradient index (GI) and conformity index (CI) were compared.

Results: All plans met the criteria for PTV and PTV-SIB coverage. PTV 40 Gy plan has higher maximum PTV and PTV-SIB doses than other plans. The PTV HI was significantly higher in the SIB 40 Gy plan (0.135 ± 0.007) compared to SIB 38.75 Gy plan (0.099 ± 0.007; $p = 0.001$), SIB 37.5 Gy (0.067 ± 0.008; $p < 0.001$), and no SIB plan (0.049 ± 0.010; $p < 0.001$), while there were no significant differences in HI, GI and CI for PTV-SIB between three plans. Four rectum and bladder plans had similar dosimetric parameters. The urethra D5 was significantly higher in SIB 40 Gy plan compared to no SIB plan (37.7 ± 1.1 Gy *vs.* 37.0 ± 0.7 Gy; $p = 0.009$) and SIB 37.5 Gy plan (36.9 ± 0.8 Gy; $p = 0.008$). There was no significant difference in monitor units between the four consecutive plans.

Conclusions: Ultra-hypofractionated dose escalation to IPL up to 40 Gy in 5 fractions with a 1.5-T MR-linac is dosimetrically feasible, potentially paving the way for clinical trials.

Key words: prostate cancer; radiotherapy; stereotactic body radiotherapy; MR-linac; dosimetry

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Introduction

Several randomized and non-randomized studies have found that patients with localized prostate cancer have lower rates of biochemical failure, post-treatment positive biopsies, and distant metastases [1, 2]. It is well known that increasing the radiation dose is beneficial in the biochemical control for prostate cancer patients [3, 4]. However, despite higher radiotherapy (RT) doses, nearly one-third of patients still experience isolated local failure, frequently originating from the primary tumor site [5, 6]. Local recurrence is clinically significant because a correlation between local control

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and distant metastasis, as well as survival, has been proposed [6, 7]. Therefore, increasing the radiation dose to intraprostatic lesion (IPL) may improve biochemical control [8, 9].

Recent advances in radiology have led to the development of functional imaging, including multiparametric magnetic resonance imaging (mpMRI), which can be used to evaluate prostate cancer, including tumor localization, aggressiveness of tumor, treatment response, and diagnosing of recurrence [10]. Modern irradiation techniques permit administering a higher dose to IPL detected with mpMRI at each fraction in conjunction with whole prostate RT, as was known as the simultaneous-integrated boost (SIB) technique [9]. A systematic review demonstrated that a focal boost to IPL with the SIB technique was effective and safe, with biochemical disease free survival (bDFS) rates ranging from 79% to 100% [11]. Recently, the FLAME trial has demonstrated that adding a focal boost to the IPL improves bDFS without affecting toxicity or quality of life in patients with localized intermediate- and high-risk prostate cancer [12].

Hypofractionation can be expected to improve the therapeutic ratio due to the growing evidence for a prostate cancer ratio of 1.5 Gy [13]. Multiple randomised phase III trials have demonstrated the safety and effectiveness of moderate- and ultra-hypofractionated RT compared to conventional fractionated RT [14, 15]. Recent studies have demonstrated the feasibility of SIB technique with moderate hypofractionated [16–18] and ultra-hypofractionated RT [19–21]. The clinical introduction of magnetic resonance (MR)-guided linear accelerators (MR-Linac) has significantly impacted RT workflows by enabling MRI prior to and during beam-on, and these systems can counteract anatomical changes between treatment fractions, including rotation and deformations of the targets and organs-at-risk (OARs), by performing interfraction plan adaptation [22, 23]. Furthermore, a reduction in PTV margin for the prostate of up to 3 mm has been suggested and used in recent MRgRT studies, allowing for safe dose escalation [24, 25].

Previously, we demonstrated the dosimetric feasibility of delivering 78 Gy to the entire prostate and 86 Gy to IPL using the SIB technique delivered in 39 fractions [9], and we routinely employ this technique in clinical practice [26]. Literature data suggest that 36.25 Gy is an appropriate dose to avoid urinary side effects, but it may not be sufficient to ensure proper local control, particularly for prostate cancer with a high-to-intermediate risk. In addition, increasing the total dose may improve local control at the expense of increased urinary and rectal toxicity. The purpose of this study is to assess the dosimetric feasibility of increasing IPL dose to 40 Gy with 1.25 Gy increments delivered in 5 fractions in patients receiving 36.25 Gy to the entire prostate in terms of target volume coverage and OARs doses.

