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ORIGINAL RESEARCH ARTICLE

Patient-reported long-term sexual morbidity in prostate cancer survivors treated with external beam radiation therapy alone or combined with high-dose-rate brachytherapy

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ABSTRACT

Background: Prostate cancer can be treated with external beam radiation therapy (EBRT) alone or combined with high-dose-rate brachytherapy (HDR-BT+), usually with additional hormonal treatment (HT). The aim of this long-term cross-sectional study was to compare patient-reported sexual function, hormonal symptoms and quality of life (QoL) after EBRT-only or HDR-BT+.

Methods: In 2016, minimum 5 years after treatment, men treated with HDR-BT+ (n = 248) or EBRT-only (n = 91) responded to a questionnaire containing the Expanded Prostate Cancer Index Composite (EPIC)-26 and the Short Form-12 (SF-12).

Results: Median age at time of answering the questionnaire was 74 years (range 54–86). The majority in the HDR-BT+ group received HT for ≥ 2 years compared to 1/3rd in the EBRT-only group. In crude analyses, the sexual domain summary score (DSS) was significantly higher in the HDR-BT+ compared to the EBRT-only group (32.3 vs. 24.1). All sexual items were significantly better in the HDR-BT+ group except sexual problem. Significantly less fatigue was seen in the HDR-BT+ group despite longer duration of HT. Physical and mental health were similar in both groups.

When adjusted for possible confounders, the differences between treatment groups were no longer statistically significant. Only age was significantly associated with lower sexual scores. Low hormonal DSS was significantly associated with decreased QoL.

Conclusion: Patients treated with HDR-BT+ had not worse long-term sexual function than men treated with EBRT-only. However, this difference disappeared when adjusted for possible confounders. Thus, the interplay of age, HT and fatigue indicates a strong impact on both QoL and sexual function.

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Introduction

External beam radiation therapy (EBRT) in combination with hormonal therapy HT has consistently shown to improve survival in men with localised prostate cancer (PCa) [1, 2]. For suitable patients, combining EBRT with high-dose-rate brachytherapy (HDR-BT+) allows for high doses of radiation to be delivered to the prostate [3]. However, higher radiation doses and HT may lead to worsening impaired sexual function, HT related adverse effects (AEs) and decreased quality of life (QoL)[4]. The length of HT must be balanced between sufficient length to achieve curation versus potential life-altering side-effects [5, 6].

We hypothesised that dose-escalation achieved by adding HDR-BT+ boost to EBRT does not compromise sexual or hormonal patient-reported outcome measures (PROMs), and that longer duration of HT will negatively impact patients' sexual function, hormonal symptoms and QoL compared to EBRT alone. Thus, the primary aim was to compare the two radiotherapy (RT) groups regarding sexual, hormonal and QoL outcomes. We performed both crude and adjusted analyses as the groups were not balanced concerning possible confounders. In addition, we assessed the same outcomes in a subgroup of patients for whom testosterone values were available.

Patients and methods

Patients with non-metastatic PCa and a life expectancy of at least 10 years were included in this study, and their primary tumour was categorised according to European Association of Urology (EAU) guidelines [7, 8]. All patients received definitive RT either by EBRT-only or in combination with HDR-BT+ (Figure 1). The treatment was administered according to the EAU guidelines at the time of treatment commencement [7, 8]. Patients who had relapse and started with HT after initial treatment were excluded (Figure 1).

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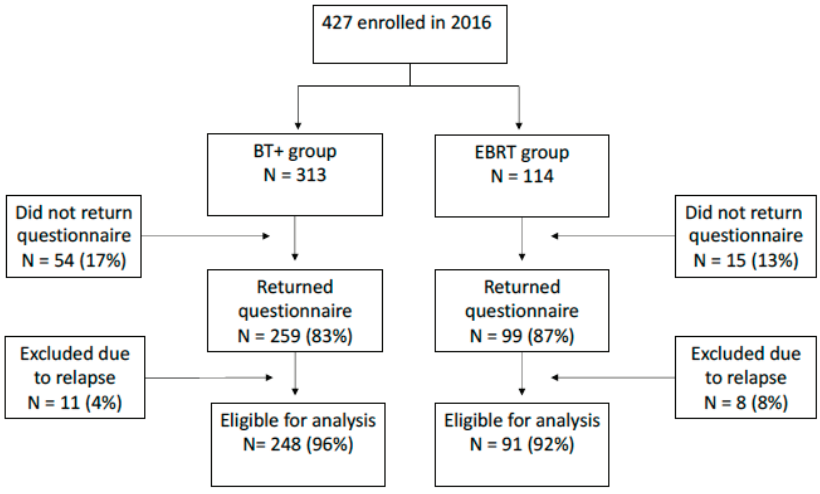

Figure 1. Flow chart of patients.

