research article

Obstructive urination problems after high-dose-rate brachytherapy boost treatment for prostate cancer are avoidable

Borut Kragelj

Institut of Oncology Ljubljana, Zaloska 2, Ljubljana, Slovenia

Radiol Oncol 2016; 50(1): 94-103.

Received 15 October 2014
Accepted 20 January 2015

Correspondence to: Assist. Prof. Borut Kragelj, M.D., Ph.D., Institute of Oncology Ljubljana, Zaloska 2, Ljubljana, Slovenia.
Phone: +386 1 5879 489; E-mail: bkragelj@onko-i.si

Disclosure: No potential conflicts of interest were disclosed.

Background. Aiming at improving treatment individualization in patients with prostate cancer treated with combination of external beam radiotherapy and high-dose-rate brachytherapy to boost the dose to prostate (HDRB-B), the objective was to evaluate factors that have potential impact on obstructive urination problems (OUP) after HDRB-B.

Patients and methods. In the follow-up study 88 patients consecutively treated with HDRB-B at the Institute of Oncology Ljubljana in the period 2006-2011 were included. The observed outcome was deterioration of OUP (DOUP) during the follow-up period longer than 1 year. Univariate and multivariate relationship analysis between DOUP and potential risk factors (treatment factors, patients' characteristics) was carried out by using binary logistic regression. ROC curve was constructed on predicted values and the area under the curve (AUC) calculated to assess the performance of the multivariate model.

Results. Analysis was carried out on 71 patients who completed 3 years of follow-up. DOUP was noted in 13/71 (18.3%) of them. The results of multivariate analysis showed statistically significant relationship between DOUP and anticoagulation treatment (OR 4.86, 95% C.I. limits: 1.21-19.61, p = 0.026). Also minimal dose received by 90% of the urethra volume was close to statistical significance (OR = 1.23; 95% C.I. limits: 0.98-1.07, p = 0.099). The value of AUC was 0.755.

Conclusions. The study emphasized the relationship between DOUP and anticoagulation treatment, and suggested the multivariate model with fair predictive performance. This model potentially enables a reduction of DOUP after HDRB-B. It supports the belief that further research should be focused on urethral sphincter as a critical structure for OUP.

Key words: prostate cancer; high-dose-rate brachytherapy boost; late effects; urinary stricture; obstructive urination problems.

Introduction

Several modes of radical local treatment are on disposal for patients with localized or locally advanced prostate cancer. Beside radical prostatectomy, radical irradiation in the form of external beam radiotherapy (EBRT), and permanent brachytherapy (PB) or high-dose-rate brachytherapy (HDRB) are established ways of treatment. Both treatment modalities should be considered as equally effective in the absence of randomized trials. Similar consideration should also be given to different ways of radiation treatment.[1,2] When radiation therapy is applied, EBRT could be combined with either form of brachytherapy. The combination of EBRT and HDRB to boost the dose to prostate (HDRB-B) is effective treatment, according to some reports more effective than EBRT alone.[3-5]

Any of above mentioned treatments could expose patients to late side effects. Especially long-term consequences could be decisive for patients' determination for one or other treatment. Well

known long-term complications are bladder neck contractures after radical prostatectomy[6], and urethral strictures after PB[7,8] or HDRB-B.[9-11]

In HDRB-B obstructive urination problems (OUP), including urethral strictures, are the most frequent urinary severe late effect. According to results of studies in the past the frequency of only strictures was 1.5–9%.[9-12] Some recent studies report even considerably higher frequency.[4,13] Previous transurethral resection of the prostate (TURP)[14-16], fractionation schedule of HDRB-B with increased risk with higher fractional dose[13], older age[14], and hypertension[15], were considered as potential patient-related risk factors but their role was not clearly defined.[17] Furthermore, there were found no reliable normal tissue absolute dose constraints for urinary toxicity.[17]

This high stricture risk with problems that evolve with stricture formation should be factored into counselling all men who are considering HDRB-B and could curtail patient's decision for HDRB-B, since with refinement of radical prostatectomy, or PB, the expected frequency of these marked lower urinary tract OUP could be considerably lower.[18-20]

At the Ljubljana Institute of Oncology HDRB-B was started in October 2006, and up to now, late effects, including OUP and stricture formation, have not been evaluated yet.

Aiming at improving treatment individualization in patients with prostate cancer treated with HDRB-B, the objective of the present study was to evaluate factors that have potential impact on OUP after HDRB-B.

Patients and methods

Patients

In the follow-up study 88 patients, consecutively treated by the author with HDRB-B at the Institute of Oncology Ljubljana in the period 2006–2011, were included.

HDRB-B treatment was primarily offered to patients with intermediate- or high-risk clinically localized or locally advanced prostate cancer (according to D'Amico risk stratification of prostate cancer patients)[21] and to low risk patients refused to get radical prostatectomy, if feasible for brachytherapy. In general, patients were considered eligible for HDRB-B if (i) ultrasound showed no pubic arch interference, (ii) were eligible to undergo regional anaesthesia with spinal block, and (iii) were eligible to perform CT/MRI scan. TURP was considered as a contraindication for the procedure.

Study protocol was approved by the Protocol and Ethical Committee of the Institute of Oncology Ljubljana.