Materials and methods

Patient selection

The clinical and dosimetric parameters of 18 low- and intermediate-risk prostate cancer patients who were treated with ultra-hypofractionated RT using 1.5T MR-Linac between June 2020 and April 2021 were retrospectively evaluated. A previous diagnostic mpMRI revealing an IPL was required. All patients provided written informed consent for the use of their anonymized data in research and education. Patients with tumors located centrally close to the urethra and those with more than or equal to three IPLs were not included in this dosimestric study.

Target volumes

The patients underwent two imaging sets: a computed tomography scan (CT) to calculate the dose distribution and diagnostic mpMRI, which included diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) images, as well as high spatial resolution T2-weighted (T2W) images in three different planes. During simulation and treatment, patients were instructed to have empty bowels and a comfortably full bladder. The planning CT images and diagnostic mpMRI were registered using a deformable registration method. An expert radiologist delineated the prostate and IPL contours on mpMRI and propagated them on CT imaging based on the resulting deformation vector field, which was approved by the radiation oncologist.

In low-risk patients, the clinical target volume (CTV) encompasses only the prostate, while in intermediate-risk patients, it encompasses both the prostate and the proximal two-thirds of the sem-

inal vesicles. The planning target volume (PTV) of the prostate was defined as a 3-mm expansion of the CTV in all directions, while the PTV-SIB was defined as a 3-mm expansion of the IPL in all directions. The OARs included the rectum, bladder, urethra and femoral heads. The rectum was delineated as extending from the anal verge to the rectosigmoid junction [27]. The femoral heads were contoured to the level of the ischial tuberosities.

Treatment planning

All patients had undergone 1-mm slice thickness CT with a comfortably full bladder and empty rectum [28]. The prescribed dose for prostate ± seminal vesicles was 36.25 Gy delivered in 5 fractions. A total of four plans were generated from the same planning CT images: no SIB, 37.5 Gy SIB, 38.75 Gy SIB and 40 Gy SIB plan. All plans were computed with the Unity MR-Linac-specific Monaco treatment planning system (v5.40.01), taking into account the 1.5 T magnetic field using a GPU-based Monte Carlo dose calculation platform (GPUMCD) [29]. All plans were created using the "step-and-shoot" technique, which is the only IMRT technique currently available in the Unity MR-Linac system. On the original CT dataset, 12 co-planar field IMRT plans were generated for each treatment plan. All plans were computed utilizing the 1.5 T-MR-Linac (Unity® MR Linac System, Elekta AB, Stockholm, Sweden) with 7 MV flattening filter-free (FFF) photons, 0.2 cm grid spacing, and 2% statistical uncertainty per control point. The Unity is designed to have a fixed-dose rate of 425 MU/min. The multi-leaf collimator (MLC) width of 1.5 T MR-Linac is 7.2 mm.

The plan was optimized to ensure that PTV and PTV-SIB receive at least 95% of prescribed dose. The volume receiving more than 107% of the prescribed dose was less than 1%. The dose constraints for OARs were summarized in Table 1. The target volumes receiving 95% (V_{95}) and 107% (V_{107}) of the prescribed dose were calculated. Target homogeneity index (HI) was calculated as:

$$HI = [(D_2 - D_{98})/D_{50}], \text{ where } D_2 \text{ and } D_{98}$$

— the minimal doses to 2% and 98% of the target volumes, respectively,were used as surrogates for maximum and minimum doses. A greater HI value indicated poorer uniformity of the dose distribution. The gradient index (GI) was calculated as: $V_{50\%.RI}$ / V_{RI},, where V_{RI} represents prescription isodose volume, and $V_{50\%.RI}$ is the volume of 50% of reference isodose [30]. The conformity index (CI) was defined as the formula: V_{RI}/TV where V_{RI} represents the volume of the reference isodose, and TV represents the target volume [31]. The value of CI ranged from 0–1, with a value closer to 1 indicating better conformity of the dose to the PTV.

Table 1. Dose constraints for organs at risk

Organs	Constraints
PTV	$V_{36.25Gy} \geq 95\%$
Rectum	$V_{36Gy} < 1$ cc
	$V_{100\%} < 5\%$
	$V_{90\%} < 10\%$
	$V_{80\%} < 20\%$
	$V_{75\%} < 25\%$
	$V_{50\%} < 50\%$
Bladder	$V_{37Gy} < 5$ cc
	$V_{100\%} < 10\%$
	$V_{50\%} < 40\%$
Urethra	$D_{5\%} < 38$ Gy
Femur	$D_{1cc} < 20$ Gy

PTV — planning target volume

The volumes of the rectum and bladder receiving 100% to 50% of the prescribed doses were calculated for each plan. The urethra dose receiving 5% of prescribed dose (5%) and doses of 1 cc of the femurs were also measured.