Patients and treatments

HDR-BT+ group

Oslo University Hospital established the Brachytherapy programme in 2004 [9]. The treatment commenced with 3–6 months of neo-adjuvant Androgen Deprivation Therapy (ADT) before two fractions of 10 Gy with HDR-BT+ were administered 2 weeks apart followed by 2 Gy × 25 of EBRT to the prostate gland and seminal vesicles. Men with Prostate-specific antigen (PSA) levels > 50 ng/mL, previous transurethral resection of the prostate, prostate volume > 60 mL and clinical/radiological stage of T3b and unfavourable anatomical conditions were excluded. Inclusion and exclusion criteria, and survival data have been published previously [3, 10]. The 2 Gy fraction Equivalent Dose (EQD2) was 102 Gy (α/β ratio = 3). Total length of (neo)-adjuvant HT ranged from 0 to 36 months in the individual patient (mean 23 months, Table 1).

In 2016, 313 patients treated between November 2004 and December 2010, were invited to complete a mailed questionnaire consisting of the Expanded Prostate Cancer Index Composite (EPIC)-26, the Short Form-12 (SF-12) and additional questions regarding comorbidities and social status [11, 12]. Of these, 259 patients returned the questionnaire (response rate 83%) of which 248 had not relapsed and were eligible for inclusion (Figure 1). Patients did not get any compensation for their participation beyond stamp costs for the return of the questionnaire.

Testosterone levels at 5 years after treatment were collected from patients charts and divided into 2 groups: testosterone < 8 nmol/L and ≥ 8 nmol/L (230 ng/dL).

EBRT-only group

From January 2009 until December 2010 the prospective Norwegian multicentre study (the Norwegian Urological Cancer Group trial VII) enrolled patients treated with either prostatectomy or EBRT [13]. The current study comprises only men from the EBRT arm of the study. Radiation dose was left to the discretion of the treating oncologist within the EAU guidelines at that time [7]. Most men received 3–6 months of neo-adjuvant ADT followed by 35–39 fractions of 2 Gy (EQD2 70–78 Gy) to the prostate gland and seminal vesicles. Total length of (neo)-adjuvant hormonal therapy ranged from 0 to 36 months (mean 13 months, Table 1).

In 2016, 114 patients received the same questionnaire as described for the HDR-BT+ group. A total of 99 patients returned a completed questionnaire (response rate 87%) of which 91 had not relapsed and were eligible for inclusion (Figure 1).

Testosterone levels at 5 years follow-up for the EBRT-only group were not available.

Questionnaires

EPIC-26 questionnaire

The questionnaire is an internationally acknowledged comprehensive instrument that assesses patient self-reported AEs after treatment for PCa. The EPIC-26 evaluates function and bother of urinary, bowel, hormone and endocrine effects.

The EPIC-26 reports individual items and Domain Summary Scores (DSSs) ranging from 0 to 100 where a higher score indicates less symptoms. The current study assessed sexual function, sexual problem and hormonal symptom burden. Substantial problem, assuming clinical relevance, was defined as moderate or big problem. The patients received the validated questionnaire in Norwegian [14].

Short Form-12

This survey is a 12-item questionnaire that evaluates patients' health related QoL after treatment. Physical Composite Score (PCS) and Mental Composite Score (MCS) range from 0–100 where higher score indicate better QoL. For the Norwegian population, a mean value of 50 with a standard deviation (SD) of 10

was considered average [15]. A score of ≤ 45 was defined as impaired QoL [16].

Background variables

Comorbidity factors collected were: heart disease, hypertension, arteriosclerotic disease, lung disease, diabetes, kidney disease, liver disease, previous stroke, neurological disease, previous other cancer, previous history of depression, rheumatic disease and other illnesses (Supplementary Table 1).

