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Prostate brachytherapy

Dosimetric feasibility of ablative dose escalated focal monotherapy with MRI-guided high-dose-rate (HDR) brachytherapy for prostate cancer

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ABSTRACT

Purpose: To determine the dosimetric feasibility of dose-escalated MRI-guided high-dose-rate brachytherapy (HDR-BT) focal monotherapy for prostate cancer (PCa).
Methods: In all patients, GTV was defined with mpMRI, and deformably registered onto post-catheter insertion planning MRI. PTV included the GTV plus 9 mm craniocaudal and 5 mm in every other direction. In discovery-cohort, plans were obtained for each PTV independently aiming to deliver $\geqslant$16.5 Gy/fraction (two fraction schedule) while respecting predefined organs-at-risk (OAR) constraints or halted when achieved equivalent single-dose plan (24 Gy). Dosimetric results of original and focal HDR-BT plans were evaluated to develop a planning protocol for the validation-cohort.
Results: In discovery-cohort (20-patients, 32-GTVs): PTV D95% $\geqslant$16.5 Gy could not be reached in a single plan (3%) and was accomplished (range 16.5–23.8 Gy) in 15 GTVs (47%). Single-dose schedule was feasible in 16 (50%) plans. In the validation-cohort (10-patients, 10-GTVs, two separate implants each): plans met acceptable and ideal criteria in 100% and 43–100% respectively. Migration to single-dose treatment schedule was feasible in 7 implants (35%), without relaxing OAR's constraints or increasing the dose (D100% and D35%) to mpMRI-normal prostate ($p > 0.05$).
Conclusion: Focal ablative dose-escalated radiation is feasible with the proposed protocol. Prospective studies are warranted to determine the clinical outcomes.
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Prostate cancer (PCa) is the most frequent non-skin malignancy in men, and among the top three cancer-related cause of death across jurisdictions [1,2]. The vast majority of patients present at localized stage, amenable for curative-intent single modality therapy. Of these, brachytherapy, traditionally delivered to the whole prostate gland, provides excellent cure rates with unparalleled cost-efficacy [3,4]. However, in the last decades a significant decline in the use of low dose rate brachytherapy (LDR-BT) has been observed [5], in part due to alternative approaches for selected patients with low- and intermediate-risk disease (i.e. active surveillance, high intensity focused ultrasound [HIFU], cryotherapy, etc.), and migration toward high dose rate brachytherapy (HDR-BT) with different doses and fractionation schedules [6].

Multiparametric MRI (mpMRI) allows identification of gross tumor volume (GTV) in a significant proportion of patients, correlating with the most frequent site of local failure after organ-preserving approaches such as radiotherapy [7]. Although dose escalation has been suggested to improve the overall survival [8], further dose increases are often limited by the tolerance of surrounding organs-at-risk (OAR). Moreover, treatment intensification to the whole gland may be unwarranted as prostate's boundaries are a flawed surrogate for defining cancer within it. In fact, mpMRI has unveiled the possibility and increasing advocacy for lesion-only targeted diagnostic (i.e. biopsies) and therapeutic (i.e. focal therapy) approaches [9]. Therefore, intensifying and focusing treatment to the GTV using mpMRI and MRI-guided HDR-BT could allow high radiation dose escalation with reduction of treatment toxicities while maintaining oncologic outcomes if used in properly selected patients.

In our department, we prospectively investigate MRI-guided HDR-BT for PCa across the disease spectrum including: targeted dose escalation to intraprostatic lesions and whole gland boost combined with external beam radiotherapy (EBRT) for intermediate- and high-risk patients respectively, and focal salvage for post-EBRT local recurrences [10–12]. With the purpose of matching advanced diagnostic mpMRI with precision therapeutics in the form of MRI-guided brachytherapy, herein we aimed to determine the dosimetric feasibility of focal dose-escalated HDR monotherapy treatment for PCa.

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Methods

Patient cohorts

Patients with evidence of intraprostatic lesion on diagnostic mpMRI from institutionally approved prospective clinical trials of MRI-guided HDR-BT for PCa were identified. The last ten consecutively treated patients of each treatment group were selected.

The discovery cohort included patients with intermediate- and high-risk PCa who received EBRT combined with a single-dose HDR-BT boost either to the whole gland (WG HDR-BT) or to the GTV only (Target HDR-BT) [10,11]. These two groups constituted the discovery cohort as they represent extremes of implant geometry to be encountered by focal monotherapy HDR-BT approach. In the former, the implanted catheters aim to encompass the whole prostate, while the latter approach targeted the GTV only with minimal (1–2 mm) expansion margin.

The validation cohort included patients with locally recurrent PCa after EBRT, who were treated with salvage HDR-BT in two separate implants. This cohort was deemed to represent a closer scenario of that to be encountered by focal HDR-BT monotherapy, and as well implant geometry aimed to encompass a prostate subregion defined by a clinical target volume (CTV) expanded from the GTV (see Fig. 1).