Treatment characteristics

Brachytherapy consisted of ultrasound guided transperineal insertion of 20 or 30 cm long close-end plastic needles (Varian, California, USA) into the prostate, and in selected patients also into the initial part of seminal vesicles. An in-house made template allowing needle fixation was used. Needles were typically placed into prostate periphery. Cystoscopy was performed to control for urinary bladder or urethral puncture. CT or MRI scan was used for planning purposes. Brachyvision planning system (Varian, California, USA) was used for image registration, contouring and dosimetry. Two planning target volumes (PTVs) were routinely defined: PTV1 and PTV2. PTV1 encircled the prostate with additional 3 mm margin around the zone of suspected capsular invasion, while PTV2 encircled peripheral part of the prostate. If visible on the MRI images, also gross tumour volume (GTV) was defined and included in the PTV2. Initially, prescribed dose was 21 Gy to PTV1 and 22.5 Gy to PTV2, with 7 Gy and 7.5 Gy per fraction, respectively. Later, the dose was reduced to 18 Gy to PTV1 and 19.5 Gy to PTV2, also given in 3 fractions in 2 consecutive days. Urethra was indentified with the urinary catheter. The contour also enclosed additional 1-2 mm margin around the catheter. Contouring of urethra started at bladder base and extended to genitourinary diaphragm inferiorly (always at least 0.5 cm caudally from the last slice of contoured apex of the prostate). Minimal dose received by 90% of the urethra volume ($D90_{urethra\ volume}$) was planned to be below 110%, while minimal dose received by 1% of the urethra volume ($D1_{urethra\ volume}$) was planned to be below 130% of the prescribed dose. Treatment was delivered with Gammamed plus device (Varian, California, USA) using ^{192}Iridium with the activity of 0.7-1.4 Ci.

EBRT was delivered as 3-dimensional conformal radiation. The details of technique have been described elsewhere.[22] The patients were simulated in supine position with knee and feet fixation device and urethrogram, to define prostatic apex. Clinical target volume (CTV) included prostate and distal 2/3 of seminal vesicles with lymph nodes along external, internal and common iliac vessels in patients with Gleason Score (GS) 8–10 or locally advanced tumours, or if the risk of positive lymph

TABLE 1. Questions addressing obstructive urination problems in Ljubljana Institute of Oncology questionnaire about adverse health effects of radiation therapy

Question	Possible answers
Did you have a sensation of not emptying your bladder in the previous month	Yes/No
Did you find stopping and starting again several times when you urinated in the previous month	Yes/No
Did you have weak urinary stream in the previous month	Yes/No
Did you have to strain to start urination in the previous month	Yes/No
If you had any of the problems, how often did they occur	Occasionally At least once a week Daily At every urination
How big were these problems for you	No problem Very small problem Small problem Moderate problem Big problem
Did you have to get urinary catheter in the last half of the year	Yes/No
Were you operated because of the mentioned problems	Yes/No
Did you still have urinary catheter	Yes/No

nodes ($Risk_{N+}$) exceeded 15% according to the equation of Roach *et al.* (Equation 1).[23]

$$Risk_{N+} = 2/3PSA + 10(GS - 6) \quad \text{[Equation 1]}$$

PSA = the pre-treatment prostate-specific antigen
GS = the pre-treatment Gleason score

Uniform 1 cm margin was added to CTV to form PTV. Prior to treatment planning three golden markers were implanted into the prostate. If treatment started with HDRB treatment, markers were implanted together with needle insertion. Prescribed dose was 50.4 Gy. The PTVs were required to be enclosed in 95% isodose relative to the prescribed dose. Basically, box technique was used, with additional small fields to homogenize the dose delivery. All patients were treated using 15 MV photons. During treatment prostate position was determined using MV portal imaging and implanted markers. Daily off-line position correction was used.

A constitutive part of treatment was also the androgen deprivation therapy. In principle 3 years of androgen deprivation was advised to high-risk patients and also to some intermediate-risk patients with cancer overgrowth in the majority of biopsy cores or with MRI evidenced infiltration of periprostatic tissue or seminal vesicles. One year of androgen deprivation was advised to the rest of intermediate-risk patients. In low-risk patients androgen deprivation therapy was given either to reduce the prostate volume, or was initiated by the referring urologist after prostate biopsy and continued afterwards until the end of radiation treatment. Patients on androgen deprivation were followed-up every 6 months. After the discontinuation of androgen deprivation, patients were seen yearly, with PSA testing every six months. After the first follow-up visit 3–6 months after treatment, the same way of annual check-ups was used in patients without adjuvant androgen deprivation.

Study instrument for assessment of obstructive urination problems

An in-house made questionnaire, used already for several years, was used as the study instrument. The questionnaire was discussed with patients at follow-up visits. The aim of the questionnaire was to detect late effects of treatment more precisely as would be by open questions, and to allow to grade late toxicity according to Radiation Therapy Oncology Group (RTOG)[24] subjective part of RTOG/EORTC Soma Scales[25] and Common Terminology Criteria for Adverse Events Ver. 3.0 (CTCAE). Late urinary toxicity was addressed with regard to dysuria, frequency, haematuria, incontinence and obstruction. In Table 1 the questions addressing OUP are presented. Patients were asked to complete the questionnaire just before the start of the HDRB-B treatment, at first follow-up visit and yearly thereafter.

Observed outcome

The observed outcome was deterioration of OUP (DOUP) during the follow-up period longer than 1 year, supposing to be a manifestation of late radiation urethral injury. It was defined in several steps.

Firstly, the presence of OUP just before the start of the HDRB-B treatment was established. The problems were graded according to the following scale: 1-occasional (less than weekly), 2-regular (about daily), 3-regular (daily) with at least one episode of urgent urethral catheter placement, 4-regular (daily) with at least one episode of urethral dilatation or endoscopic intervention, 5-refractory obstruction (permanent urinary catheter, supravesical urine derivation).