Quality assurance

For point dose and fluence verification PTW Octavius® 1500MR (PTW Freiburg, Germany) was used. The phantom was placed on the MR-linac couch top without a comfort mattress for quality assurance (QA) of the patient plan. The majority of treatment plans are measured with the phantom centered laterally on the couch using the sagittal laser. The Unity MR-linac's isocenter is fixed in lateral and vertical position relative to the patient. The correct alignment of the phantom/chamber array was established using the on-board MR-linac MV imaging panel and by examining the location of the dose maximum of open fields measured with the phantom/array. Using a 3 mm/3% gamma criterion, comparing measured and simulated dose distributions relative to the local dose (Fig. 1). Passing rates of more than

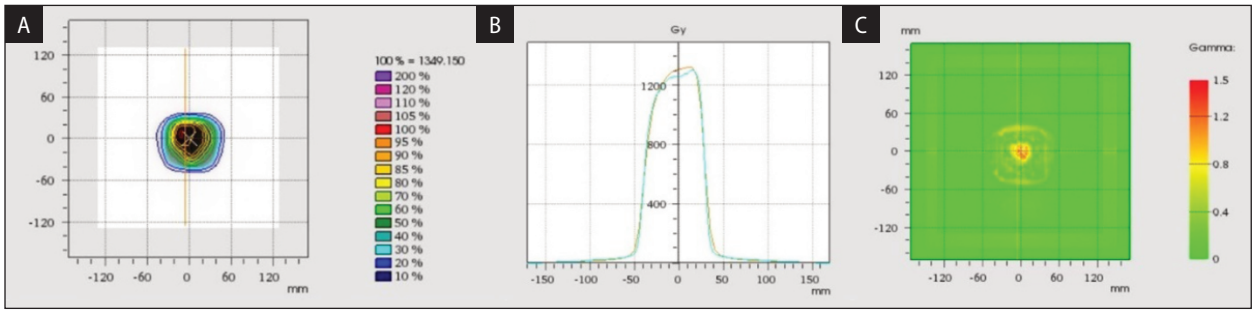

Figure 1. The fluence analysis demonstrating (**A**) greyscale and isodoses, (**B**) TG profile, and (**C**) gamma distribution of a representative plan

95% were considered acceptable, with a median pass rate of 98.2% (range: 96.7–100%).

Statistical analysis

For the statistical analysis, SPSS 22.0 (SPSS for Windows, IBM Corp., Armonk, NY, USA) and MedCalc version 20.111 (MedCalc Software Ltd., Ostend, Belgium) were used. Means and standard deviations, medians and ranges were calculated for descriptive analysis. The D_n and V_n were calculated for PTV and OARs. V_n represents percentage organ volume receiving ≥ *n*Gy and D_n is the percentage of organ receiving *n*% of the prescribed dose. In four plans, PTV doses, OARs doses, HI for PTV and PTV-SIB were compared. To determine the significance of differences in PTV and OARs doses in each plan, the one-way analysis of variance (ANOVA) test and Wilcoxon's matched-pairs test were used. All reported *p* values are two-sided, with $p < 0.05$ considered statistically significant.

Results

Patients

The median age and serum PSA levels were 71 years (range, 60–82 years) and 9.3 ng/mL (range, 2.3–18.0 ng/mL), respectively. Four patients (22%) had clinical T2a disease, eight (45%) had T2b disease, and six (33%) had T2c disease. Five patients (28%) had tumors with a Gleason score (GS) of 6, and 13 (72%) had tumors with a GS of 7. Seven patients (39%) had low risk and 11 patients (61%), intermediate risk disease according to D'Amico risk stratification criteria [32].

Median number of IPLs was 1 (range, 1–3), 12 patients having one IPL, 4 patients with two IPLs, and two patients with three IPLs. The mean IPL volume was 6.4 ± 2.1 cm^3.

Target-volume doses

The mean PTV and PTV-SIB volumes were 81.0 ± 26.1 cm^3 and 12.5 ± 7.3 cm^3, respectively. All plans met the criteria for PTV and PTV-SIB coverage and Figure 2 shows planning CT axial sections depicting the PTV and PTV-SIB dose distributions for four plans of a representative patient. The mean D2 for no SIB was significantly lower than those calculated in SIB 37.5 Gy, SIB 38.75 Gy and SIB plans 40 Gy (all $p < 0.001$). Similarly, mean D2 was significantly higher in SIB 40 Gy plan compared to that of SIB 38.75 Gy plan ($p = 0.002$) and SIB 37.5 Gy pan ($p < 0.001$). However, there was no significant difference between the minimum PTV and PTV-SIB doses prescribed by the four different plans (Tab. 2).

