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Original article

Combined high dose rate brachytherapy and external beam radiotherapy for clinically localised prostate cancer

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ABSTRACT

Purpose: To report the clinical outcomes and treatment-related toxicities after combined high-dose-rate (HDR) brachytherapy (BRT) with external beam radiotherapy (EBRT) for patients with clinically localised high-risk prostate cancer.

Material and methods: Between 2008 and 2012, three hundred and three consecutive patients with organ-confined high-risk prostate cancer were treated with definitive radiotherapy consisting of HDR-BRT followed by supplemental EBRT. The transrectal 3D-ultrasound-based HDR-BRT boost consisted of two single-fraction implants of 10.5 Gy, prescribed to the 90% of the gland (D90), for a total physical dose of 21.0 Gy delivered to the prostatic gland. EBRT was delivered with conventional fractionation, prescribing 45.0 Gy to the prostatic gland and seminal vesicles. Biochemical failure was defined according to the Phoenix Consensus Criteria, genitourinary (GU)/gastrointestinal (GI) toxicity was evaluated using the Common Toxicity Criteria for Adverse Events (version 3.0).

Results: The median follow-up was 71.6 months. The 7-year overall survival, biochemical control and metastasis-free-survival rates for the entire cohort were 85.7%, 88.3% and 93.8%, respectively. Androgen deprivation therapy was initiated prior to treatment for 92.7% of patients with a median duration of 12 months. Toxicity was scored per event with late Grade 2, 3 and 4 GU adverse events and was found to be 15.3%, 2.2% and 0.3%, respectively. Late Grade 2 GI toxicity accounted for 0.3% with no instances of Grade 3 or higher late adverse events.

Conclusion: HDR-BRT with supplemental EBRT results in low biochemical relapse-free survival rates associated with a very low incidence of higher-grade late adverse events.

In the management of localised prostate cancer, radiotherapy (RT) and radical prostatectomy have shown to be equieffective local treatments with RT being an established modality for the management of organ-confined disease in all risk groups. Several studies have demonstrated that radiation dose escalation is translated into improved biochemical control (BC) and metastasis-free survival (MFS), especially for high risk patients [1–3]. Furthermore, the combination of high-dose-rate (HDR) brachytherapy (BRT) and external beam radiation therapy (EBRT) can offer intraprostatic dose escalation with good dose coverage to periprostatic tissue harbouring extraprostatic disease. Randomised controlled trials have validated the combined modality approach as superior to EBRT alone in the definitive RT treatment of clinically localised prostate cancer [4–6].

In the current analysis, we report our long-term clinical outcomes using combined HDR BRT with EBRT for the definitive treatment of localised prostate cancer, in a cohort consisting entirely of high-risk patients. Our data have shown that the combined treatment modalities resulted in favourable BC rates and low incidence of late gastrointestinal (GI) and genitourinary (GU) adverse events. Our findings are consistent with published data from other institutions [7–13].

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Patients and methods

Patient characteristics

Between March 2008 and December 2012, three hundred and three patients with histologically proven prostate adenocarcinoma were treated with HDR BRT followed by EBRT. Pre-treatment assessment included digital rectal examination, serum prostate specific antigen (PSA) testing, transrectal ultrasound (TRUS), abdominal computed tomography (CT), magnetic resonance imaging (MRI) and on some occasions, bone scintigraphy [14,15]. Patients were staged based on the American Joint Committee on Cancer (AJCC) 6th edition [16] and stratified into risk category groups based on the Memorial Sloan Kettering Cancer Center group definition [17]. Briefly, the risk stratification system divides patients into low-risk (T1c-T2a and GS $\leq$ 6 and PSA $\leq$ 10), intermediate-risk (T2b and/or GS = 7 and/or PSA > 10–20) and high-risk ($\geq$T2c or PSA > 20 or GS 8–10 or 2 intermediate-risk criteria). Our cohort consisted of 303 high-risk patients.

Eligibility criteria for combined modality RT were clinically organ-confined disease in the absence of lower urinary tract symptoms that would require treatment. Patients who had previously transurethral resection of the prostate (TURP) were included in the cohort with the stipulation that treatment would be scheduled six months post resection. Patients with metastatic disease, prior pelvic EBRT for another malignancy, or prior surgery for prostatectomy were excluded.

Androgen deprivation treatment (ADT) was prescribed to 281 high-risk patients (92.7%), with 245 (87.2%) and 36 (12.8%) patients receiving neo-adjuvant plus adjuvant or only adjuvant treatment, respectively. The median duration of ADT was administered by the referring urologists and treatment had a median duration of 12 months (range of 9–18 months). Patient and tumour characteristics are shown in Table 1.

