Original paper

Five-year quality of life in patients with high-risk localized prostate cancer treated with external beam radiotherapy alone versus external beam radiotherapy with high-dose-rate brachytherapy boost: a prospective multicenter study

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Abstract

Purpose: Brachytherapy (BT) and external beam radiation therapy (EBRT) are effective treatments for high-risk prostate cancer (PCa). However, the impact of these treatments on health-related quality of life (HRQL) remains unclear. In this study, we compared EBRT alone with EBRT plus a boost with high-dose rate (HDR)-BT to determine the impact on HRQL in patients with high-risk PCa.

Material and methods: Prospective, multicenter study comparing patients with high-risk PCa treated with EBRT alone or EBRT + HDR-BT from 2004 to 2006. HRQL was assessed at baseline (pre-treatment) and periodically over the 5-year follow-up, using the SF-36 (v.2), EPIC, and FACT-G and FACT-P questionnaires.

Results: A total of 129 patients were included in the study, of these, 41 received EBRT alone and 88 EBRT + HDR-BT. All patients received hormonotherapy. Baseline clinical characteristics were similar, except for a slightly higher mean number of comorbidities in the EBRT group. During follow-up, the only significant between-group difference was a greater worsening on EPIC hormonal domain in the EBRT alone group ($p = 0.028$). There were no significant differences in time and interaction of treatment in SF-36, and FACT-G and FACT-P questionnaires or EPIC urinary incontinence, urinary irritative-obstructive, and bowel and sexual domains over the 5-year follow-up. Oncological outcomes were similar in both groups.

Conclusions: After five years of follow-up, EBRT alone or combined with HDR-BT boost had a similar impact on HRQL in patients with high-risk localized PCa. However, patients in the EBRT alone group experienced greater worsening of hormonal domain according to EPIC questionnaire.

J Contemp Brachytherapy 2021; 13, 1: 1–11
DOI: https://doi.org/10.5114/jcb.2021.103580

Key words: quality of life, prostate cancer, external beam radiotherapy, high-dose-rate brachytherapy.

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Received: 27.09.2020
Accepted: 24.12.2020
Published: 18.02.2021

Purpose

Radical radiotherapy is a well-established treatment option for clinically localized and locally advanced prostate cancer (PCa) [1]. Technological advances in radiotherapy have been rapidly incorporated into clinical practice to reduce treatment-related morbidity and improve oncological outcomes [2,3]. Several randomized trials have demonstrated that dose-escalated radiotherapy-external beam radiotherapy (EBRT) or EBRT plus high-dose-rate (HDR) brachytherapy (BT) boost, improve both local and biochemical control in intermediate- and high-risk PCa [3,4,5,6], despite an increased risk of late genitourinary and gastrointestinal toxicities. The addition of HDR-BT boost allows for highly conformal dose escalation and greater sparing of the surrounding healthy organs [5].

All of the main treatments for PCa have side effects, and radical prostatectomy (RP) seems to produce greater urinary incontinence. BT is associated with an increase in urinary irritative/obstructive symptoms, while EBRT has a greater impact on bowel-related indications [7,8,9]. In selected patients, BT is an alternative to RP, limiting the risk of urinary incontinence as well as the potential impact of sexual dysfunction on health-related quality of life (HRQL) [7].

In this context, the main objective of this study was to determine whether EBRT alone or EBRT + HDR-BT was associated with better HRQL outcomes in patients with high-risk PCa, five years after the treatment. Secondary outcome measures included biochemical relapse-free survival (BRFS), overall survival (OS), and cancer-specific survival (CSS) at 5 years.

Material and methods

Design and study population

This was a prospective, multicenter study of patients with high-risk PCa, treated at participating centers from 2004 to 2006, and followed for ≥ 5 years after the treatment. The study protocol was approved by clinical research ethics committees of the six participating hospitals. Written informed consent was obtained from all patients.

Staging and risk group classification were performed using a TNM staging system of the American Joint Committee on Cancer [10] and a risk group classification system developed by D'Amico *et al*. [11].

Inclusion criteria were biopsy-proven high-risk PCa (≥ stage T2c, prostate specific antigen [PSA] > 20 ng/ml, or Gleason > 7) without previous transurethral resection.

Clinical evaluation

Serum PSA levels were measured at all follow-up visits, performed every six months for the first two years and annually thereafter. Biochemical failure was defined as an increase in PSA levels ≥ 2 ng/ml above the nadir after radiotherapy, in accordance with updated recommendations from the Radiation Therapy Oncology Group-ASTRO Phoenix consensus panel [12].