The PTV HI was significantly higher in the SIB 40 Gy plan compared to SIB 38.75 Gy plan ($p = 0.001$) and SIB 37.5 Gy ($p < 0.001$), while the PTV dose distribution was significantly better in the no SIB ($p < 0.001$) plan when compared to other plans (Fig. 3). We were unable to compare CI and GI for PTV due to the fact that high doses of IPL may cause significant changes in dose gradient and conformity within the prostate. Instead, only comparisons were made for PTV-SIB. There were no significant differences in HI, GI and CI for PTV-SIB between three plans.

Organs at risk doses

Table 3 depicts the OARs doses according to four different plans. OAR dose constraints were met by all plans. There was no significant difference in D_{100}, D_{99}, D_{95}, D_{75} and D_{50} values between four plans for

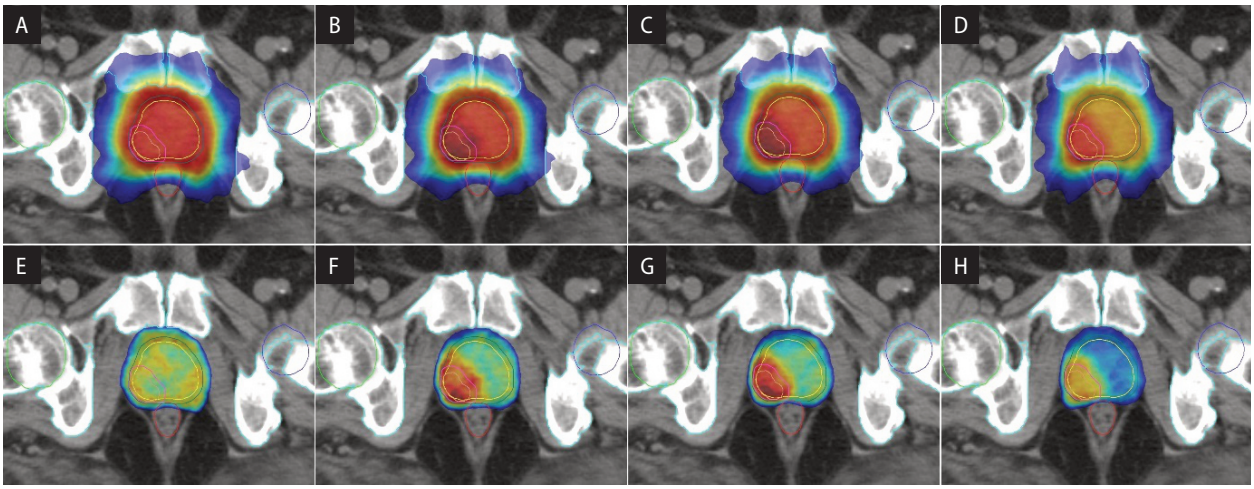

Figure 2. Representative axial computed tomography (CT) slices showing 95% of prescribed dose distributions for (**A**) no SIB, (**B**) 37.5 Gy SIB, (**C**) 38.75 Gy SIB, and (**D**) 40 Gy SIB plans, and 50% of prescribed dose distributions for (**E**) no SIB, (**F**) 37.5 Gy SIB, (**G**) 38.75 Gy SIB, and (**H**) 40 Gy SIB plans

Table 2. Planning target volume doses according to four different plans

	No SIB [Gy]	37.5 Gy SIB [Gy]	38.75 Gy SIB [Gy]	40 Gy SIB [Gy]
PTV				
D_2	37.9 ± 0.2	38.7 ± 0.2	39.9 ± 0.2	41.3 ± 0.2
D_{50}	37.2 ± 0.2	37.3 ± 0.3	37.7 ± 0.4	38.0 ± 0.7
D_{95}	36.5 ± 0.2	36.5 ± 0.2	36.5 ± 0.2	36.5 ± 0.1
D_{98}	36.1 ± 0.3	36.2 ± 0.2	36.2 ± 0.2	36.2 ± 0.2
HI	0.049 ± 0.010	0.067 ± 0.008	0.099 ± 0.007	0.135 ± 0.007
PTV-SIB				
D_2	–	38.9 ± 0.2	40.2 ± 0.2	41.6 ± 0.2
D_{50}	–	38.2 ± 0.2	39.5 ± 0.1	40.9 ± 0.1
D_{95}	–	37.7 ± 0.1	38.8 ± 0.1	40.2 ± 0.2
D_{98}	–	37.6 ± 0.1	38.7 ± 0.1	39.9 ± 0.2
HI	–	0.035 ± 0.003	0.039 ± 0.006	0.041 ± 0.005
GI	4.59 ± 0.26	4.59 ± 0.27	4.59 ± 0.27	4.60 ± 0.26
CI	0.57 ± 0.26	0.58 ± 0.26	0.58 ± 0.26	0.58 ± 0.26
MU	1912 ± 163	1874 ± 120	1831 ± 128	1931 ± 210