Table 1. Descriptive medical and sociodemographic characteristics all patients.

Characteristics	HDR-BT+ (n = 259)	EBRT (n = 99)	P*
Age at diagnosis, mean (SD) Median (range)	65.8 (5.6) 66 (50–79)	67.1 (5.8) 68 (48–79)	0.168
Age at filling in questionnaire mean (SD)	74.5 (5.5)	74.2 (5.8)	0.932
Median (range)	74 (57–86)	74 (54–85)	
Time to filling out questionnaire in years, mean (range)	8.6 (5–12)	6.7 (5–7)	
Married/living as married	207 (81%)	77 (81%)	0.654
Occupation: Paid work	28 (11%)	13 (13%)	0.537
cT stage: T1	24 (9%)	24 (24%)	**< 0.001**
T2	73 (28%)	37 (37%)	0.092
T3	162 (63%)	38 (38%)	**< 0.001**
Gleason: ≤ 6	22 (8%)	22 (22%)	**< 0.001**
3+4	79 (31%)	33 (34%)	0.605
4+3	74 (29%)	15 (15%)	**0.009**
8	56 (22%)	21 (21%)	0.933
≥ 9	28 (11%)	7 (7%)	**< 0.001**
PSA at time of diagnosis mean (range)	20.9 (1.0–66.0)	18.7 (4.2–81.0)	
≤ 10	61 (24%)	44 (44%)	**< 0.001**
10.1 – 19.9	85 (33%)	27 (27%)	0.311
≥ 20	113 (44%)	28 (28%)	**0.008**
D'Amico risk group: Low	1 (< 1%)	16 (16%)	**< 0.001**
Intermediate	29 (11%)	22 (22%)	**0.008**
High	229 (88%)	61 (62%)	**< 0.001**
Radiotherapy EQD2 dose** ≤ 70	0 (0%)	22 (23%)	
74	0 (0%)	32 (33%)	
78	0 (0%)	42 (44%)	
102	259 (100%)	0 (0%)	
Neoadj hormones: None	1 (< 1%)	17 (24%)	**< 0.001**
3 months	55 (21%)	34 (48%)	**0.010**
6 months	203 (78%)	20 (28%)	**< 0.001**
Hormone treatment: (total length)			
None	1 (0.4%)	17 (17.2%)	< 0.001
< 5.9 months	13 (5.0%)	0 (0%)	
6–11 months	25 (9.7%)	13 (13.1%)	0.339
12 months	15 (5.8%)	12 (12.1%)	**0.043**
24 months	149 (57.5%)	23 (23.2%)	**< 0.001**
36 months	56 (21.6%)	6 (6.1%)	**< 0.001**
unknown	0 (0%)	28 (28.3%)	

*Significant level: $P < 0.05$ (bold)

**Calculated with alfa/beta = 3

HDR-BT+: High-Dose-Rate Brachytherapy in combination with External Beam Radiation Therapy; cT stage : clinical T stage; PSA: Prostate Specific Antigen.

Significant level:p<0.05 (bold)

Statistical analyses

The EPIC-26 scores and PCS/MCS were calculated using the official scoring instructions [11, 12]. Continuous variables were described with mean and SD if normally distributed, or with median and range for variables with skewed distributions. Categorical data are presented with counts and percentages.

Crude between treatment group comparisons were performed using t-tests. As the groups were not balanced regarding possible confounders, we also fitted linear regression models with the dependent variables being the respective sexual and hormonal/vitality DSSs and PCS/MCS. Only comorbidities where the between group difference reached $P < 0.1$ were included in the linear regression analyses (Supplementary Table 1).

Other collected variables such as marital status and occupation were excluded from the analyses as they were similarly distributed between the groups. Results are expressed as regression coefficients (B) with 95% confidence intervals (CIs).

Statistical significance was set to $P < 0.05$. As all analyses are considered exploratory, no correction for multiple testing was done.

For clinical relevance for the DSSs, Minimally Important Difference (MID) (Table 2) set by Skolaris et al. were used: sexual DSS: MID ≥ 10, hormonal DSS: MID ≥ 4 [17]. For each individual item, a score difference of ≥ 10 was defined as clinically relevant.

All analyses were performed in Statistical Package for the Social Sciences (SPSS) [18].