During the follow-up period the grade of OUP was checked-up in the 2nd, the 3rd, the 4th and the 5th year after the beginning of the HDRB-B treatment.

Finally, the difference in grade of OUP between OUP at the start of the HDRB-B treatment and latter follow-up visits was assessed. The following scale was used: 1-major improvement (decrease in OUP for two or more grades), 2-minor improvement (decrease in OUP for one grade), 3-no change, 4-minor deterioration (increase in OUP for one grade), 4-major deterioration (increase in OUP for two or more grades). Since minor and major deterioration were the categories of interest, these two categories were combined in the observed outcome - DOUP (0 = no, 1 = yes).

In order to achieve a sufficiently large number of observed persons, analysis of association between observed outcome and potential risk factors was carried out only in patients who completed 3 years of follow-up. The occurrence of DOUP in the 2nd or in the 3rd year of follow-up was considered.

Risk factors for deterioration of obstructive urination problems

Two groups of risk factors were observed. The first group consisted of HDRB-B and supportive treatment factors, while the second group consisted of patients' characteristics.

In the group of HDRB-B and supportive treatment factors following factors were observed: number of implanted needles ($N_{implanted\ needles}$), planning imaging (1 = CT, 2 = MRI), number of interventions ($N_{interventions}$) (0 = 1, 1 = 2+), and dosimetric factors, being PTV1, minimal dose received by 100% of the PTV1 ($D100_{PTV1}$), minimal dose received by 90% of the PTV1 ($D90_{PTV1}$), minimal dose received by 100% of the PTV2 ($D100_{PTV2}$), urethral volume ($V_{urethra}$), mean urethral dose ($D\text{-}MEAN_{urethra}$), $D90_{urethra\ volume}$, minimal dose received by 10% of the urethra volume ($D10_{urethra\ volume}$), and $D1_{urethra\ volume}$. All of dosimetric factors were retrospectively extracted from Dose-Volume Histograms stored in electronic patients' files. As supportive treatment factor the duration of androgen deprivation therapy was included (0 = < 12 months, 1 = ≥ 12 months).

In the group of patients' characteristics the following factors were observed: age, co-morbidity (hypertension: 0 = no, 1 = yes, diabetes: 0 = no, 1 = yes, coronary insufficiency: 0 = no, 1 = yes, hyperlipidemia: 0 = no, 1 = yes, history of cerebrovascular insult or peripheral deep venous thrombosis: 0 = no, 1 = yes), and anticoagulant treatment (vitamin K antagonist or antiplatelet drug) (0 = no, 1 = yes). All of them were extracted from patients' files.

Statistical analysis

All data were first statistically described. Parametric (mean ± standard deviation, minimum and maximum) or nonparametric methods (median, range) for numerical data, or percentages for attributable data were used.

Afterwards the univariate and multivariate relationship analysis between DOUP and potential risk factors (treatment factors, patients' characteristics) was carried out. Univariate analysis was carried out by using binary logistic regression or Fisher's exact test (in one variable logistic regression analysis could not be performed due to no observed outcome in one category). In multivariate analysis binary logistic regression was used. All variables that were meaningful for the observed outcome and univariately at least marginally statistically significantly associated with DOUP ($p < 0.250$) were included in the multivariate model.[26] On the basis of logistic regression model, the risk-score (logit) for each participant was calculated (Equation 2) and afterwards converted to the risk estimates (p(x)) for the observed outcome (Equation 3).[26]

$$\text{logit} = \ln\left[\frac{p(x)}{1-p(x)}\right] = a + b_1 x_1 + b_2 x_2 + \ldots + b_n x_n$$

[Equation 2]

$$p(x) = \frac{e^{\text{logit}}}{1+e^{\text{logit}}} = \frac{e^{a+b_1x_1+b_2x_2+\ldots+b_nx_n}}{1+e^{a+b_1x_1+b_2x_2+\ldots+b_nx_n}}$$

[Equation 3]

Finally, the risk estimate values were put in an ordered series from the lowest to the highest value.

TABLE 2. Characteristics of dosimetric parameters of high-dose-rate brachytherapy in Ljubljana Institute of Oncology study of late toxicity after high-dose-rate brachytherapy boost treatment for prostate cancer

Dosimetric parameter	Minimum	Maximum	Mean±SD
PTV1	18 ml	95 ml	37.6 ± 14.8 ml
$D100_{PTV1}$	8.3 Gy	17.1 Gy	11.8 ± 1.9 Gy
$D90_{PTV1}$	13.4 Gy	24.6 Gy	19.2 ± 2.0 Gy
$D100_{PTV2}$	12.8 Gy	23.7 Gy	17.3 ± 2.1 Gy
$V_{urethra}$	1.2 ml	4.0 ml	1.9 ± 0.8 ml
$D\text{-}MEAN_{urethra}$	14.4 Gy	26.1 Gy	19.0 ± 2.6 Gy
$D90_{urethra\ volume}$	7.5 Gy	18.9 Gy	13.2 ± 2.9 Gy
$D10_{urethra\ volume}$	17.8 Gy	31.1 Gy	23.1 ± 2.7 Gy
$D1_{urethra\ volume}$	17.3 Gy	36.0 Gy	24.5 ± 3.4 Gy