SIB — simultaneous integrated boost; PTV — planning target volume; SIB — simultaneous integrated boost; Dn — percent of target volume n% of the prescribed dose; HI — homogeneity index; GI — gradient index; CI — conformity index; MU — monitor unit

the rectum and bladder (Fig. 4). There was no statistically significant difference in the mean rectum doses and D_{1cc} for no SIB, SIB 37.5 Gy, SIB 38.75 Gy, and SIB 40 Gy plans, which were 11.9 ± 2.3 Gy, 12.2 ± 2.2 Gy, 12.4 ± 2.3 Gy, and 12.0 ± 2.4 Gy, respectively (Fig. 5). Similarly there was no significant difference in mean bladder doses and D_{1cc} between four consecutive plans. The urethra D_5 was significantly higher in SIB 40 Gy plan compared to no SIB plan (37.7 ± 1.1 Gy *vs.* 37.0 ± 0.7 Gy; p = 0.009) and SIB 37.5 Gy plan (36.9 ± 0.8 Gy; p = 0.008) (Fig. 6). However there was no significant difference in the urethra D_5 value between SIB 40 Gy and SIB 38.75 Gy plan (37.3 ± 0.8 Gy; p = 0.12). The femur D_{1cc} were 14.0 ± 2.0 Gy, 14.0 ± 1.6 Gy, 13.5 ± 2.1 Gy, and 13.5±2.0 Gy, respectively, for four consecutive plans, with no significant difference.

The mean monitor units for no SIB, 37.5 Gy SIB, 38.75 Gy SIB and 40 Gy SIB plans were 1912 ± 163, 1874 ± 120, 1831 ± 128, and 1931 ± 210, respective-

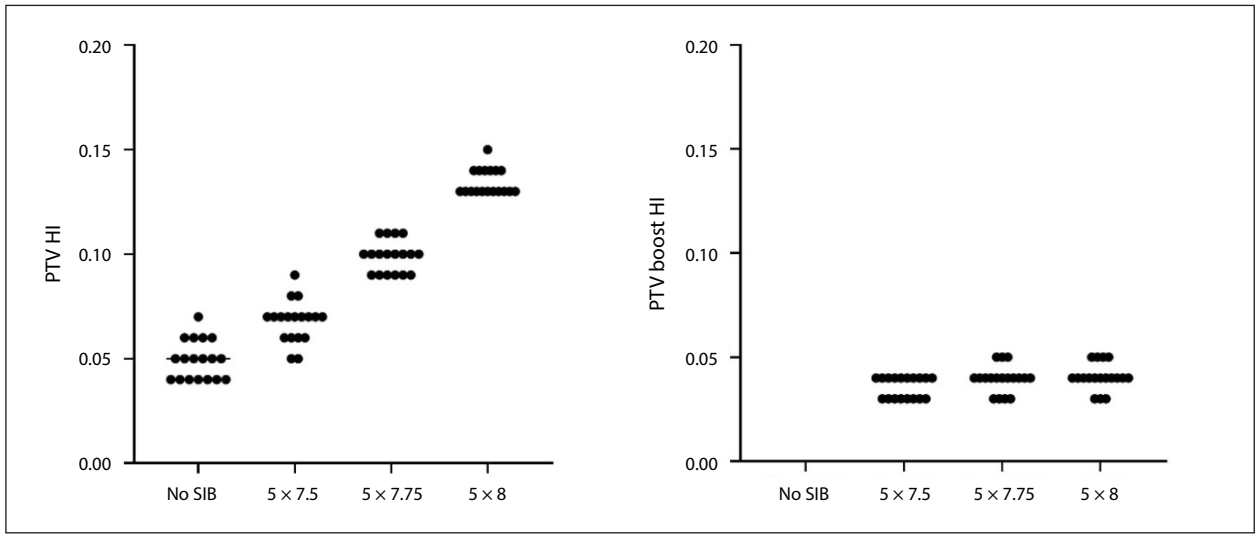

Figure 3. Homogeneity index (HI) for prostate planning target volume (PTV) and intraprostatic lesion (PTV-SIB)