Treatment

Treatment decisions were made jointly by patients and physicians. All patients received neoadjuvant androgen deprivation therapy (ADT). Adjuvant ADT was prescribed for 2-3 years, in accordance with clinical guidelines [13]. In most cases, patients received an antiandrogen combined with LHRH analogues.

In all cases, EBRT was performed with the patient in supine position, with legs and feet immobilized. All patients underwent a computed tomography (CT) scan in the treatment position. The results of this scan were entered into three-dimensional (3D) treatment planning system and used to contour the prostate, vesicles, bladder, and rectum. External beam clinical target volume (CTV) was defined on CT imaging to cover the prostate gland and seminal vesicles with a 1 cm margin, except posteriorly, where the margin was reduced to 5 mm to create planning target volume (PTV). Custom blocking with multileaf collimators was designed using a beam's-eye-view, and additional margins were adjusted to provide minimum dose of 95% to the prostate PTV. Risk organ constraints included the femoral heads (mean dose ≤ 45 Gy) and bladder/rectum (V_{70} < 25%; V_{60} preferably < 40%, maximum 60%; V_{40}< 60%, maximum 80%) [14]. Off-line setup control was assessed weekly by comparing orthogonal portal images with the corresponding digitally-reconstructed radiographs.

External beam radiation therapy was performed using 3D conformal technique by photons from 15 to 18 MV isocentric conformal fields. In most patients, a six-field technique without pelvic irradiation was used. The EBRT alone group received daily fractions of 1.8/2 Gy, 5 days per week, for a mean total dose of 73 Gy to the PTV.

For the HDR-BT boost, the patients were placed in lithotomy position under spinal anesthesia. A needle guidance template was attached to an ultrasound probe close to the perineum, and the needles were inserted under transrectal ultrasound guidance. Needle depth was determined by direct visualization on ultrasound and fluoroscopy. A CT scan was performed for volume delineation of the prostate and risk organs. The dose constraints for the HDR-BT boost after EBRT were as follows: PTV with V_{100} ≥ 98%, V_{150} ≤ 50%, and 105% < D_{90} < 115%. The constraints for the rectum were: D_{2cc} ≤ 75% and D_{max} < 100%; and for the urethra: $D_{2\%}$ < 120%. The details of radiotherapy technique performed at our center have been published elsewhere [15]. The HDR-BT boost was administered using a temporary iridium-192 implant in one or two fractions separated by 6 hours: 21 patients (23.5%) received one fraction (20/2: 9 Gy and 1/21: 9.5 Gy) and 68 patients (76.4%) received two fractions (dose range, 6-11.5 Gy). For the patients treated with EBRT + HDR-BT, the mean EBRT dose was 51.08 Gy and the mean BT dose was 17 Gy.

Assessment of HRQL

Health-related quality of life questionnaires were administered telephonically by trained interviewers with wide expertise on this population, before treatment and during follow-up at 1, 3, 6, 12, 24, 36, 48, and 60 months after the treatment.

HRQL was evaluated using validated Spanish-language versions of the following instruments: Short form-36 (SF-36), version 2 [16], Functional Assessment of Cancer Therapy – general and prostate (FACT-G and FACT-P) [17], Expanded Prostate Cancer Index composite (EPIC) [18], and International Prostate Symptom Score (IPSS) [19]. The SF-36 contains 36 items with two summary scores: the physical and mental component summary (PCS and MCS), with scores ranging from 0 to 100 on each dimension. The FACT-G (version 4.0) contains 27 items in four dimensions, measuring physical, social, emotional, and functional well-being. The prostate module (FACT-P) is specific for PCa patients and includes 12 questions about urinary symptoms, bowel and sexual function, and pain. Scores range from 0 to 108 on the FACT-G and from 0-48 on the FACT-P. The 50-item EPIC instrument evaluates four domains (urinary, bowel, sexual, and hormonal), with two urinary scales that distinguish between irritative/obstructive symptoms and incontinence. The final score ranges from 0 to 100. Higher scores indicate better quality of life (QoL) in all these questionnaires.

The IPSS assesses urinary symptoms, with one question about HRQL. The total score range from 0 to 35, with higher score indicating worse symptoms.

Sample size

Sample size calculations were based on expected between-group differences on change of HRQL scores as being the principal objective of the present study. It was calculated that a total of 129 patients would be required to detect a difference in change between treatments' groups of 0.5 standard deviation in any HRQL score, given a statistical power of at least 80% at a significance level of 5%.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables as mean and standard deviation (SD). Differences in the distribution of variables between the study groups were compared using chi-square (χ^2) test or one-way analysis of variance (ANOVA) with post-hoc Tukey's procedure, whenever appropriate.