Ethical considerations

Both cohorts were approved by the Regional Ethics committees for medical ethics in Norway (no 2015/429 and 2016/100).

Results

Baseline characteristics of the cohorts

The median age at diagnosis was 66 years (range 50–80) for the HDR-BT+ group and 68 years (range 48–79) in the EBRT-only group. The median age at the current study participation was 74 years for both groups (Table 1). Time from treatment to filling in questionnaire was 8.6 years in the HDR-BT+ group and 6.7 years in the EBRT-only group. Marital status and employment were similar between the groups. Majority of men had high-risk disease, 88% in the HDR-BT+ group and 62% in the EBRT-only group (Table 1).

All but one in the HDR-BT+ group received concomitant HT. For the HDR-BT+ group, 58% had a total length of HT of 2 years

Table 2. EPIC-26 sexual and hormonal Domain Summary Scores, item scores and PCS/MCS.

(Last 4 weeks)	HDR-BT+ Mean (SD) *n* = 248	EBRT Mean (SD) *n* = 91	*P*	Clinically Relevant*
Sexual				
Sexual DSS	32.3 (33.1) (*n* = 242)	24.1 (27.9) (*n* = 88)	**0.039**	No
Ability to have an erection (item 57)	24.3 (26.7) (*n* = 247)	17.1 (21.2) (*n* = 89)	**0.023**	No
Ability to reach an orgasm (item 58)	27.7 (29.1) (*n* = 240)	20.4 (24.4) (*n* = 86)	**0.037**	No
Quality of erections (item 59)	42.0 (39.0) (*n* = 238)	28.4 (33.4) (*n* = 88)	**0.004**	**Yes**
Frequency of erections (item 60)	29.1 (38.4) (*n* = 239)	18.5 (31.6) (*n* = 88)	**0.021**	**Yes**
Ability to function sexually (item 64)	22.7 (28.0) (*n* = 245)	14.9 (21.6) (*n* = 89)	**0.018**	No
How big of a problem has sexual function been (item 68)	48.0 (37.6) (*n* = 244)	45.2 (35.1) (*n* = 89)	0.551	No
Substantial problem† *n* (%)	101 (41.6%)	40 (44.4%)	0.562	
Hormonal				
Hormonal DSS	86.0 (23.7) (*n* = 240)	82.5 (24.9) (*n* = 87)	0.245	No
Hot flashes (item 74)	90.8 (20.7) (*n* = 239)	86.7 (26.0) (*n* = 88)	0.136	No
Breast tenderness/enlargement (item 75)	94.9 (17.8) (*n* = 240)	96.2 (11.9) (*n* = 85)	0.538	No
Feeling depressed (item 77)	87.3 (23.6) (*n* = 239)	86.1 (25.3) (*n* = 86)	0.668	No
Lack of energy (item 78)	72.7 (30.5) (*n* = 241)	61.9 (34.8) (*n* = 88)	**0.007**	**Yes**
Change in body weight (item 79)	84.2 (26.0) (*n* = 240)	81.7 (26.7) (*n* = 86)	0.451	No
Quality of life				
PCS	46.5 (10.5) (*n* = 214)	43.8 (10.3) (*n* = 75)	0.055 **0.022**	No
Impaired PCS (score ≤ 45) *n* (%)	71 (33.2%)	36 (48.0%)		
MCS	53.8 (7.7) (*n* = 214)	52.1 (9.5) (*n* = 75)	0.124 0.116	No
Impaired MCS (score ≤ 45) *n* (%)	34 (15.5%)	18 (23.7%)		

*Clinically relevance for the Domain Summary Score (DSS) was determined by Minimally Important Difference [17] and for the single item scores a point difference of ≥ 10 (ref).

HDR-BT+: High-Dose-Rate Brachytherapy in combination with External Beam Radiation Therapy; EPIC: Expended Prostate Index Composite; HT: hormonal therapy; PCS/MCS: Physical/Mental Composite Score.

Significant level:p<0.05 (bold)

and 22% for 3 years (Table 1). For the EBRT-only group, 17% received no HT, 13% for 6–12 months, 23% for 2 years, and 6% for 3 years (Table 1).

