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Original article

Toxicity and quality of life after high-dose-rate brachytherapy as monotherapy for low- and intermediate-risk prostate cancer

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ABSTRACT

Background and purpose: The use of HDR brachytherapy (HDR-BT) as monotherapy for prostate cancer (PC) is increasing worldwide with good tumour control rates and acceptable toxicity. We report our results on toxicity and quality of life (QoL) after HDR-BT monotherapy for PC patients.

Materials and methods: 166 low- and intermediate-risk localized PC patients were treated with HDR-BT to a total dose of 38 Gy in four fractions. Genitourinary (GU) and gastrointestinal (GI) toxicities were prospectively assessed using EORTC-RTOG questionnaires and physicians charts. QoL was evaluated using EORTC QLQ-PR25 questionnaires.

Results: Three months after treatment, acute GU and GI toxicities were reported in 10.8% and 7.2%. Acute toxicity resolved within two months in the majority of patients (61%). Late grade $\geqslant 2$ GU and GI toxicity were reported in 19.7% and 3.3% of patients 12 months after HDR-BT. Mean QLQ-PR25 scores showed clinically relevant changes from baseline for urinary symptoms and sexual functioning. With a mean follow-up of 35 months, biochemical failure was observed in 2.4%. Overall survival at 60 months was 93.6% and cancer-specific survival was 100%.

Conclusions: HDR-BT monotherapy for localized PC showed excellent clinical outcome and acceptable acute and late toxicity. Urinary symptoms and sexual function QoL decreased after treatment.

High-dose-rate brachytherapy (HDR-BT) is a safe and effective treatment option for prostate cancer (PC) [1–3]. There is accumulating evidence that PC cells have a higher sensitivity to fraction dose, which suggests a significant therapeutic benefit of hypofractionation [4,5]. HDR-BT is the ideal technique for extreme hypofractionation because of its highly conformal dose distribution within the prostate with a rapid dose fall-off outside, sparing the organs at risk [6].

The biochemical control rate in favourable risk PC patients has been shown to be good for different radiotherapy treatment options [1–3,7–9]. Therefore, toxicity rates and health-related quality of life (QoL) are important and relevant factors for patients to choose between the different treatment options.

The literature on toxicity and clinical outcome in HDR-BT using a scheme of four fractions of 9.5 Gy is scarce [10–13]. Prospective validated questionnaires to monitor long-term toxicity of HDR-BT are hardly used and data on QoL for this treatment option is lacking in literature.

In this paper, we report long-term toxicity and QoL of HDR-BT as monotherapy for patients with low- and intermediate-risk PC.

Methods and materials

Patients

This study was approved by our institution's medical ethics committee (MEC-2012-364). Between September 2007 and December 2013, 166 patients with histologically confirmed PC clinical stage T1b-T2b, Nx-0, Mx-0, Gleason score (GS) $\leqslant 7$, PSA $\leqslant 16$ ng/ml and WHO performance status of 0–2 were treated with HDR-BT monotherapy. TNM scoring was according to the AJCC 2003 guidelines [14]. Patients with clinical stage T1c-T2a, GS 6 and PSA $\leqslant 10$ ng/ml were defined as low-risk PC (67%), whereas patients with PSA >10 ng/ml, T2b and/or GS 7, were defined as intermediate-risk PC (33%) [15]. The concomitant use of androgen deprivation therapy (ADT) was not allowed. Patient characteristics are shown in Table 1.

Radiotherapy

HDR-BT was performed in one transperineal implant during a two-day admission [1,16]. Before implantation, four fiducials were

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Table 1
Patient and tumour characteristics.

		n (%)	Mean (min–max)
Patients		166	
Age (year)			68 (47–79)
Follow-up (months)			35 (2–78)
Clinical stage	T1c	112 (67%)	
	T2a	52 (31%)	
	T2b	2 (1%)	
Gleason score	2 + 2	1 (1%)	
	2 + 3	1 (1%)	
	3 + 3	142 (86%)	
	3 + 4	21 (13%)	
	4 + 3	1 (1%)	
PSA (ng/ml)			8 (1–16)
Risk group	Low	112 (67%)	
	Intermediate	54 (33%)	
Prostate volume (cm^3)			34 (15–55)
IPSS baseline score			6 (0–24)
Urinary flow baseline (Qmax; ml/s)			16 (2–41)

inserted: two at the base and two at the apex of the prostate. Plastic needles were inserted using transrectal ultrasound guidance and a template. Needle depth was controlled by cystoscopy to ensure that the needle tips were placed just beyond the prostate base for a good coverage of the base. After implantation a planning CT scan was acquired, in which the prostate, rectum, bladder and urethra were delineated. The Planning Target Volume (PTV) was the prostate without margins. Anatomy-based inverse planning was used such that the prescribed dose (PD) covered $\geqslant$95% of PTV. The doses to 1 cm^3 of the rectum and the bladder were limited to 80% of PD. The dose to 1% of the urethra volume was limited to 120% of PD. The total dose administered was 38 Gy in four fractions within 36 h with a minimum interval between fractions of six hours. All fractions were delivered according to one treatment plan. Before each fraction a lateral X-ray was acquired to check needle positions relative to the implanted markers. Needle displacements >3 mm were corrected to ensure good conformity of the dose distribution [16].