To assess HRQL changes over time, while accounting for correlation among repeated measures, separate generalized estimating equation (GEE) models were constructed for each specific HRQL score (FACT-P and EPIC) and for the generic ones (SF-36 and FACT-G), all included as dependent variables. Time was included in the model as a categorical variable, and interactions between treatment and time were considered to test differences in trends among treatment groups, after adjusting for age, risk group, and pre-treatment prostate volume.

Differences in BRFS, OS, and CSS at 5 years were analyzed with Kaplan-Meier method and log-rank test. Statistical significance was set at $p < 0.05$. SPSS, v.22.0 and SAS/STAT®, v.9.4. were used to perform data analyses.

Results

The study population was comprised of 129 patients, 41 treated with EBTR alone and 88 with EBRT + HDR-BT. All patients received neoadjuvant ADT. Adjuvant ADT was prescribed for 2-3 years in accordance with clinical guidelines [13], although the final date of ADT administration was not registered.

Table 1 shows patients' clinical characteristics at baseline, mean pre-treatment HRQL scores, and response rate during follow-up. The only statistically significant differences between treatment groups at baseline were a slightly higher mean number of comorbidities in the EBRT group (3.1 with EBRT vs. 2.5 with EBRT + HDR-BT, $p = 0.043$) and a higher SF-36 PCS score in the EBRT + HDR-BT group (50.8 vs. 53, $p = 0.04$). Overall, the response rate to the HRQL questionnaires during the study period was high in both study groups: at 5-years of follow-up, the response rate was 100% (EBRT) and 97.1% (EBRT-BT), without significant between-group differences ($p = 0.354$).

Mean changes in QoL scores from baseline to 5-year follow-up are shown in Table 2. Compared with patients treated with EBRT + HDR-BT, the EBRT alone group had significantly lower (worse) hormonal scores (–10.6 vs. –2.4, respectively, $p = 0.028$).

Tables 3 and 4 present the results from GEE models constructed for the specific and generic HRQL scores, respectively. For the EBRT alone group, statistically significant differences from baseline were only found 5 years after the treatment for FACT-P ($\beta = -2.4$), EPIC bowel and hormonal ($\beta = -3.1$ and $\beta = -10.4$, respectively), among the specific HRQL scores evaluated. No statistically significant differences were found between the two treatment groups, with the exception of a lower impact on the hormonal domain at the EBRT + HDR-BT group.

At 5-years post-treatment, the EBRT alone group showed greater deterioration in SF-36 PCS ($\beta = -9.8$ at years) and in SF-36 MCS ($\beta = -7.1$) compared to the combined group. The same pattern was demonstrated by almost all FACT-G domains (Table 3).

Figures 1 and 2 show the differences between groups in the mean HRQL scores during 5-year follow-up. We did not observe any substantial short- or long-term differences between the groups. Moreover, no statistically significant differences in BRFS, OS, and CSS between the study groups were observed (Figures 3-5).

Discussion

Health-related quality of life is an important outcome measure in patients with prostate cancer. However, long-term differences in HRQL outcomes in these patients have rarely been reported. Most of the available data on HRQL comes from studies, which have assessed the impact of treatment (BT, RP, and EBRT) on low- and intermediate-risk patients [20,21,22]. Few studies have compared EBRT alone to EBRT + HDR-BT in high-risk PCa patients in terms of HRQL [23,24].

In our study, we did not observe any significant between-group differences in mean changes in the HRQL questionnaire scores from baseline to 5-year follow-up. However, we did notice a significant difference in the EPIC hormonal domains. Although both groups experienced substantial deterioration in this domain, the EBRT

Table 1. Patients' characteristics and quality of life scores at pre-treatment evaluation and response rate at each follow-up assessment