$D100_{PTV1}$ = minimal dose received by 100% of the PTV1; $D90_{PTV1}$ = minimal dose received by 90% of the PTV1; $D100_{PTV2}$ = minimal dose received by 100% of the PTV2; PTV1 = planning target volume 1; PTV2 = planning target volume 2; $D\text{-}MEAN_{urethra}$ = mean urethral dose; $D90_{urethra\ volume}$ = minimal dose received by 90% of the urethra volume; $D10_{urethra\ volume}$ = minimal dose received by 10% of the urethra volume; $D1_{urethra\ volume}$ = minimal dose received by 1% of the urethra volume; $V_{urethra}$ = urethral volume

At every value the cut-point was placed, a decision matrix defined taking into account the actual status of presence/absence of observed outcome, and nosological (true-positive, false-positive, true-negative and false-positive rates) as well diagnostic test validity measures (positive and negative predictive values) calculated.[27-29] Also the receiver operating characteristic (ROC) analysis was performed (ROC curve constructed and the area under the curve calculated).[29] Decision about the best possible cut-point (the cut-point with the highest true positive rate at the highest acceptable false positive rate) was supported by calculating Youden index (the maximum vertical distance between the ROC curve and the diagonal/chance line).[30]

In all statistical tests p-value 0.05 or less was considered significant. SPSS statistical package for Windows Ver. 21.0 was used for analysis.

Results

Description of the study group

Patients in the study group were aged 67.6 ± 6.1 years, with following tumour characteristics: Gleason score: £ 6 22/88 (25.0%), 7 37/88 (42.0%), ≥ 8 29/88 (33.0%); percent of positive cores: median 50 (range 10–100); PSA: median 10 ng/ml (range 4–60 ng/ml); stage: T1 18/88 (20.5%), T2 40/88 (45.5%), T3 30/88 (34.0%); risk category: low 13/88 (14.8%), intermediate 27/88 (30.7%), high 48/88 (54.5%). Androgen deprivation treatment was received by 81/88 (92.0%) patients (median duration 24 months (1–60 months); duration less than 12 months: 10/81 (12.3%) patients).

In most patients the comorbidities were present. The most frequent was hypertension (46/86, 53.5%), followed by hyperlipidemia (20/85, 23.5%), coronary insufficiency (17/86, 19.8%), history of cerebrovascular insult or peripheral deep venous thrombosis (11/86, 12.8%) and diabetes (10/85, 11.8%).

During the HDRB-B treatment 22/86 (25.6%) of patients were receiving anticoagulation therapy.

Description of the treatment

Regarding the dose to PTV1, 21 Gy was delivered to 27/88 (30.7%) patients, while 18 Gy to 61/88 (69.3%) patients. Target volume was restricted to prostate in 79/88 (89.8%), while in 9/88 (10.2%) of patients it was enlarged to enclose infiltrated parts of seminal vesicles. Dosimetric parameters of HDRB-B applied in the study are summarized in Table 2.

Mean $N_{implanted\ needles}$ was 15±3, while $N_{interventions}$ was one in 80/88 (90.9%), and two or more in 8/88 (9.1%) patients. CT based planning was used in 30/88 (34.1%), while MRI was used in 58/88 (65.9%) patients.

Obstructive urination problems at the beginning of the study

At the start of treatment OUP were declared in 52/82 (63.4%) patients that had complete entry data. In majority of them problems were not significant and were assessed as grade 1 in 46/52 (88.5%). In the rest of patients, problems were more pronounced and assessed as grade 2 in 5/52 (9.6%) and as grade 3 in 1/52 (1.9%) patients.

Analysis of deterioration of obstructive urination problems during the follow-up period

The course of OUP after treatment in relation to initial problems is presented as a prevalence rates during the 2nd, the 3rd, the 4th and the 5th year of observation (Table 3). In this time frame the proportion of patients with DOUP after initial increase remained stable. On the other hand it seemed that the proportion of patients that experienced improvement of initial obstructive problems increased (Table 3).

TABLE 3. Prevalence rates of alteration of obstructive urination problems in Ljubljana Institute of Oncology study of late toxicity after high-dose-rate brachytherapy boost treatment for prostate cancer

Year of follow-up	N	Major improvement	Minor improvement	No change	Minor deterioration	Major deterioration
2nd year	80	1 (1.3%)	10 (12.5%)	57 (71.3%)	12 (15.0%)	0 (0%)
3rd year	71	1 (1.4%)	11 (15.5%)	51 (71.8%)	8 (11.3%)	0 (0%)
4th year	45	2 (4.4%)	7 (15.6%)	31 (68.9%)	4 (8.9%)	1 (2.2%)
5th year	25	0 (0%)	6 (24.0%)	16 (64.0%)	3 (12.0%)	0 (0%)

Analysis of association between deterioration of obstructive urination problems and potential risk factors

Analysis of association between observed outcome and potential risk factors was carried out in 71 patients who completed 3 years of follow-up. DOUP occurred in the 2nd or in the 3rd year in 13/71 (18.3%) of patients.

In the group of HDRB-B and supportive treatment factors none of them was statistically significantly associated with the DOUP (Table 4). However, according to predefined criterion PTV1 and $D90_{urethra\ volume}$ were candidates for entering the multivariate analysis.