Table 1
Patient and tumour characteristics.

Characteristics	(n = 303)
Median follow-up (months)	71.6 (16.0–99.8)
Age at treatment (years)	
Mean	71.3
Median	71.8
Pre-treatment PSA (ng/ml)	
Mean	21.0
Median	11.3
	n (%)
Stage	
T1b-c	20 (6.6%)
T2a	29 (9.6%)
T2b	50 (16.5%)
T2c	192 (63.4%)
T3a	8 (2.6%)
T3b	4 (1.3%)
Gleason Score	
$\leq$6	59 (19.5%)
7	147 (48.5%)
>7	97 (32.0%)
Pre-treatment PSA (ng/ml)	
$\leq$10	132 (43.6%)
11–20	91 (30.0%)
>20	80 (26.4%)
Age at treatment (years)	
<60	12 (4.0%)
60–69	100 (33.0%)
$\geq$70	191 (63.0%)
Androgen deprivation therapy	281 (92.7%)
Neoadjuvant	245 (87.2%)
Adjuvant	36 (12.8%)

HDR brachytherapy boost

Our TRUS as a monotherapy clinical workflow has been described in detail elsewhere [18]. In short, transperineal catheter implantation was performed under TRUS-guidance in high-lithotomy position using a high resolution (2,5 mm grid) perineal template. For preplanning, transversal ultrasound (US) images were acquired in real-time using a continuous probe movement technique and three-dimensional (3D) volumes were automatically reconstructed from evenly spaced (1.0 mm apart) axial US images. The planning target volume (PTV) was defined as the entire prostatic gland with no additional margins. The intraprostatic urethra was defined with a 5 mm extension beyond the apex to include the relevant membranous urethral region. The anterior rectal wall and bladder were contoured and were identified in the planning as organs at risk (OARs). Based on the acquired 3D anatomy, appropriate virtual catheter positions were generated using the intraoperative treatment planning system Oncentra Prostate (Elekta Brachy, Elekta AB, Stockholm, Sweden). Dose volume histograms (DVHs) for the PTV and the OARs were calculated for evaluation of the anatomy-based dose optimisation [19]. TRUS-guided implantation of steel catheters (200 mm length, 1.9 mm diameter) was then performed based on the approved patient pre-plan. At the conclusion of the implantation, a final 3D TRUS data set was acquired for intraoperative real-time treatment planning including catheter reconstruction and PTV/OARs contour adjustment. Evaluation of implant quality was based on dose-volume parameters for PTV coverage in compliance with OAR dose constraints (Fig. 1 and Table 2). Dose was prescribed to cover the 90% of the PTV (D90). Using two, single-fraction implants separated by 21 days, the prescribed reference dose was 10.5 Gy per fraction for a total of 21 Gy. The parameters used for the dosimetric assessment and the OAR constraints for the HDR-brachytherapy are shown in Table 2. All implants were performed under either spinal or general anaesthesia. All treatments were delivered using an Iridium-192 HDR afterloading system (microSelectron-HDR, Elekta-Brachytherapy, Elekta AB, Sweden). Written informed consent was obtained from all patients.

External beam radiation therapy

External beam irradiation was initiated three weeks after the second HDR implant. It consisted of 45 Gy delivered in 25 fractions, 1.8 Gy per fraction, over 5 weeks using a conventional 4-field 3D beam arrangement technique. A computed tomography-based treatment planning was created individually for each patient where the PTV was defined as the prostatic gland, seminal vesicles and the periprostatic tissues with a margin of 1.5 cm in all directions except dorsally where a 1.0 cm margin was used. The tumour volume was encompassed by the 100% isodose line ±5% based on ICRU 50 [20]. The biological equivalent dose (BED) of the combined treatment, HDR BRT plus EBRT, was estimated using the LQ model [21]. Using an α/β-value of 3 Gy for prostate cancer cells the total BED was 166.5 Gy (EQD2 = 99.9 Gy). Alternatively, using a lower α/β-value of 1.5 Gy, which is supported by newer radiobiological analyses [22,23], the total BED was 267 Gy (EQD2 = 114.4 Gy).

Follow-up and statistical analysis

All patients presented in our department at six weeks after completion of treatment and then every three months for the first year, every six months for the second year and annually thereafter. During those visits, PSA control values were recorded and GU/GI toxicities were documented. Our follow-up visits were independent from the follow-up that was done the by referring urologists

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