Table 3. Organs at risk doses according to four different plans

	No SIB (%)	37.5 Gy SIB (%)	38.75 Gy SIB (%)	40 Gy SIB(%)
Rectum				
$V_{36.25Gy}$	0.6 ± 0.3	0.7 ± 0.6	0.8 ± 0.7	0.8 ± 0.9
V_{36Gy}	0.6 ± 0.4	0.7 ± 0.5	0.9 ± 0.7	0.9 ± 0.9
$V_{32.63Gy}$	5.0 ± 1.5	5.0 ± 2.0	5.1 ± 2.2	4.4 ± 2.0
V_{29Gy}	8.7 ± 2.4	8.7 ± 2.9	8.9 ± 3.3	7.8 ± 3.0
$V_{27.19Gy}$	10.6 ± 2.8	10.5 ± 3.2	10.9 ± 3.8	9.6 ± 3.5
$V_{18.13Gy}$	24.2 ± 6.0	24.4 ± 8.4	27.3 ±8 .1	24.5 ± 7.3
Bladder				
$V_{36.25Gy}$	1.6 ± 1.5	1.5 ± 1.3	2.0 ± 1.6	2.2 ± 1.7
V_{36Gy}	2.2 ± 1.5	2.4 ± 1.5	2.7 ± 1.5	2.8 ± 1.5
$V_{18.13Gy}$	23.3 ± 9.4	24.4 ± 9.7	27.7 ± 11.5	28.8 ± 13.2

PTV — planning target volume; SIB — simultaneous integrated boost; Vn — percentage organ volume receiving ≥ nGy

ly. There was no significant difference in monitor units between the four consecutive plans.

Discussion

In this dosimetric study, we found that ultra-hypofractionated dose escalation to IPL up to 40 Gy given in 5 fractions with a 1.5-T MR-linac is feasible with adequate dose distribution in target volumes and without an increase in OAR doses, except for urethral doses, which are higher in the SIB 40 Gy plan than in other plans, but still within dose constraint limits. Although dose homogeneity in the prostate worsens with increasing IPL doses, there was no significant difference in IPL dose homogeneity and conformity across plans.

Given that the α/β ratio for prostate cancer is estimated to be around 1.5 Gy, the linear-quadratic model suggests that higher doses per fraction may result in a better therapeutic ratio by sparing organs at risk with a higher α/β [13, 33]. As a result, prostate stereotactic body radiation therapy (SBRT) is now recognized as an emerging technology that may be considered an appropriate alternative to conventional fractionation in clinics equipped with appropriate technology and expertise. Previous studies showed that ultra-hypofractionated RT with a total dose of 36.25 Gy delivered in 5 fractions to the entire prostate gland was as-

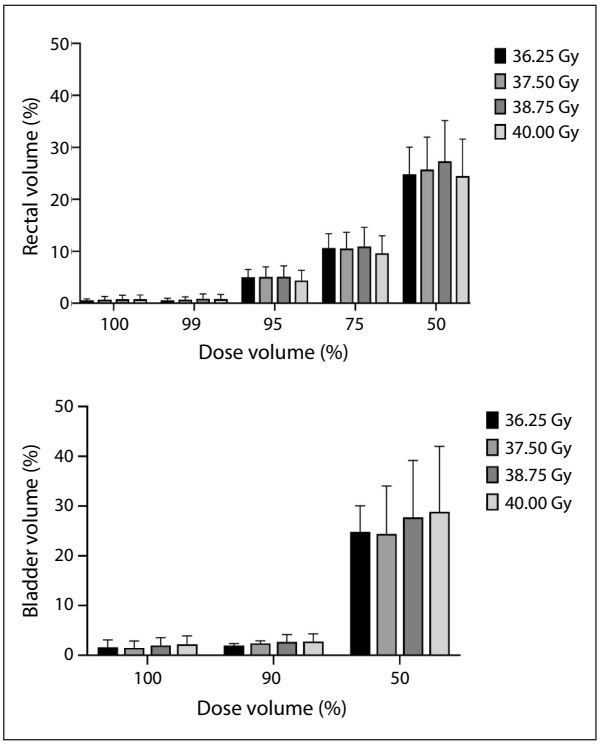

Figure 4. Box and whisker plot demonstrating rectum and bladder doses according to dose volume parameters across each plan; PTV — planning target volume; HI — homogeneity; SIB — simultaneous integrated boost