In the group of patients' characteristics also the vast majority of factors did not show statistically significant association with DOUP (Table 5). The only exception was anticoagulation treatment in which association with observed outcome was statistically significant, and thus was a candidate for entering the multivariate analysis. In the majority of patients receiving this treatment, it consisted of acetyl salicylic acid either alone (11/17 patients) or in the combination with warfarin (2/17 patients). Tidapidine was given to 2/17, warfarin to 1/17,

TABLE 4. Results of univariate logistic regression analysis of association between deterioration of obstructive urination problems and treatment factors in Ljubljana Institute of Oncology study of late toxicity after high-dose-rate brachytherapy boost treatment for prostate cancer

Risk factor		N_{tot}	N_{det}/N_{cat} (%)	OR	95 % C.I. limits for OR		p-value
					Lower	Upper	
$N_{implanted\ needles}$		71		0.89	0.71	1.11	0.305
Planning imaging	CT	71	3/25 (12.0%)	1.00			
	MRI		10/46 (21.7%)	2.04	0.51	8.22	0.317
$N_{interventions}$	1	71	10/63 (15.9%)	1.00			
	2+		3/8 (37.5%)	3.18	0.65	15.48	0.152
PTV1 (ml)		70		1.03	0.99	1.07	0.149
$D100_{PTV1}$ (Gy)		71		1.08	0.76	1.53	0.656
$D90_{PTV1}$ (Gy)		71		0.93	0.68	1.28	0.673
$D100_{PTV2}$ (Gy)		70		0.99	0.75	1.31	0.941
$V_{urethra}$ (ml)		70		1.22	0.55	2.74	0.626
$D\text{-}MEAN_{urethra}$ (Gy)		70		1.06	0.84	1.35	0.629
$D90_{urethra\ volume}$ (Gy)		71		1.18	0.95	1.47	0.145
$D10_{urethra\ volume}$ (Gy)		70		1.07	0.87	1.31	0.521
$D1_{urethra\ volume}$ (Gy)		71		1.03	0.86	1.22	0.780
Androgen deprivation	< 12 months	69	2/9 (22.2%)	1.00			
	≥ 12 months		11/60 (18.3%)	0.79	0.14	4.31	0.781

N^{tot}=total number of observations, N^{det}= number of patients with deterioration; N^{cat}= number of patients within the category; $N_{implanted\ needles}$ = number of implanted needles; $N_{interventions}$ = number of interventions; PTV1 = planning target volume 1; PTV2 = planning target volume 2; $D100_{PTV1}$ = minimal dose received by 100% of the PTV1; $D90_{PTV1}$ = minimal dose received by 90% of the PTV1; $D100_{PTV2}$ = minimal dose received by 100% of the PTV2; $V_{urethra}$ = urethral volume; $D\text{-}MEAN_{urethra}$ = mean urethral dose; $D90_{urethra\ volume}$ = minimal dose received by 90% of the urethra volume; $D10_{urethra\ volume}$ = minimal dose received by 10% of the urethra volume; $D1_{urethra\ volume}$ = minimal dose received by 1% of the urethra volume

TABLE 5. Results of univariate logistic regression analysis of association between deterioration of obstructive urination problems and patients' characteristics in Ljubljana Institute of Oncology study of late toxicity after high-dose-rate brachytherapy boost treatment for prostate cancer

Risk factor		N_{tot}	N_{det}/N_{cat} (%)	OR	95 % C.I. limits for OR		p-value
					Lower	Upper	
Age		70		1.05	0.94	1.17	0.372
Hypertension	No	69	5/32 (15.6%)	1.00			
	Yes		7/37 (18.9%)	1.26	0.36	4.44	0.719
Diabetes	No	68	12/62 (19.4%)	NA			
	Yes		0/6 (0.0%)	NA	NA	NA	0.581*
Hyperlipidemia	No	68	8/52 (15.4%)	1.00			
	Yes		4/16 (25.0%)	1.83	0.47	7.14	0.382
CVI	No	69	10/62 (16.1%)	1.00			
	Yes		2/7 (28.6%)	2.08	0.35	12.26	0.418
Coronary insufficiency	No	69	8/54 (14.8%)	1.00			
	Yes		4/15 (26.7)	2.09	0.53	8.22	0.291
Anticoagulation treatment	No	69	6/52 (11.5%)	1.00			
	Yes		6/17 (35.5%)	4.18	1.13	15.48	0.032

N^{tot}=total number of observations, N^{det}= number of patients with deterioration; N^{cat}= number of patients within the category; NA = not applicable; * = Fisher exact test results; C.I. = confidence interval; CVI = history of cerebrovascular insult or peripheral deep venous thrombosis; OR = odds ratio

TABLE 6. Results of multivariate logistic regression analysis of association between deterioration of obstructive urination problems and selected treatment factors and patients' characteristics in Ljubljana Institute of Oncology study of late toxicity after high-dose-rate brachytherapy boost treatment for prostate cancer (N = 68)

Risk factor		OR	95% C.I. limits for OR		p
			lower	upper	
PTV1 (ml)		1.02	0.98	1.07	0.292
$D90_{urethra\ volume}$ (Gy)		1.23	0.96	1.57	0.099
Anticoagulation treatment	No	1.00			
	Yes	4.86	1.21	19.61	0.026

$D90_{urethra\ volume}$ = minimal dose received by 90% of the urethra volume; OR = odds ratio; PTV1 = planning target volume 1; OR = odds ratio

while acenocoumarol to 1/17 patients. In the group of 6 patients with DOUP, anticoagulation treatment consisted of acetyl salicylic acid in 4 patients, a combination of acetyl salicylic acid and warfarin in one, and warfarin alone in one patient.

All data necessary to perform multivariate analysis were present in 68/71 patients (95.8%). The results of the logistic regression model showed that anticoagulation treatment not only remained statistically significantly associated with observed outcome but even increased (the odds for DOUP were about 4.9-times higher in patients on anticoagulation treatment). In addition, $D90_{urethra\ volume}$ came closer to the border of statistical significance (for a one-Gy increase in $D90_{urethra\ volume}$, about 23% increase in odds of experiencing observed outcome could be expected). All other results are presented in Table 6.