Follow-up and questionnaires

All patients were followed up prospectively and were seen every three months in the first year, and twice yearly thereafter. Toxicity questionnaires were sent to all patients at baseline (before treatment), at 1, 2, 3, 6, 12, 18, 24 months after treatment and yearly thereafter. QoL questionnaires were sent following the same scheme, except at 1 and 2 months.

The European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) toxicity score based questionnaires were used to assess genitourinary (GU) and gastrointestinal (GI) toxicities [17,18]. The International Prostate Symptom Score (IPSS) was used to evaluate the urinary function after treatment. QoL was assessed by the prostate-specific EORTC QLQ-PR25 questionnaire [19]. The QLQ-PR25 is a validated QoL instrument and consists of four domains: urinary symptoms, bowel symptoms, hormonal treatment related symptoms and sexual activity and functioning. The hormonal domain is not analysed as all treated patients were hormone-naïve.

Oncologic outcome and PSA

Biochemical failure (BF) was determined according to the Phoenix definition (every rise of PSA $\geqslant$2 ng/ml above nadir) [20]. A PSA bounce was defined as a $\geqslant$0.4 ng/ml rise in PSA level with subsequent normalization of PSA values [21]. Freedom from BF (FFBF) was defined as the percentage of patients still alive without evidence of BF. Cancer-specific survival (CSS), defined as mortality due to PC, and overall survival (OS) were also analysed. Patients who died from other causes than PC or who were lost to follow-up were censored at the date of last PSA test or contact for the survival analysis.

Data analysis

The date of the implantation was considered day 0. GI and GU toxicities were evaluated according to EORTC-RTOG toxicity scores, using a combination of patient questionnaires and physician charts (as was also used in other multicentre trials before [17,22]). The highest toxicity score of the two was taken. Toxicity within 100 days after HDR-BT was considered acute toxicity, and toxicity after 100 days as late toxicity. IPSS scores were assessed and compared to baseline to evaluate the effect of treatment on urinary function and symptoms. In the IPSS analysis, the question on QoL was left out, resulting in scores ranging from 0 to 35. QLQ-PR25 scores were analysed to obtain the net effect on QoL compared to baseline. Raw QLQ-PR25 scores were linearly transformed to values between 0 and 100, where higher scores reflect more symptoms in the urinary and bowel symptoms domain or higher levels of sexual functioning [19]. For all domains changes of $\geqslant$10 points were considered clinically relevant [23]. Statistical significance was tested with the Wilcoxon signed-rank test for differences between 12, 24 and 36 months versus baseline.

Logistic (univariate) regression was applied to determine the effect of prognostic factors presented in Table 2 on acute toxicity, while Cox regression was applied for the effect on late toxicity. The cut-off points of these factors were based on mean values of our patient population in general. The Kaplan–Meier method was applied to estimate survival probabilities. Two-tailed tests were used and p-values <0.05 were considered significant. Statistical analyses were performed using Stata® 13.1 (StataCorp).

Results

Mean follow-up (FU) was 35 months (2–78), with a median of 25 months. The overall response rate on all sent questionnaires was 90.3%. For the toxicity questionnaires the mean response rate per patient was 89.8%, with a median of 100% (range 33.3–100). The QoL questionnaires had a mean response rate of 90.9% (median 100%, range 14.3–100). From 3 months after treatment on, all questionnaires were sent together to the patients. Therefore, return rates are similar.

Acute toxicity

The chronological incidences of grade $\geqslant$2 GU and GI toxicities are depicted in Fig. 1A and B, respectively. The incidence of grade

Table 2
Variables tested in univariate logistic regression for the effect on acute and late GU and GI toxicity.

	Lower limit	Upper limit
Age (year)	$\leqslant$70	>70
IPSS score before treatment	$\leqslant$12	>12
Number of needles used	$\leqslant$17	>17
PTV volume (cm^3)	$\leqslant$40	>40
Urinary flow before treatment (Qmax; ml/s)	$\leqslant$15	>15
Urinary residue before treatment (ml)	$\leqslant$30	>30
Prostate volume before treatment (cm^3)	$\leqslant$40	>40

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