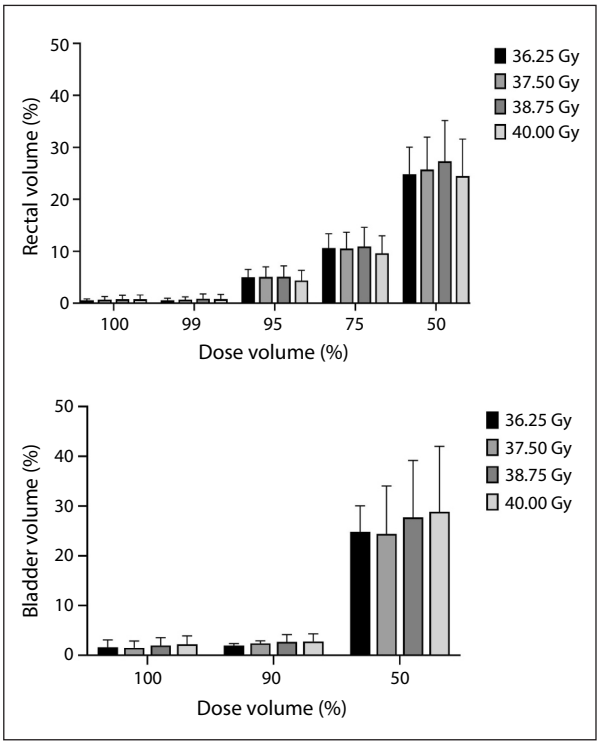

Figure 5. Box and whisker plot demonstrating rectum and bladder doses received by 1 cc volume and mean doses measured in four different plans

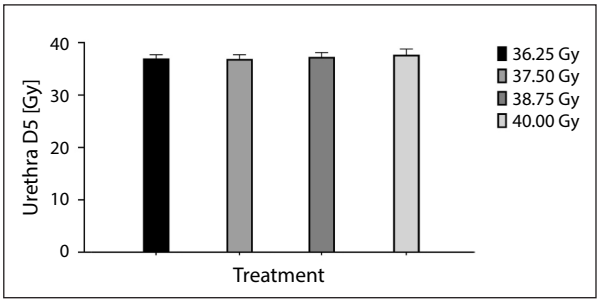

Figure 6. Box and whisker plot demonstrating dose receiving 5% of urethra volume

sociated with acceptable levels of acute and late toxicity [15, 34, 35]. A meta-analysis supports the routine use of five-fraction SBRT with a median fraction dose of 7.25 Gy in five fractions in localized prostate cancer [36]. The reported 5- and 7-year rates of bRFS were 95.3% and 93.7%, respectively, and the estimated rates of late grade 3 and higher genitourinary and gastrointestinal toxicity were 2% and 1%, respectively. However, it is unknown whether this dose is sufficient to achieve long-term biochemical control, particularly in men with intermediate- to high-risk characteristics.

Higher doses of 50 Gy in 5 fractions to the entire prostate, on the other hand, have been associated with excellent rates of 5-year biochemical control, at the potential cost of an increased risk of high-grade toxicity [37]. Therefore, rather than increasing the SBRT dose to the entire prostate gland, another approach is to selectively increase the dose to tumor nodules within the prostate, where the majority of local recurrences occur.

In most cases, mpMRI protocols can identify prostate cancer foci, and MR-defined lesions have reasonable spatial agreement when compared to whole mount prostatectomy specimens [38]. There is a growing body of evidence demonstrating the efficacy of IPL focal dose escalation using conventional fractionation or moderate hypofractionation. A recent systematic review identified 22 trials of prostate RT with focal dose escalation to the IPL that reported biochemical control rates between 80% and 100% [11]. Previous research has shown that planning a SIB to MR-defined tumor nodules during prostate SBRT appears to be dosimetrically feasible [19, 21, 39]. The results of these studies, however, varied due to differenc-