Expanded Prostate Cancer Index Composite (EPIC)-26 scores

Sexual function and problem

In crude analyses, the sexual DSS was significantly higher in the HDR-BT+ group compared to the EBRT-only group (32.3 vs 24.1, *P* = 0.039) (Table 2). The difference for the sexual DSS was 8.2 and therefore not considered clinically relevant. There were significantly higher scores of HDR-BT+ for all single items related to sexual function with clinically relevant differences seen both for quality and frequency of erections (Table 2). No statistically significant difference was detected between the groups for sexual problem (Table 2).

Hormonal morbidity

In crude analyses, the hormonal DSS was 86.0 for the HDR-BT+ group and 82.5 for the EBRT-only group (*P* = 0.245) with a score difference of 3.5 and hence not clinically relevant (Table 2). There were neither clinically nor statistically significant differences between the groups for hot flashes, breast tenderness/enlargement, low mood or change in weight. Men treated with HDR-BT+ reported statistically significantly higher scores for lack of energy compared to men treated with EBRT-only (*P* = 0.007). This difference was 10.8 and therefore also clinically relevant (Table 2).

Table 3. Linear regression analyses of sexual and hormonal Domain Summary Scores.

Domain Summary Score	Regression coefficient B	95% CI	*P*
Sexual Domain Summary Score			
Treatment (HDR-BT/BT+^)	-5.43	-15.27, 4.40	0.278
Risk group			
Low (ref)			
Intermediate	-6.91	-32.10, 18.28	0.590
High	-15.93	-41.21, 9.35	0.216
Time from diagnosis to questionnaire	-0.07	-0.26, 0.13	0.494
Age at time of diagnosis	-1.62	-2.14, -1.09	**< 0.001**
Heart disease	8.02	-15.07, 31.11	0.495
High blood pressure	10.13	-21.39, 41.65	0.527
Diabetes mellitus (type I and II)	-28.37	-75.08, 18.34	0.233
Previous episodes of depression	23.48	-13.97, 60.92	0.218
Length neo-adjuvant hormonal treatment No HT (ref)			
3 months	21.57	-14.06, 57.20	0.234
6 months	20.69	-15.44, 56.82	0.260
Length of hormone treatment No HT (ref)			
< 6 months	-12.81	-56.03, 30.41	0.560
6–12 months	-16.20	-57.55, 25.15	0.441
12 months	-8.34	-50.56, 33.87	0.697
24 months	-9.63	-51.08, 31.82	0.648
36 months	-11.38	-53.73, 30.97	0.597
Hormonal domain summary score			
Treatment (HDR-BT/BT+^)	-6.21	-12.53, 0.11	0.054
Risk group			
Low (ref)			
Intermediate	-4.99	-20.61, 10.63	0.530
high	-9.92	-25.55, 5.71	0.213
Time from diagnosis to questionnaire	-0.09	-0.21, 0.03	0.147
Age at time of diagnosis	0.25	-0.08, 0.58	0.132
Heart disease±	3.67	-12.25, 19.58	0.651
High blood pressure±	-5.63	-27.97, 16.71	0.620
Diabetes mellitus (type I and II)±	14.90	-36.25, 66.05	0.567
Previous episodes of depression±	1.10	-33.95, 36.16	0.951
Length neo-adjuvant hormonal treatment No HT (ref)			
3 months	-12.12	-34.37, 10.12	0.284
6 months	-16.25	-38.83, 6.34	0.158
Length of hormonal therapy No HT (ref)			
< 6 months	20.48	-6.51, 47.48	0.136
6–12 months	10.95	-14.90, 36.81	0.405
12 months	16.53	-9.87, 42.92	0.219
24 months	16.43	-9.48, 42.34	0.213
36 months	19.62	-6.85, 46.08	0.146

±Reported as yes/no where no = reference

HDR-BT+: High-Dose-Rate Brachytherapy in combination with External Beam Radiation Therapy; EPIC: Expended Prostate Index Composite; HT: hormonal therapy.

Significant level:p<0.05 (bold)

Multiple analyses on domain summary scores

The variables examined in the multiple linear regression were treatment modality, risk group, time from diagnosis to questionnaire, age at time of diagnosis, heart disease, high blood pressure, diabetes mellitus I/II, previous history of depression, length of neo-adjuvant hormonal therapy and total length of hormonal therapy. When adjusted for possible confounders, the treatment group was no longer statistically significant (B = –5.43, 95% CI[15.27;4.40]). Moreover, only age remained statistically significantly associated (B = –1.62, 95% CI [–2.14; –1.09]) with the sexual DSS (Table 3).