Finally, the risk of DOUP was estimated for each patient. The values varied between 0.02509 and 0.62421, with the median value 0.10973. The value of area under ROC curve was 0.755, indicating fair predictive performance of the model. The best cut-point was placed at value 0.16441 (true positive rate: 9/12 or 0.750; false positive rate: 16/56 or 0.286; true negative rate: 40/56 or 0.714; false negative rate: 3/12 or 0.250; positive predictive value: 9/25 or 0.360; negative predictive value: 40/43 or 0.930; Youden index: 0.464).

Discussion

The main results of the study

The most prominent result of present study was strong association of DOUP after HDRB-B with anticoagulation treatment. Based on the available literature this association has not been reported yet up to now. Generally, patient-related risk factors, with exception of age and prior TURP, were only

exceptionally considered in the studies of OUP after HDRB-B. In the available literature only one study that considered patients' characteristics could be found. In this study hypertension was identified as an independent predictor of urinary tract obstruction grade 2 or more according to CTCAE after HDRB-B, but anticoagulation treatment was not considered.[15] Anticoagulation treatment, however, was found to be, together with total dose, the most important predictive factor for 5-year risk of global urinary toxicity in a large study of 965 patients who received definitive EBRT. One of the conclusions of the study was that urinary toxicity might be more related to patients' risk factors than dose parameters.[31] A similar conclusion can be drawn on the basis of results of present study. They pointed out that perhaps higher dose sensitivity of urethral sphincter region in comparison to the urethra, as already suggested by Hindson[13], is further increased with anticoagulation treatment (with almost 5-times higher odds of DOUP in patients receiving either vitamin K antagonists or antiplatelet agents in present study). One can only speculate about exact aetiology of this increased radiosensitivity. Since anticoagulation treatment is as a rule considered in patients with vasculopathy, poor circulation could be the underlying cause. However, other parameters that implicate this mechanism and were considered in present study (hypertension, diabetes, hyperlipidemia, history of cerebrovascular insult and deep venous thrombosis) did not show significant association with the observed outcome.

Other important results of the study

Additionally, study offered other results that could be interesting. Urethra is, as suggested by Hsu[32], with regard to late urinary toxicity, a dose limiting structure. In present study $D90_{\text{urethra volume}}$ expressed the strongest, although statistically only marginal, association with observed outcome. This relation of dose applied to the major part of urethra to OUP seems to be reasonable as the location of stricture formation is at or beyond the prostatic apex, which is at the margin or beyond the contoured urethra.[13,15,33] Apparently, this is in the area of external urethral sphincter. This way it is more likely that the dose applied to the major part of urethra is a better representative of the actual sphincter dose than are dose parameters that represent high doses to small parts of (contoured) urethra. Some similarity can be found between the significance of the $D90_{\text{urethra volume}}$ and the minimum dose to bulbomembranous urethra which was found to be (with regard to maximum prostatic urethral dose, the mean, maximum and minimum bulbomembranous urethral doses, and bulbomembranous urethral doses 10 and 15 mm from apex) the stongest predictor of stricture formation in a large study of patients treated with PB.[18] However, in two studies that addressed whole range of dose-volume histogram urethral data, and related them to late urinary toxicity grade 2 or higher according to CTCAE[32], or late urinary toxicity grade 3 or higher according to RTOG[34], small urethral volumes and high doses were emphasized. In the study of Ischiyama this was the volume that received minimal 13 Gy per fraction with the prescribed dose of 5×7.5 Gy, and in the study of Hsu multiple dose levels above 110% of the prescribed 19 Gy in 2 fractions. Although in 8/12 patients with grade 3 toxicity in the study of Ischiyama was due to stricture formation, studies that focused only on strictures, failed to prove the value of high-dose urethral volumes. In the study of Hindson this was the minimal dose received by the »hottest« 10% of the urethral volume[13], and in the study of Ghadjar the minimal dose to the urethral volumes that received at least 100%, 120%, 125% of the prescribed target dose and the minimal dose received by the »hottest« 1% urethral volume.[35] Both were negative as no significant association was found with 5-year stricture-free survival in the study of Ghadjar, and no correlation was recorded within dose groups of 18 Gy in 3 fractions, 20 Gy in 4 fractions, 19 Gy in 2 fractions, or 16 Gy in 2 fractions between $D10_{\text{urethra volume}}$ and stricture risk in the study of Hindson. Nevertheless, low-dose urethral volumes were decisive for obstructive or any other urinary toxicity after HDRB-B. We can only speculate that with analogy to EBRT data, different dose-volume histogram parameters should be emphasized for different grades of toxicity. In all of patients that were included in the present study, OUP would either be missed if RTOG criteria were used, or graded as grade 1 morbidity according to CTCAE. As it is suggested by the results of present study, low-dose parameters may be crucial for this low-grade urinary toxicity.

