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Phase II trial

Dose escalation to dominant intraprostatic lesions with MRI-transrectal ultrasound fusion High-Dose-Rate prostate brachytherapy. Prospective phase II trial

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ABSTRACT

Background and purpose: To demonstrate the feasibility, safety and effectiveness of dose escalation to intraprostatic lesions with MRI-transrectal ultrasound fusion High-Dose-Rate (HDR) brachytherapy.

Materials and methods: 15 patients with intermediate-high risk prostate cancer and visible dominant intra-prostatic nodule on mpMRI have been treated. The treatment consisted of combined MRI-TRUS fusion HDR-brachytherapy (1 fraction of 1500 cGy) and hypofractionated external beam (3750 cGy in 15 fractions).

A dose of 1875 Gy was delivered to at least 98% of the DIL volume.

Results: Median prostate volume was 23.8 cc; median number of needles was 16 (13–18). Dose escalation to DIL was feasible in 14/15 patients (93%) without violating dosimetric constraints and 1 patient presented a minimal deviation of dosimetric restrictions.

With a median follow-up of 18 months (17–24), none of the patients developed acute urinary retention or grade $\geqslant$3 toxicity.

In addition to standard PSA follow-up, response has been assessed by mpMRI at 12 months. All patients presented adequate morphological responses on anatomical and functional sequences.

Conclusions: HDR brachytherapy using MRI-transrectal ultrasound fusion for image guidance is a suitable technique for partial prostate dose escalation. Tolerance and toxicity profiles are excellent and results are encouraging in terms of biochemical, morphological and functional response.

The fact that dose escalation increases local control and decreases biochemical failure in patients with localized prostate cancer is well established [1–5]. However, even with the latest technologic advances of image-guidance, dose escalation to the entire prostate is limited by normal tissue tolerance. Observational studies have demonstrated that local recurrence of prostate cancer after conventional external beam radiation therapy most frequently occurs in the regions with the greatest tumor burden. Selective dose escalation to the dominant intraprostatic lesion (DIL), may therefore be a good strategy to further increase local control [6–8] without the price of unacceptable toxicity. Furthermore, radiobiological studies suggest that the alpha-beta ratio of prostate cancer may be as low as 1.5 Gy, supporting the concept of increasing biologically effective dose through hypofractionation, [9].

Advances in imaging over the past decade have vastly improved our ability to localize the lesion within the prostate and detect relatively early evidence of extraprostatic spread. Multiparametric MRI (mpMRI), using multiple sequences with T1- and T2 weighting, dynamic contrast enhancement (DCE) to assess perfusion, and diffusion weighted imaging (DWI) to calculate the different diffusion capability of prostate cancer vs. normal tissue has improved the sensitivity and specificity of MRI to detect and characterize prostatic lesions [10]. Moreover, the way of interpreting these images has been standardized in the PiRads system [11].

Brachytherapy arguably provides the best conformal dose escalation for prostate cancer, compared to other image-guided modalities including carbon ions, protons and photons [12]. The accuracy in delivery, and the rapid dose fall-off, provide a means to escalate

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dose to defined intra-prostatic regions without exceeding tolerance to organs at risk.

In 2013, we launched a prospective phase II clinical trial to assess the feasibility, tolerance and safety of dose escalation to the DIL with image-guided High-Dose Rate (HDR) brachytherapy using mpMRI for lesion definition and intra-operative fusion with transrectal ultrasound (TRUS) for treatment localization and delivery.

Methods and materials

All patients had histological confirmation of intermediate to high risk prostate adenocarcinoma in accordance with the National Comprehensive Cancer Network practice guidelines. The intermediate-risk patients had clinical stage $\leqslant$T2c, Gleason score 7 and initial prostate-specific antigen level (iPSA) $\leqslant$20 ng/mL, or Gleason score $\leqslant$6 and iPSA >10 and $\leqslant$20 ng/mL, whereas high-risk patients had at least one of clinical stage T3, Gleason score 8–10, or PSA > 20 ng/mL.

All MRI studies were performed on a 1.5-Tesla scanner (Achieva 1.5T, Philips Medical systems) using a body-phased array coil (Sense-Cardiac Philips MS). The sequence parameters had been previously optimized for the coil. All patients were imaged in the supine position following a cleansing rectal enema, and suppression of bowel peristalsis by administration of intramuscular butylscopolamine (Buscopan®).

After a localizer scan, axial, sagittal and coronal T2-weighted fast spin echo sequences including the prostate and seminal vesicles were acquired, followed by axial T1- weighted images of the whole pelvis from the iliac crests to the pubic symphysis, and finally, axial T2-weighted volumetric sequences (VISTA) were obtained for brachytherapy guidance. For sequence details see Table 1.