Our data did not reveal any statistically significant associations between selected variables and hormonal DSS (Table 3).

Mental and physical composite score

In crude analyses, in the HDR-BT+ group, the PCS was 46.5 and the MCS 53.8. In the EBRT-only group, the PCS was 43.8 and the MCS 52.1. There were a significantly higher number of men with impaired PCS in the EBRT-only group compared to the HDR-BT+ group (48% vs. 33%, $P = 0.022$). There were neither statistically nor clinically relevant differences between the groups for MCS (Table 2).

In multivariate linear regression, we investigate if the following possible predictive factors were associated with PCS and MCS (as the dependent): treatment modality, risk group, time from diagnosis to filling in questionnaire, age at time of diagnosis, heart disease, high blood pressure, diabetes mellitus I/II, previous episodes of depression, total length of hormonal therapy, sexual DSS and hormonal DSS.

Hormonal DSS was the only predictive factor that statistically significantly impacted both PCS (B = 0.33, 95% CI [0.26;0.40]) and MCS (B = 0.24, 95% CI [0.18;0.29]) (Table 4).

Subgroup analysis

Impact of hormonal therapy

Patients in the HDR-BT+ group had a final out-patient consultation at 5 years follow-up with blood tests. Of the patients (n = 127) with available testosterone levels measured at this follow-up, all but 5 had high-risk disease, and therefore a total duration of HT of 2–3 years. There were 43 patients with testosterone level < 8 nmol/L and 84 with levels ≥ 8 nmol/L, showing that almost 1/3 of men had persistently low testosterone levels 5 years after treatment (Table 5). Men with persistent low testosterone had statistically and clinically significantly lower sexual DSS (Table 5). Our data did not reveal any further differences between the two groups based on testosterone levels for hormonal DSS, PCS or MCS variables (Table 5).

Discussion

In this cross-sectional study we report patient-reported differences in long-term sexual and hormonal functions and QoL after HDR-BT+ compared to EBRT alone. As a major finding, elderly PCa survivors treated with lengthy duration of HT and HDR-BT+ reported significantly better, although low, crude scores for the EPIC-26 items related to sexual function. This

Table 4. Linear regression analysis for physical and mental health (n = 251).

Variable names	PCS			MCS		
	Regression coefficient B	95% CI	*P*	Regression coefficient B	95% CI	*P*
Treatment (HDR-BT+^)	-1.43	-4.62, 1.74	0.374	1.96	-0.55, 4.47	0.125
Risk group						
Low						
Intermediate	-3.64	-11.91, 4.63	0.387	2.25	-4.28, 8.78	0.498
High	-0.17	-8.28, 7.93	0.966	2.31	-4.08, 8.72	0.476
Time from diagnosis to questionnaire	-0.01	-0.08, 0.05	0.649	0.01	-0.04, 0.06	0.616
Age at time of diagnosis±	-0.16	-0.35, 0.02	0.084	0.08	-0.07, 0.23	0.287
Heart disease±	-3.93	-14.48, 6.62	0.464	-2.05	-10.38, 6.28	0.629
High blood pressure±	-4.06	-18.82, 10.70	0.588	6.92	-4.74, 18.57	0.244
Diabetes mellitus (type I and II) ±	-0.62	-3.60, 2.37	0.684	1.22	-1.14, 3.58	0.310
Previous episodes of depression±	-1.61	-5.51, 2.8	0.415	-9.59	-26.27, 7.10	0.259
Length of hormonal therapy No HT (ref)						
< 6 months	-0.76	-9.60, 8.07	0.865	-2.40	-9.38, 4.58	0.498
6–12 months	1.16	-6.70, 9.02	0.772	1.06	-5.15, 7.26	0.738
12 months	-0.78	-9.04, 7.50	0.853	0.36	-6.17, 6.89	0.914
24 months	-0.60	-8.49, 7.30	0.883	0.27	-5.97, 6.50	0.932
36 months	-2.02	-10.20, 6.16	0.628	-0.47	-6.93, 5.99	0.887
EPIC sexual domain score	0.04	-0.005, 0.08	0.084	0.01	-0.02, 0.04	0.475
EPIC 26 hormonal domain score	0.33	0.26, 0.40	**< 0.001**	0.24	0.18, 0.29	**< 0.001**

± *Reported as yes/no where no = reference*

HDR-BT+: High-Dose-Rate Brachytherapy in combination with External Beam Radiation Therapy; EPIC: Expended Prostate Index Composite; HT: hormonal therapy; PCS/MCS: Physical/Mental Composite Score.

