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Original article

High dose rate brachytherapy as monotherapy for localised prostate cancer ☆

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ABSTRACT

Background and purpose: To evaluate the oncological outcome of a three-implant high dose rate (HDR) brachytherapy (BRT) protocol as monotherapy for clinically localised prostate cancer.
Material and methods: Between February 2008 and December 2012, 450 consecutive patients with clinically localised prostate cancer were treated with HDR monotherapy. The cohort comprised of 198 low-, 135 intermediate- and 117 high risk patients being treated with three single-fraction implants of 11.5 Gy delivered to an intraoperative real-time, transrectal ultrasound defined planning treatment volume up to a total physical dose of 34.5 Gy with an interfractional interval of 21 days. Fifty-eight patients (12.8%) received ADT, 32 of whom were high- and 26 intermediate-risk. Biochemical failure was defined according to the Phoenix Consensus Criteria and genitourinary/gastrointestinal toxicity evaluated using the Common Toxicity Criteria for Adverse Events version 3.0.
Results: The median follow-up time was 56.3 months. The 60-month overall survival, biochemical control and metastasis-free-survival rates were 96.2%, 95.0% and 99.0%, respectively. Toxicity was scored per event with late Grade 2 and 3 genitourinary adverse events of 14.2% and 0.8%, respectively. Late Grade 2 gastrointestinal toxicity amounted 0.4% with no instances of Grade 3 or greater late adverse events to be reported.
Conclusions: Our results confirm HDR BRT to be a safe and effective monotherapeutic treatment modality for clinically localised prostate cancer.

High-dose-rate (HDR) brachytherapy (BRT) has been successfully implemented as high-precision radiotherapy modality [1] for the safe monotherapy of localised prostate cancer [2] with biochemical control (BC) rates comparable to radical prostatectomy [3], low-dose-rate (LDR) BRT [4] and dose-escalated external beam radiotherapy (EBRT) [5]. In the absence of phase 3 comparative efficacy data, however, the optimal management of locally-confined prostate adenocarcinoma remains controversial with treatment assignment being influenced mainly by physician's bias and patient's preference. Against this background, quality of life issues are gaining increasing importance with HDR monotherapy sustaining momentum due to its low morbidity [6] and excellent long term clinical results [7–9]. In line with these experiences, our most recent publication reported on HDR monotherapy for localised prostate cancer including 226 patients treated with a three-implant scheme [10]. This current report updates and expands our previous results for this three-implant approach encompassing in total 450 consecutive patients.

Patients and methods

Patient characteristics

Since 2002, we have treated more than 1000 patients with HDR monotherapy for clinically localised prostate cancer. During this period, three different protocols were implemented reflecting an evolution aiming to improve clinical workflow and patient comfort. From January 2002 to February 2004, 141 patients were treated with one implant of four fractions á 9.5 Gy. From March 2004

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to January 2008, 351 patients received two implants, separated by 14 days, each of two fractions ά 9.5 Gy. From February 2008, our HDR scheme consists of three single-fraction implants, each delivering 11.5 Gy, with an interfractional interval of 21 days. The current report encompasses our clinical experience with this three-implant approach during the time frame from February 2008 to December 2012 when we treated a cohort of 456 consecutive patients. Six patients, however, have been excluded from analysis due to loss of follow-up thus resulting in 450 patients included for data evaluation.

All patients had histologically proven adenocarcinoma of the prostate and were staged according to the American Joint Committee on Cancer, 6th edition, staging guidelines [11]. Pre-treatment staging included digital rectal examination, transrectal ultrasound (TRUS) and, if clinically indicated, computed tomography (CT)/magnetic resonance imaging (MRI) and bone scintigraphy. The Memorial Sloan Kettering group definition [12] was used to classify patients into risk groups. Briefly, this 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). Eligibility criteria were clinically organ-confined disease in the absence of lower urinary tract symptoms requiring treatment. Patients who had previous transurethral resection of the prostate (TURP) were not excluded from treatment but assigned at six months after resection. High-risk patients who were clinically diagnosed as unsuitable for prostatectomy or dose-escalated EBRT, or who rejected prostatectomy or definitive EBRT were also assigned for HDR monotherapy at the discretion of the treating physician. Exclusion criteria were metastatic disease, previous pelvic EBRT for another malignancy or previous open surgery of the prostate.