Multi-parametric MRI and catheter insertion

MRI-guided HDR-BT procedure has been previously described [11,12]. In brief, a sterile MRI-compatible perineal template affixed perpendicular to the endorectal coil was positioned and immobilized against the perineum. Subsequently, MRI images were acquired with a 3T MRI scanner (IMRIS, Minnetonka, MN), and more recently with a brachytherapy suite-dedicated on-rails 1.5T MRI scanner (Magnetom Espree; Siemens, Erlangen, Germany). Imaging protocol included T2- and diffusion-weighted sequences acquired immediately prior to catheter (ProGuide, Nucletron) insertion, which was guided using navigation software (Aegis, Hologic, Massachusetts, USA).

In the discovery cohort, catheter placement aimed to provide coverage of the whole gland (WG HDR-BT) or GTV-only (Target HDR-BT), whereas in the validation cohort, catheters were placed to provide coverage of a CTV including the GTV plus an isotropic 5 mm expansion. After clinically-satisfactory catheter placement, high-resolution T2-weighted axial images were acquired and exported to the treatment planning software (Oncentra Masterplan, Elekta).

Target and organs-at-risk (OAR) definition

Prior diagnostic mpMRI (T2-, diffusion-weighted, and dynamic contrast-enhanced sequences) acquired in our departmental 1.5/3T scanner with endorectal coil was used to define the prostate and fiduciary contours. Intraprostatic lesion was contoured by adding volumes from concordant mpMRI sequences showing a conspicuous focal lesion, and consistent with the regional localization of the tumor in the diagnostic biopsies. These contours were subsequently co-registered with the post catheter insertion planning MRI using deformable registration (Morfeus; in house development) which has been shown to enable accurate co-registration for improved target delineation [13,14]. The rectum, bladder, and urethra contoured as solid structures were defined as OAR. The deformably registered mpMRI-defined intraprostatic lesion was outlined as the GTV, and subsequently produced the CTV which included the GTV plus 7 mm craniocaudal and 5 mm in every other direction expansions, within the prostate boundaries, and excluding rectum, bladder and urethra. The planning target volume (PTV) was generated by adding 2 mm craniocaudal margin to account for the uncertainties introduced with slice thickness volume averaging, and brachytherapy source dwell positioning.

Plan optimization of the discovery cohort

In the discovery cohort, new plans (Oncentra Brachy v4.3; IPSA algorithm, and manual optimizations) were obtained for each of the PTVs independently through iterative optimizations according to objectives/constraints based on GEC-ESTRO recommendations and our current departmental protocols [11,15], adding a fringe cutback to approximately 90% of these guidelines. Bioequivalent dose volume constraints per fraction included: D0.5cm^3 of the bladder and urethra $\leqslant$15 Gy (corresponding to our high-risk PCa protocol allowed constraint of D0.5cm^3 to bladder/urethra of 45 Gy/25Fx in EBRT and 18 Gy in the single HDR-BT fraction), and D2cm^3 of rectum $\leqslant$ 10.8 Gy (corresponding to ICRU89/GEC-ESTRO report on brachytherapy, D2cm^3 of rectum to be less than 65 Gy EQD2) [15].

Our *a priori* approach was to generate plans for a two-session treatment schedule aiming to deliver $\geqslant$16.5 Gy per fraction to 100% of the GTV and >95% of the PTV (total treatment dose 33 Gy; $EQD2_{2.5}$ = 139 Gy). This was based on previous works showing feasibility of intraprostatic lesion dose escalation (125%) in the context of WG HDR-BT [16], and considering as baseline a WG HDR-BT monotherapy schedule of 13.5 Gy in two sessions [17]. Moreover, this is consistent with our ongoing Target HDR-BT study which in addition to 76 Gy in 38 fractions IMRT/VMAT to the whole gland includes a single 10 Gy HDR-BT boost to the GTV, corresponding to >125% dose escalation for the total $EQD2_{2.5}$ dose. Plans were iteratively optimized until reaching a maximally attainable PTV D95% doses limited by our predefined OAR constraints, or halted when an equivalent dose in a single session HDR-BT was reached (24 Gy; $EQD2_{2.5}$ = 141 Gy).

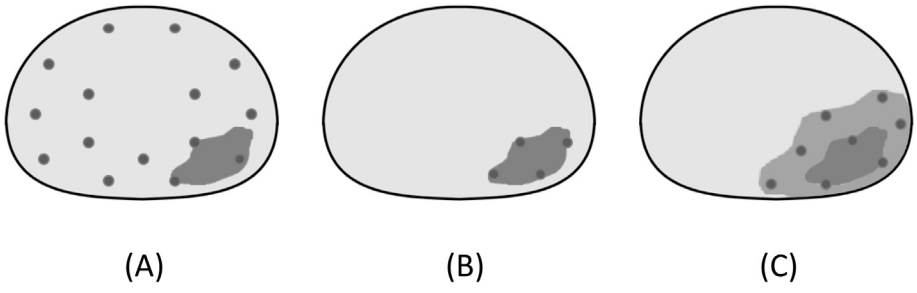

Fig. 1. Illustration of the relationship between implant's geometry and target volumes in the discovery and validation cohorts. Schematic representation of the discovery whole gland HDR-brachytherapy (A), Target HDR-brachytherapy (B), and validation salvage HDR-brachytherapy (C) cohorts. Dots represent brachytherapy catheters. Dark and light shaded regions represent the gross tumour volume and planning target volume respectively.