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Prostate brachytherapy

Re-distribution of brachytherapy dose using a differential dose prescription adapted to risk of local failure in low-risk prostate cancer patients

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ABSTRACT

Background and purpose: We investigated the application of a differential target- and dose prescription concept for low-dose-rate prostate brachytherapy (LDR-BT), involving a re-distribution of dose according to risk of local failure and treatment-related morbidity.

Material and methods: Our study included 15 patients. Multi-parametric MRI was acquired prior to LDR-BT for gross tumor volume (GTV) delineation. Trans-rectal ultrasound (US) images were acquired during LDR-BT for prostate gland- ($CTV_{Prostate}$) and organs at risk delineation. The GTV contour was transferred to US images after US/MRI registration. An intermediate-risk target volume ($CTV_{Prostate}$) and a high-risk target volume (CTV_{HR} = GTV + 5 mm margin) were defined. Two virtual dose plans were made: $Plan_{risk\text{-}adapt}$ consisted of a de-escalated dose of minimum 125 Gy to the $CTV_{Prostate}$ and an escalated dose to 145–250 Gy to the CTV_{HR}; $Plan_{ref}$ included the standard clinical dose of minimum 145 Gy to the $CTV_{Prostate}$. Dose-volume-histogram (DVH) parameters were expressed in equivalent 2 Gy fractionation doses.

Results: The median $D_{90\%}$ to the GTV and CTV_{HR} significantly increased by 44 Gy and 17 Gy, respectively when comparing $Plan_{risk\text{-}adapt}$ to $Plan_{ref}$. The median $D_{10\%}$ and $D_{30\%}$ to the urethra significantly decreased by 9 Gy and 11 Gy, respectively and for bladder neck by 18 Gy and 15 Gy, respectively. The median rectal $D_{2.0\ cm^3}$ had a significant decrease of 4 Gy, while the median rectal $D_{0.1\ cm^3}$ showed an increase of 1 Gy.

Conclusions: Our risk adaptive target- and dose prescription concept of prescribing a lower dose to the whole gland and an escalated dose to the GTV using LDR-BT seed planning was technically feasible and resulted in a significant dose-reduction to urethra and bladder neck.

Excellent long-term biochemical control rates have been reported after permanent low-dose-rate (LDR) brachytherapy (LDR-BT) in patients with low-risk prostate cancer (T1–T2b, PSA < 10 ng/mL, Gleason score ⩽6) [1–5]. One study reported a 7 year actuarial freedom from biochemical recurrence rate of 94% and an overall survival rate of 93.4% in 1006 low-risk and intermediate-risk patients [1]. Another study observed 575 low-risk patients and reported a 12 year biochemical progression-free survival of 98.6% [2].

However, treatment-related side-effects after LDR-BT are frequent, such as irritative and obstructive urethral symptoms, urinary incontinence, acute urinary retention (AUR) i.e. inability to empty the bladder and flare, which is a recurrent worsening of urinary symptoms after experiencing a symptom-free period [6–8]. These side-effects are usually temporary and most intense between 1 and 3 months post LDR-BT and decrease gradually to normal condition after 1–3 years [6]. AUR is classified as the most predominant severe acute toxicity post LDR-BT and requires catheterization, and patients who obtain AUR experience a significantly worse quality of life compared to patients without [8]. AUR rates of 6% and 34% have been reported [8–9]. In one study 92 out of 225 patients experienced increased lower urinary tract symptoms, including high-voiding frequency and urinary retention [6], while another study reported an incidence of flare in 370 (International Prostate Symptom Score (IPSS) ⩾5) and 214 (IPSS ⩾8) out of 712 patients [7].

The high tumor control rates in combination with treatment-related toxicity has resulted in an increased interest in

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partial- and focal therapy, aiming to achieve comparable cancer control rates with less side-effects by irradiating only the known disease areas within the prostate [10–14]. Partial- and focal therapy is feasible by using established multi-parametric MR imaging (mpMRI) with T_2-weighted (T_2W)-, diffusion-weighted (DW)- and dynamic contrast-enhanced (DCE) sequences to visualize the gross tumor volume (GTV) [15–16].

However, studies on histology and MR imaging (MRI) have shown that mpMRI fails to visualize smaller tumors [17–19]. In addition, a study on biochemical failure after partial prostate irradiation to the peripheral zone in 318 patients (low-risk- and intermediate-risk patients), showed a median PSA failure-free survival rate at 8 years of only 78.1% with a 95%-confidence interval of 69.5–84.5 [13].

Thus, performing radiotherapy to selected prostatic sub-volumes introduces the risk of under-dosing cancerous sections, which are not visible on mpMRI and hence not included in the GTV. The clinical significance of undetected tumors is not clear, however, small satellites with a more adverse Gleason grade are common [20].

Rather than choosing between not treating these invisible satellites and fully treating them, we propose an alternative target- and dose prescription concept where the prostate gland without visible macroscopic disease is assumed to be at lower risk of local failure than visible GTV lesions. According to this concept, intermediate-risk- and high-risk clinical target volumes were defined, related to the prostate gland and the GTV, respectively. An adaptive dose prescription was applied such that the entire prostate gland was irradiated but to a lower dose than the high-risk volume. Such a risk adaptive target volume concept with a stepwise dose prescription is similar to what is currently being used in gynecological brachytherapy, where the high-risk target volume is prescribed to a dose higher than 85–90 Gy and the intermediate-risk target volume is prescribed to a dose of minimum 60 Gy [21]. Another study investigated the application of dual-isotope seed implants and found that the biological effective dose (BED) to the prostatic tumor could be increased simultaneously as decreasing the peripheral dose [22].