A total of 58 patients (12.8%) received androgen deprivation therapy (ADT), 32 (55.2%) of whom were high-risk, 16 (27.6%) intermediate-risk, and ten (17.2%) low-risk. Hormonal therapy was prescribed either neoadjuvantly and continued concurrently with radiation or adjuvantly for an overall duration of median nine months (range, 3–14 months). The duration of ADT for the subgroups of low-risk, intermediate-risk, and high-risk patients was median 4 months (range, 3–6 months), 6 months (range, 6–10 months) and 9 months (range, 9–14 months), respectively. Androgen deprivation therapy was supervised by the referring urologists. Patient and tumour characteristics are shown in Table 1.

Table 1
Patient and tumour characteristics.

Characteristics	(n = 450)
Median follow-up (months)	56.3 (4.4–91.7)
Age at treatment (years)	
Mean	69.1
Median	70.3
Pre-treatment PSA (ng/ml)	
Mean	7.5
Median	6.6
	n (%)
Stage	
T1b-c	151 (33.6%)
T2a	153 (34.0%)
T2b	80 (17.8%)
T2c	64 (14.2%)
T3a	2 (0.4%)
Gleason Score	
≤6	303 (67.3%)
7	102 (22.7%)
>7	45 (10.0%)
Pre-treatment PSA (ng/ml)	
≤10	403 (89.6%)
11–20	42 (9.3%)
>20	5 (1.1%)
Age at treatment (years)	
<60	54 (12.0%)
60–69	160 (35.6%)
≥70	236 (52.4%)
Androgen deprivation therapy	58 (12.8%)
Risk group	
Low	198 (44.0%)
Intermediate	135 (30.0%)
High	117 (26.0%)

Brachytherapy protocol

Our solely TRUS-based clinical workflow has been described in detail elsewhere [10,13]. In short, transperineal catheter implantation was performed under TRUS-guidance in high-lithotomy position using a perineal template. For inverse preplanning, transversal ultrasound (US) images of the prostate, bladder, urethra and anterior rectal wall were acquired in real-time using a continuous probe movement technique and three-dimensional (3D) volumes were reconstructed based on 1.0 mm image distance. The planning target volume (PTV) was defined as the entire prostate gland without margins. Based on the acquired 3D anatomy, appropriate virtual catheter positions were generated using the intraoperative treatment planning system Oncentra Prostate (Oncentra Brachy, Elekta AB, Stockholm, Sweden) and dose volume histograms (DVHs) for the PTV and the organs at risk (OARs, i.e. bladder, urethra and rectum) were calculated for evaluation of the anatomy-based dose optimisation. As the preplanning dosimetry parameters fulfilled our clinical protocol, TRUS-guided implantation of steel catheters (200 mm length, 1.9 mm diameter) was performed at previously defined positions. After completion of implantation, a final 3D TRUS data set was acquired for intraoperative real-time treatment planning including catheter reconstruction and PTV/OARs contouring according to the new image set. Evaluation of implant conformity was based on dose-volume parameters for PTV coverage in compliance with OAR dose constraints (Fig. 1). Dose specification was given as the mean dose on the PTV surface. Using three single-fraction implants separated by 21 days, the prescribed reference dose was 11.5 Gy delivered to a total physical dose of 34.5 Gy. Dosimetry assessment parameters and OAR constraints are shown in Table 2. All implants were performed under spinal, or if indicated, general anaesthesia. All treatments were performed using a ^{192}Iridium HDR afterloading system (microSelectron–HDR, Elekta-Brachytherapy, Elekta AB, Sweden). Written informed consent was obtained from all patients. In our series, two patients were staged with cT3a disease. The PTV in these cases was defined as the prostate capsule plus 5.0 mm in all directions (except for the posterior rectal margin), allowing for coverage of extracapsular invasion as confirmed on pre-treatment pelvic MRI.

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 these visits, gastrointestinal/genitourinary toxicities were evaluated-documented and the performed PSA control values recorded. Radio-oncological follow up visits were independent from PSA controls performed by referring urologists based on national recommendations regarding PSA controls after treatment for prostate cancer (i.e. at 3 month-intervals for the first two years, every 6 months for the 3rd and 4th year and annually onwards). Upon request additional information were deduced from attending urologists. For the current analysis, the patient sample was deduced from our prospectively maintained database and

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