Significant level:p<0.05 (bold)

supports our hypothesis that dose-escalation by HDR-BT+ boost does not lead per se to increased sexual impairment. However, after adjusting the crude data for confounders, only age persisted as independent variable for sexual functioning.

Subgroup analyses in the HDR-BT+ group showed that persistent hypogonadal testosterone levels decrease sexual function.

Hormonal therapy is an important pillar of curative PCa treatment as it diminishes testosterone production with resulting tumour cell death [19–21]. However, arguments have been made that the hallmark studies were conducted prior to new developments in radiation delivery, such as stereotactic body radiation therapy. These techniques leverage the unique sensitivity of PCa to higher doses of radiation per treatment fraction and have much shorter treatment duration than conventionally fractionated radiation therapy [22, 23]. This is in line with our previous studies where we showed that HDR-BT+ boost improved oncological outcome compared to EBRT with acceptable acute and long-term side effects [3, 24]. Given the long survival in men treated for localised PCa, the impact of HT has to be balanced between toxicity and clinical gain. ADT is the most commonly used HT, but it is also a good treatment option as is usually associated with less side-effects. Spratt et al. showed a long-term survival benefit of additional adjuvant HT to RT but not in the length of neo-adjuvant treatment [25]. Kishan et al. compared the length of ADT using single institutions results (including two Randomised Controlled Trials (RCT), the RADAR trial and the DART trial) of 3,410 men. They found an optimal HT duration for patients treated with HDR-BT+ to be less than 18 months while men treated with EBRT alone required a duration of > 18 (range 18–28) months [26]. Yorozu et al. did not find that 30 months HT yielded better biochemical control than 6 months when combined with brachytherapy and EBRT in their RCT [27]. In view of the published results, a shorter duration of HT could possibly be applied for patients treated with HDR-BT+. Shortening of HT could have considerable impact on other side-effects such as muscle wasting, muscle and joint stiffness/pain and cardiovascular disease [4]. In the current study, 80% of patients

Table 5. Sub-analysis: Outcome divided by testosterone level at 5 years for the HDR-BT+ group.

EPIC-26 DSS, MCS, PCS	Testosterone < 8 Mean (SD) *N* = 43	Testosterone ≥ 8 Mean (SD) *N* = 84	*P*	Clinically relevant
Sexual EPIC domain score	22.9 (19.8) *N* = 42	33.8 (27.8) *N* = 82	**0.026**	**Yes**
Hormonal EPIC domain score	82.4 (14.6) *N* = 43	85.8 (20.5) *N* = 80	0.337	No
PCS	43.5 (11.0) *N* = 33	47.7 (10.5) *N* = 74	0.062	No
MCS	54.1 (7.8) *N* = 33	54.1 (7.9) *N* = 74	1.000	No

PCS/MCS: Physical/Mental Composite Score; EPIC: Expanded Prostate Cancer Index Composite

Significant level:p<0.05 (bold).

treated with HDR-BT+ received concomitant HT of > 2 years. Considering our own and findings by others, a reduction in length of HT for patients treated with HDR-BT+ should be tested in an appropriate clinical trial.

There is a paucity of long-term published reports using the EPIC-26 instrument to document sexual and hormonal function for patients treated with HDR-BT+ compared to EBRT-only [28]. Pompe et al. found that EBRT causes high rates (75%) of testosterone decrease and biochemical hypogonadism (40%) suggesting EBRT in itself is a contributing factor to low sexual and hormonal scores [29]. Our findings suggest as many as 1/3rd of men remained in a hypogonadal state many years after stopping HT which is consistent with other published studies [30]. In these patients, we found that low plasma testosterone levels were associated with persisting decreased sexual function. Because of the small number of patients further analysis with adjustment for age and comorbidities were not performed.