Magnetic resonance spectroscopy sequences (PRESS) were 3D chemical shift imaging with point-resolved spectroscopy, voxel excitation, and band-selective inversion with gradient dephasing for water and lipid suppression. Parametric maps (of the choline and creatine to citrate ratio) were displayed in correlation with the T2-weighted anatomical images. Diffusion-weighted imaging (DWI) was performed using a single-shot echoplanar imaging technique and b values 0, 150, 500, and 1000 s/mm^2. We previously established that a b value of 1000 s/mm^2 provided the highest image contrast between normal and malignant prostate tissue on our 1.5-T system. Apparent diffusion coefficient (ADC) values were obtained from the DWI sequences performed with b values of 0, 150, 500 and 1000 s/mm^2. ADC maps were generated by calculating the ADC value in each pixel of every slice. Dynamic MRI was performed applying a 3D fast field echo sequence (4.4/2.1; flip angle: 12°) in the axial plane. From the resulting imaging data, various perfusion curves were analyzed to allow the detection and localization of prostate cancer.

All MRI studies were evaluated by two specialists in uro-radiology (A.U, A.E). As well as describing all zones suspected to harbor malignancy, with ADC values and perfusion curves for each zone, the prostate was divided into 27 regions of interest, as recommended in the PI-RADS™ classification [11].

The standard treatment in our department for patients with intermediate- or high-risk prostate cancer consists of a single HDR fraction of 15 Gy, followed in 2–4 weeks by external beam radiation therapy (EBRT) to a dose of 37.5 Gy in 15 fractions over 3 weeks.

For more accurate co-registration with the ultrasound images, all patients underwent a second mpMRI on the same day as the HDR procedure. A 2.5-cm diameter rectal cylinder was placed to simulate the presence of the ultrasound probe, facilitating the non-deformable image fusion between MRI and TRUS.

The axial T2-weighted volumetric sequence (VISTA) was imported directly from the picture archiving and communication system (PACS), and sent to the Oncentra® Prostate v. 4.0 software (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). MR images were reconstructed and segmented. Target volumes including the prostate gland, DILs, any areas of extracapsular extension, the urethra, and rectum were delineated. A transrectal sagittal volumetric ultrasound image was acquired with images obtained every 0.5°. A rapid reconstruction algorithm converts the series of 2D images into a 3D volume, which is then displayed in axial, sagittal, and coronal views and transferred to the fusion module. The MR images and the real-time ultrasound examination are displayed on a split-screen with the possibility of overlaying the images live. A graphical user interface is used for rigid manual registration of the ultrasound and MR images. This interface allows for displacements in three dimensions as well as rotations, until the two image sets are satisfactorily superimposed. The contoured structures from the MRI are transferred to the ultrasound dataset. These contours may be slightly modified until a perfect match with the ultrasound images is achieved.

The homogeneity parameters used for dose optimization aim for prostate V100 >98%, V150 of 25–33%, and V200 <8%, where Vn is the fractional volume of the organ that receives *n*% of the prescribed dose; maximum point dose inside the urethral volume (urethral Dmax) <115%; and the dose to 1 cc of rectal wall (RD1 cc) is limited to <70% of the prescribed dose. A deviation of up to 2% from these constraints was considered acceptable.

Follow-up clinical examinations were performed at 1, 3, and 6 months for all patients, and then every 3–6 months for the first 5 years, depending on symptoms and prostate-specific antigen (PSA) readings.

The primary objective of this trial was to determine the feasibility of escalating the HDR brachytherapy dose to the DIL to 18.75 Gy, while maintaining the rest of the dosimetric constraints established for patients receiving standard HDR brachytherapy. Secondary objectives were to assess the tolerance, acute and chronic toxicity, and clinical, morphological and functional response. Acute tolerance was described in terms of the incidence of episodes of acute urinary retention in the first 48 h after the procedure and changes in the International Prostatic Symptoms (IPS) Score from baseline. Acute toxicity was assessed in terms of the incidence and severity of genitourinary (GU) and gastrointestinal

Table 1
mpMRI sequence specifications.

Scan	Volume	TR/TE	ETL	FOV	Matrix	Slice thickness (mm)	Gap	NEX
T2-FSE	P + SV	2800/140	16	23	256 × 176	4	0.4	3
VISTA (3D-T2-FSE)	P + SV	2000/200	94	28	232 × 158	1.2		2
T1 axial	Pelvis	619/10		25	292 × 231	4	0.4	2
DWI	Pelvis	3112/80		29	156 × 123	4	0	4
DCE	P + SV	3.0/1.41		23	92 × 90	4	0	1

TR: Repetition Time; TE: Echo Time; ETL: Echo Train Length; NEX: Number of Excitations; FSE: Fast-Spin-Echo; DWI: Diffusion Weighted Imaging; DCE: Dynamic Contrast Enhanced; P + SV: Prostate And Seminal Vesicles.