Another parameter that was included in predictive model in present study was PTV1. It was also only marginally significantly associated with observed outcome and was included in the final model primarily due to results of other studies that reported positive correlation between late genitourinary toxicity and PTV.[32,36] Additionally, the study of Pinkawa *et al.* showed that PTV may relate to the length of prostatic urethra that is also predictive for late genitourinary toxicity.[37]

Limitations of the study

The presented study has some potential limitations. Firstly, one could argue that in the study the internationally validated International Prostate Symptom Score (I-PSS) Questionnaire was not used as a study instrument instead of in-house made questionnaire. This is certainly a limitation, however, the in-house made questionnaire was used already for several years at Ljubljana Institute of Oncology and replacing the questionnaire would affect the comparability of responses in time. Secondly, a shortcoming of the study was that patients with OUP did not undergo cystoscopic evaluation so it was unclear weather OUP were actually a consequence of urethral obstruction. The deduction from OUP to urethral stricture, at least if assessed by I-PSS, may not be so straightforward, as it has been already shown.[13] Thirdly, some caution may be posed also to two different prescribed target doses. However, as the technique and the fractionation remained the same and not prescribed doses but dose volume parameters obtained at planning were considered, this concern may be redundant. Perhaps more plausible may be the effect of either CT or MRI based planning. It may be expected that the dose that urethra was actually exposed is different when CT or MRI based planning is used. Delineated volume of urethra is different with different imaging technique - urethra with inserted urinary catheter is more clearly visible on MRI and impression is that urethral volumes are larger on MRI even if urethral sphincter is not considered, in contrast to other organs involved in the contouring of prostate cancer.[38] Finally, according to merely statistical criterion also $N_{interventions}$ could be considered in the model. However, as this factor primarily reflects excessive needle movement during treatment that could not be predicted in the phase of treatment planning, it was not treated as important in the present study. Actually, only one intervention was planned in all patients. Exact evaluation of needle movement with regard to apical fiducial marker using orthogonal x-ray or CT images was done only before third fraction was applied in the morning next day after needle placement. Separate intervention was considered only if needle movement could not be compensated with additional planning. This primarily caudal needle translocation after HDRB-B is well documented but potential detrimental effect, as perhaps suggested by the results of presented study, is less obvious.

The importance of the study results for clinical practice

The study stresses the importance of clinical patients' data in the evaluation of late toxicity after HDRB-B. Considering clinical patients' data together with treatment and dosimetric parameters it is possible to estimate toxicity of HDRB-B more precisely and also give better opportunity to alleviate side effects. The implementation of results of presented study can hopefully reduce OUP after HDRB-B, and can perhaps also reduce stricture formation that requires surgical intervention.

Possibilities for further research in the field

Further research in the field should be focused in improvement of safety of HDRB-B treatment. For improvement of safety in terms of late adverse effects it is vital to recognize structures which could be at risk for certain type of toxicity. It seems that the critical structure for OUP may be urethral sphincter. However, it is needed to confirm a relation between urethral sphincter, potential risk factors and OUP. Among potential risk factors also anticoagulation treatment should be considered.

Conclusions

Treatment factors as well as patients' characteristics that are associated with OUP, and can predict it, and eventually prevent overt stricture formation after HDRB-B, are not sufficiently known. The study emphasizes the relationship between DOUP and anticoagulation treatment and suggests a fair predictive performance of the model which includes its high negative predictive value. It supports the belief that further research should be focused on urethral sphincter as a critical structure for OUP.

References

1. Mottet N, Bastian PJ, Bellmunt J, Van den Bergh RCN, Bolla M, Van Casteren NJ, et al. *Guidelines on prostate cancer.* Arnhem: European Association of Urology; 2014.

2. Grimm P, Billiet I, Bostwick D, Dicker AP, Frank S, Immerzeel J, et al. Comparative analysis of prostate specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int* 2012; **(109 Suppl 1):** 22-9.

3. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012; **103:** 217-22.
4. Khor R, Duchesne G, Tai KH, Foroudi F, Chander S, Van Dyk S, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. *Int J Radiat Biol Phys* 2012; **85:** 679-85.
5. Pieters BR, de Back DZ, Koning CC, Zwinderman AH. Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. *Radiother Oncol* 2009; **93:** 168-173.
6. Lepor H. Prevention and management of complications associated with open radical retropubic prostatectomy. In: Kirby RS, Partin AW, Feneley M, Parsons JK, editors. *Prostate cancer principles and practice*. London: Taylor & Francis; 2006. p. 789-97.
7. Cesaretti JA, Stone NN, Kao J. Brachytherapy for the treatment of prostate cancer. In: Kirby RS, Partin AW, Feneley M, Parsons JK, editors. *Prostate cancer principles and practice*. London: Taylor & Francis; 2006. p. 817-29.
8. Elliott SP, Meng MV, Elkin EP, McAninch JW, Duchane J, Carroll PR, CaPSURE Investigators. Incidence of urethral stricture after primary treatment for prostate cancer. *J Urol* 2007; **178:** 529-34.
9. Deger S, Boehmer D, Roigas J, Schink T, Wernecke KD, Wiegel T, et al. High dose rate (HDR) brachytherapy with conformal radiation therapy for localized prostate cancer. *Eur Urol* 2005; **47:** 441-8.
10. Vargas CE, Martinez AA, Boike TP, Spencer W, Goldstein N, Gustafson GS, et al. High-dose irradiation for prostate cancer via a high-dose-rate brachytherapy boost: results of a phase I to II study. *Int J Radiat Biol Phys* 2006; **66:** 416-23.
11. Yamada Y, Bhatia S, Zaider M, Cohen G, Donat M, Eastham J, et al. Favorable clinical outcomes of three dimensional computer-optimized high-dose-rate prostate brachytherapy in the management of localized prostate cancer. *Brachytherapy* 2006; **5:** 157-64.
12. Demanes DJ, Rodriguez RR, Schour L, Brandt D, Altieri G. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. *Int J Radiat Biol Phys* 2005; **61:** 1306-16.
13. Hindson BR, Millar JL, Matheson B. Urethral strictures following high-dose-rate brachytherapy for prostate cancer: analysis of risk factors. *Brachytherapy* 2013; **12:** 50-5.
14. Martínez-Monge R, Moreno M, Ciérvide R, Cambeiro M, Pérez-Gracia JL, Gil-Bazo I, et al. External-beam radiation therapy and high-dose-rate brachytherapy combined with long-term androgen deprivation therapy in high and very high prostate cancer: preliminary data on clinical outcome. *Int J Radiat Biol Phys* 2012; **82:** 469-76.
15. Sullivan L, Williams SG, Tai KH, Foroudi F, Cleeve L, Duchesne GM. Urethral stricture following high dose rate brachytherapy for prostate cancer. *Radiother Oncol* 2009; **91:** 232-6.
16. Galalae RM, Kovács G, Schultze J, Loch T, Rzehak P, Wilhelm R, et al. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. *Int J Radiat Biol Phys* 2002; **52:** 81-90.
17. Yamada Y, Rogers L, Demanes DJ, Morton G, Prestidge BR, Pouliot J, et al. American brachytherapy society consensus guidlines for high-dose-rate prostate brachytherapy. *Brachytheapy* 2012; **11:** 20-32.
18. Merrick GS, Butler WM, Wallner KE, Galbreath RW, Anderson RL, Allen ZA, et al. Risk factors for the development of prostate brachytherapy related urethral strictures. *J Urol* 2006; **175:** 1376-81.
19. Parihar JS, Ha YS, Kim IY. Bladder neck contracture-incidence and management following contemporary robot assisted radical prostatectomy. *Prostate Int* 2014; **1:** 12-8.
20. Breyer BN, Davis CB, Cowan JE, Kane CJ, Carroll PR. Incidence of bladder neck contracture after robot-assisted laparoscopic and open radical prostatectomy. *BJU Int* 2010; **106:** 1734-8.
21. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. A. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; **280:** 969-74.
22. Grabec D, Kragelj B. The sigmoid colon and bladder shielding in whole pelvic irradiation at prostate cancer (forward planned IMRT from Institute of oncology Ljubljana). *Radiol Oncol* 2009; **43:** 56-64.
23. Roach M 3rd, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, et al. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1994; **28:** 33-7.
24. Cox JD, Stetz JA, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Biol Phys* 1995; **31:** 1341-6.
25. Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Biol Phys* 1995; **31:** 1257-80.
26. Hosmer DW, Lemeshow S. *Applied logistic regression*. New York (NY): John Wiley & Sons; 2000.
27. McNeil BJ, Keeler E, Adelstein JS. Primer on certain elements of medical decision making. *N Engl J Med* 1975; **293:** 211-215.
28. Bradley GW, editor. *Disease, diagnosis and decisions*. Chichester: John Wiley & Sons; 1993.
29. Kallin Westin L. *Receiver operating characteristic (ROC) analysis: valuating discriminance effects among decision support systems*. Umea: Umea University, Department of Computing Science; 2001.
30. Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cut-point and corresponding Youden index to discriminate individuals using pooled blood samples. *Epidemiology* 2005; **16:** 73-81.
31. Mathieu R, Arango JD, Beckendorf V, Delobel JB, Messai T, Chira C, et al. Nomograms to predict late urinary toxicity after prostate cancer radiotherapy. *World J Urol* 2014; **32:** 743-51.
32. Hsu IC, Hunt D, Straube W, Pouliot J, Cunha A, Krishnamurthy D, et al. Dosimetric analysis of radiation therapy oncology group 0321: The importance of urethral dose. *Pract Radiat Oncol* 2014; **4:** 27-34.
33. McLaughlin PW, Narayana V. High-dose-rate strictures: A theory of cancer meets anatomic reality. *Brachytherapy* 2013; **12:** 199-201.
34. Ishiyama H, Kitano M, Satoh T, Kotani S, Uemae M, Matsumoto K, et al. Genitourinary toxicity after high-dose-rate (HDR) brachytherapy combined with hypofractionated external beam radiotherapy for localized prostate cancer: an analysis to determine the correlation between dose-volume histogram parameters in HDR brachytherapy and severity of toxicity. *Int J Radiat Biol Phys* 2009; **75:** 23-8.
35. Ghadjar P, Rentsch CA, Isaak B, Behrensmeier F, Thalmann GN, Aebersold DM. Urethral toxicity vs. cancer control – lessons to be learned from high-dose rate brachytherapy combined with intensity-modulated radiation therapy in intermediate- and high-risk prostate cancer. *Brachytherapy* 2011; **11:** 286-94.
36. Pellizzon ACA, Salvajoli JV, Maia MAC, Ferrigno R, Dos Santos Novaes PER, Fogarolli RC, et al. Late urinary morbidity with high dose prostate brachytherapy as a boost to conventional external beam radiation therapy for local and locally advanced prostate cancer. *J Urol* 2004; **171:** 1105-8.
37. Pinkawa M, Fischedick K, Asadpour B, Gagel B, Piroth MD, Eble MJ. Low-grade toxicity after conformal radiation therapy for prostate cancer-impact of bladder volume. *Int J Radiat Biol Phys* 2006; **64:** 835-41.
38. Ali AN, Rossi PJ, Godette KD, Martin D, Liauw S, Vijayakumar S, et al. Impact of magnetic resonance imaging on computed tomography –based treatment planning and acute toxicity for prostate cancer patients treated with intensity modulated radiation therapy. *Pract Radiat Oncol* 2013; **3:** e1-9.