es in RT techniques, treatment planning systems, treatment devices, and dose constraints for OARs used. Murray et al. [39] examined boosting IPL in the context of SBRT with a dose prescription of 42.7 Gy in 7 fractions; IPL was initially prescribed 115% of the PTV-Prostate prescription; and IPL dose was increased in 5% increments until OAR constraints were reached in 10 prostate cancer patients. The authors found that increasing the IPL dose to a median of 125% of the PTV-Prostate prescription was feasible, albeit at the expense of an increased rectal normal tissue complication probability, which in some cases became unacceptable. McDonald et al. [21] assessed the dosimetric outcomes and early toxicity results of 26 prostate cancer patients treated with SBRT consisting of a dose of 36.25 Gy to the entire prostate and a SIB of 40 Gy to the MRI-defined lesions delivered in 5 fractions. The authors concluded that a focal SIB to intraprostatic tumor nodules was feasible and can be incorporated into prostate SBRT without significantly worsening acute toxicity. Nicholls et al. [20] published an interim analysis of 8 patients who received 36.25 Gy in 5 fractions with a simultaneous boost to a maximum of 47.5 Gy, as allowed by OAR constraints. Of the dose constraints, 10 of 80 were not achieved, but all with minor dose variations. All of these studies, however, were generated for treatment with conventional linear accelerators [21, 39] or CyberKnife [20], both of which require PTV margins of 5–7 mm to compensate for target motion and lower resolution image guidance during treatment [40, 41].

In recent years, MRI has been integrated into linear accelerators for MRgRT, which provides better image quality than CT, online adaptive radiation therapy, and real-time cross-sectional imaging [42]. Recent studies have suggested and utilized a 3 mm PTV margin for the prostate due to the ability of MR Linac to adapt the dose distribution daily and perform imaging with high soft tissue contrast during beam delivery [25]. Single center retrospective series demonstrated the feasibility of MRgRT in the treatment of prostate cancer [43, 44]. In a phase 2 study, Bruynzeel et al. [45] evaluated 101 patients treated with 7.25 Gy to the target volume using daily plan adaptation in 5 fractions using MRgRT. The maximum cumulative grade ≥ 2 early GU and GI toxicity, as determined by any symptom at any study time point, was found to be 23.8% and 5.0%, respectively. Tight margins used during MRgRT allow for safe dose escalation to IPL without increasing OARs doses. In this current study, we evaluated whether dose escalation to IPL by 0.25 Gy increments in each fraction has any impact on target volume and OARs doses. Our findings show that dose escalation has no effect on prostate and SIB doses, with the exception of dose homogeneity in prostate, which worsened as IPL doses increased. This may be because higher IPL doses also increase maximum doses in the prostate. However, there were no significant differences in dose homogeneity and conformity for IPL doses across each plan. The OARs doses, particularly rectum and bladder, were all similar and increasing doses to IPL did not alter OARs doses, except for urethra doses. Urinary toxicity after SBRT has been extensively studied, and literature data suggest that 36.25 Gy is an appropriate dose to avoid urinary side effects but may not be enough to ensure proper local control. Dose escalation using a urethral sparing approach is feasible with a strict dose maximum dose constraint to the urethra of D_5 38 Gy, which was met in all plans, demonstrating the potential safety of our dose escalation regimen using the SIB technique [46].

Our study has some limitations, including a small sample size and the possibility of enrollment bias. Second, in a small number of patients, we compared the dosimetric parameters of MR-Linac plans. A large number of patients with different planning algorithms are required to reach definitive conclusions. Furthermore, for clinical decisions, the efficacy and toxicity of SIB plans with longer follow-up are required. Thirdly, we assessed the dose escalation up to 40 Gy for IPL delivered in 5 fractions, as our objective was to determine the technical feasibility of these doses. Dosimetric feasibility of doses higher than 40 Gy for IPL or the entire prostate may be the subject of additional research. Last, we could only use step-and-shoot IMRT plans, which are the only technique available in the Unity MR-Linac system. However, once VMAT systems are in place, another study evaluating the dose distributions of step-and-shoot IMRT plans and VMAT plans for MRgRT could be considered. Aside from these limitations, our study is significant in demonstrating the dosimetric feasibility of dose escalation up to 40 Gy to IPL in five fractions delivered with MR-Linac, which

opens the door for further clinical trials. Furthermore, with the potential benefit of DWI, which is currently available in the Elekta Unity MR-Linac system, an adaptive plan could be performed using high resolution 1.5-Tesla MR, and a dose painting plan could be generated based on treatment response measured with DWI-MR after each fraction, potentially paving the way for more precise personalized treatment.

Conclusions

Our findings demonstrated that in patients with localized prostate cancer, MRgRT dose escalation up to 40 Gy to IPL in five fractions was dosimetrically feasible. To demonstrate its efficacy, researchers will need to investigate the toxicity profiles and clinical outcomes of targeting IPL with a focal SIB to 40 Gy using a 1.5-T MR-Linac over longer time periods. Our future clinical practice and clinical trials will be based on the results of this study.

Conflict of interest

The authors declare no conflicts of interest.

Funding

None declared.

Data sharing statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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