Scattered dose from EBRT to testicular tissue can cause testicular atrophy and variations in male sex hormones [31]. Several studies have shown that the absorbed dose to the neuro-vascular structures at the penile base have an impact on erectile dysfunction but found no difference between conventionally fractionated and hypo fractionated regimes of EBRT [32–34]. We addressed this issue of dose distribution to normal tissue and performed a small investigation of 10 randomly selected patients from each group by retrospectively contouring the penile bulb (on CT) according to guidelines [35] and calculating the dose to this structure. The contribution from the HDR-BT was estimated by calculating the dose 1–2 cm from the apex for each BT-application. We found a significantly lower dose to the penile bulb in men who had undergone HDR-BT+ compared to those treated with EBRT-only. This may indicate that the rapid dose fall achieved with BT could partially explain the better sexual function observed in the HDR-BT+ group compared to EBRT-only group.

Although large differences and overall low sexual functions scores were reported between the treatment groups, there was no difference between the groups for sexual problem. Only age was an influencing factor of sexual DSS. Our findings are in line with other studies, suggesting that elderly men do not view their poor sexual function as a big problem, as could be expected from the low sexual functional scores, and it does not severely impact their QoL [36, 37]. The study conducted by Sanda et al. found that adjuvant HT decrease QoL across multiple aspects [38]. In our study, overall MCS (combined mean score of 53) was slightly higher than the general population, who has a mean score of 50 [15]. This indicate that elderly men having undergone radical cancer treatment might value cure most and that sexual performance and hormonal morbidity are less important taken in account their age and overall life situation.

Fewer patients reported lack of energy in the HDR-BT+ group than in the EBRT-only group, despite patients in the HDR-BT+ group having more advanced disease. Overall, cancer-related fatigue prevalence rates are 25%–99% and can persist for years after treatment completion and is often underreported and multidimensional in nature [39]. In one of our previous studies, we found high-level of fatigue and high prevalence of chronic fatigue affecting men receiving EBRT combined with long-term HT [40]. The finding of lack of energy, which is closely related to fatigue, and its impact on QoL, was not further explored with appropriate instruments in this study. Our findings highlight the clinical implications for PCa survivors. Physicians must be aware of possible patients' needs for additional support such as patients counselling, referral to sexologist or urologist for information of available aids. In our study, patients were also asked about their experience of sexual aids and counselling (Supplementary Table 2). Our findings show that patients treated at a specialised tertiary hospital are more likely to be informed and offered support for their sexual function. Overall, the effect of the various treatment options does not seem to differ between the treatment groups.

Our study has some limitations. Unfortunately, it was not possible to assess the patients' change over time because of lack of longitudinal data. Ideally patients should be assessed prior to treatment, after treatment and throughout the follow-up period. This allows track of the outcomes over time, identifying causal relationships and to determine how the individual patients' symptoms have varied with time and lead to better-informed treatment and support strategies for PCa survivors.

The time interval between the treatment and inclusion to this study was up to 12 years for the HDR-BT+ group and 7 years for the EBRT-only group. However, time since treatment was not statistically significant in the linear regression analyses, it is less likely to confound our results. Patients in the EBRT-only group were treated at multiple hospitals in the country and there was no available information regarding radiation techniques, such as intensity-modulated radiation therapy (IMRT) or fiducial markers, which could potentially result in less AEs.

There were some patients who switched from ADT to Anti-Androgen treatment (AAT) or terminated their HT early. Therefore, further analyses of the possible difference between ADT versus AAT on sexual and hormonal function could not be performed. Other possible confounding variables such as psychological/lifestyle factors (e.g. smoking, alcohol use, diet) partner relationship quality and adherence to follow-up care programme were not available.

The study has several strengths. All men treated with HDR-BT+ received treatment at a regional specialist cancer hospital. The two groups were comparable regarding age and comorbidities; however, the HDR-BT+ group had more advanced disease. In addition, both groups received HT although the duration of HT varied reflecting change in guidelines since the study has evolved. Therefore, we have also performed multiple regression analyses to adjust for all these possible confounders.

Conclusion

Patients receiving dose-escalation by HDR-BT+ with prolonged HT had not worse long-term patient-reported sexual function compared to men treated with EBRT alone. However, in multiple analyses the sexual function was completely confounded by

age. The interplay of age, HT and lack of energy indicates a strong impact on both QoL and sexual function. Future randomised longitudinal studies are needed to determine sufficient duration of HT in combination with BT+.

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