The aim of this study was to investigate the feasibility of performing a re-distribution of dose using LDR-BT seeds, such that a de-escalated dose was prescribed to the entire prostate gland and an escalated dose to the MRI-visible prostatic tumor lesion. It is hypothesized that this strategy would achieve equal rates of tumor control as well as reduced dose to organs at risk (OAR) to a degree that has potential to reduce short- and long-term morbidity.

Materials and methods

Patients

For this study, we used the clinical images and delineations of 15 consecutive patients with low-risk prostate cancer (T1c-T2b, 6 < PSA (ng/mL) <13.5, Gleason score 6 or 7) who were treated according to our standard permanent LDR-BT procedure using I-125 seeds.

Imaging

MpMRI sequences (T_2W-, DW- and DCE-MRI) were acquired on a 3T MRI scanner (Achieva, Philips, Best, The Netherlands) as part of the routine screening of these patients for their suitability for brachytherapy treatment. The T_2W-MRI included an axial-, a sagittal- and a coronal turbo-spin-echo sequence with echo time (TE) = 120 ms, repetition time (TR) = 8800 ms and slice thickness = 3 mm. The DW-MRI included a single-shot echo planar sequence with *b*-values: 0, 188, 375, 563 and 750 s/mm^2. The DCE-MRI included a spoiled gradient echo sequence with TE = 1 ms, TR = 4 ms, flip angle = 13 degrees, 120 time points at 2.5 s time resolution. Trans-rectal ultrasound (US) images (slice spacing = 1 mm) were acquired during the implantation. A manual rigid registration based on the prostate gland was performed between the US images and the T_2W-MRI.

Targets and OAR

The largest of the visible tumors i.e. the index lesion (GTV) was contoured on the axial T_2W-MRI, using information from all mpMRI sequences based on a hypodense T_2W-MRI image, a low apparent diffusion coefficient on DW-MRI and a high K-trans value on DCE-MRI. The GTV structure was transferred to the US images after US/T_2W-MRI registration [23]. A high-risk clinical target volume (CTV_{HR}) was defined on the US images as the GTV plus a 5 mm isotropic margin constrained to the OAR and allowing no margin expansion outside the prostate volume [23]. The added 5 mm margin was applied to account for uncertainties related to contouring, image registration and seed migration [23]. An intermediate-risk clinical target volume was defined as the entire prostate: $CTV_{Prostate}$. The $CTV_{Prostate}$ and OAR (urethra, rectum, bladder and bladder neck) were defined on US images. The bladder neck volume included the intersection between bladder and urethra on US images plus a 5 mm isotropic margin. In addition, $CTV_{Prostate}$ plus a 3 mm isotropic margin ($CTV_{Prostate+3mm}$) constrained to the anterior rectal wall and the bladder wall was defined for dose reporting purposes according to GEC/ESTRO/EAU recommendations [24].

Dose planning strategy

Our risk adaptive dose plan ($Plan_{risk\text{-}adapt}$) involved de-escalation from 145 Gy (standard clinical dose) to 125 Gy to the $CTV_{Prostate}$ and an escalated dose to 145–250 Gy to the CTV_{HR}. The minimum dose ($D_{100\%}$) required to CTV_{HR} was 145 Gy to ensure comparable clinical local control for the GTV lesion. For comparison purposes a reference plan ($Plan_{ref}$) was made, based on current clinical LDR-BT dose planning concept at the Netherlands Cancer Institute in Amsterdam, The Netherlands. Planning aims for targets and OAR for $Plan_{risk\text{-}adapt}$ and $Plan_{ref}$ are presented in Table 1.

The LDR-BT doses (D_{LDR}) were converted into BED dose and dose given in equivalent 2 Gy fractionation doses (EQD2) using the following formulas for the BED calculation:

$$BED_{LDR} = D_{LDR}\{1 + 2(d_0\lambda)(\beta/\alpha)\kappa/(\mu - \lambda)\} - 0.693T/(\alpha T_p)$$

Table 1
Planning aims for targets and OAR.

$Plan_{risk\text{-}adapt}$ (125 Gy = 100%)		$Plan_{ref}$ (145 Gy = 100%)	
$CTV_{Prostate}$	[1]$D_{90\%} \geqslant$ 143.75 Gy (115%)	$CTV_{Prostate}$	[1]$D_{90\%} \geqslant$ 166.8 Gy (115%)
	[1]$V_{100\%} \geqslant$ 95% of vol.		[1]$V_{100\%} \geqslant$ 95% of vol.
CTV_{HR}	[1]$D_{100\%} >$ 145 Gy		
	[3]$D_{100\%} \leqslant$ 250 Gy		
Urethra*	[1]$D_{10\%} <$ 217.5 Gy		
	[2]$D_{30\%} <$ 188.5 Gy		
Rectum*	[1]$D_{1.0\ cm^3} <$ 145 Gy		
Bladder neck*	[1]$D_{0.5\ cm^3} <$ 174 Gy		

[1] First priority.
[2] Second priority.
[3] Third priority.
* Constraint applied for both plans.