Variables	EBRT (n = 41)	EBRT + HDR brachytherapy (n = 88)	P-value
Age (years), mean (SD)	71.1 (5.6)	70.5 (38.5)	0.921
PSA (ng/ml), mean (SD)	28.7 (46.8)	19.8 (13.8)	0.103
≤ 10	12 (29.3)	30 (34.1)	0.771
10-20	12 (29.3)	21 (23.9)	
> 20	17 (41.5)	37 (42.0)	
Gleason score, mean (SD)	7.3 (0.8)	7.0 (1.1)	0.142
< 7	6 (15.0)	27 (30.7)	0.060
≥ 7	34 (85.0)	61 (69.3)	
Clinical T stage, n (%)			
T1	5 (12.2)	6 (6.8)	0.581
T2	15 (36.6)	36 (40.9)	
T3	21 (51.2)	46 (52.3)	
Prostate volume, mean (SD)	44.6 (29.8)	40.5 (19.0)	0.520
Comorbidities, n (%)	3.1 (1.7)	2.5 (1.5)	0.043
0	1 (2.4)	8 (9.1)	0.465
1	7 (17.1)	19 (21.6)	
2	8 (19.5)	14 (15.9)	
3	25 (61.0)	47 (53.4)	
Quality of life scores, mean (SD)			
SF-36 PCS	50.8 (7.2)	53.0 (4.4)	0.040
SF-36 MCS	56.2 (5.3)	55.3 (5.3)	0.362
FACT-G	79.2 (10.0)	79.6 (7.4)	0.777
FACT-P	38.0 (5.2)	39.0 (4.0)	0.237
FACT physical well-being	26.4 (2.4)	26.7 (1.8)	0.453
FACT social well-being	17.5 (3.9)	17.8 (2.9)	0.613
FACT emotional well-being	19.2 (3.7)	18.9 (3.3)	0.677
FACT functional well-being	16.2 (3.8)	16.3 (3.3)	0.954
EPIC urinary			
Incontinence	90.8 (17.2)	94.8 (14.6)	0.181
Irritative/obstructive	94.1 (9.1)	93.2 (10.3)	0.662
EPIC bowel	97.8 (7.6)	98.5 (3.6)	0.477
EPIC sexual	38.6 (23.2)	37.2 (23.4)	0.742
EPIC hormonal	93.7 (8.6)	90.8 (10.6)	0.135
IPSS	9.0 (7.9)	6.6 (6.5)	0.078
Response rate HRQL questionnaires, n (%)			
Pre-treatment	41/41 (100.0)	88/88 (100.0)	
Follow-up, month 1	34/41 (82.9)	50/88 (56.8)	0.004
Follow-up, month 3	40/41 (97.6)	78/88 (88.6)	0.091
Follow-up, month 6	39/40 (97.5)	81/87 (93.1)	0.313
Follow-up, month 12	39/40 (97.5)	79/86 (91.9)	0.227
Follow-up, month 24	39/39 (100.0)	79/83 (95.2)	0.163
Follow-up, month 36	34/37 (91.9)	65/82 (79.3)	0.088
Follow-up, month 48	24/33 (72.7)	73/77 (94.8)	0.001
Follow-up, month 60	29/29 (100.0)	67/69 (97.1)	0.354

EBRT – external beam radiotherapy, HDR – high-dose-rate, SF-36 – medical outcomes study 36-item short form, PCS – physical component summary, MCS – mental component summary, FACT-G and FACT-P – Functional Assessment of Cancer Therapy (general and prostate module), EPIC – Expanded Prostate Cancer Index composite, IPSS – International Prostate Symptom Score. Data as frequencies and percentages in parenthesis unless otherwise stated

Table 2. Mean differences in scores in HRQL questionnaires at 5 years of follow-up as compared with baseline

Variables	EBRT (n = 41)	EBRT + HDR brachytherapy (n = 88)	P-value
SF-36 PCS	–10.2 (8.5)	–7.2 (8.7)	0.121
SF-36 MCS	–6.3 (11.1)	–2.7 (10.5)	0.131
FACT physical well-being	–3.0 (4.9)	–1.9 (3.7)	0.212
FACT social well-being	–2.1 (3.6)	–1.6 (2.8)	0.433
FACT emotional well-being	–2.5 (4.0)	–1.6 (3.6)	0.290
FACT functional well-being	–1.0 (5.2)	1.0 (4.6)	0.062
FACT-G	–8.7 (12.5)	–4.2 (10.2)	0.064
FACT-P	–2.6 (6.3)	–2.6 (5.7)	0.989
EPIC domains			
Urinary incontinence	–6.1 (24.7)	–12.8 (24.8)	0.238
Urinary irritative/obstructive	–4.8 (22.7)	–8.6 (19.1)	0.416
Bowel	–2.5 (7.2)	–3.6 (11.1)	0.614
Sexual	0.8 (30.1)	–0.8 (26.4)	0.798
Hormonal	–10.6 (17.2)	–2.4 (16.2)	0.028
IPSS	–0.8 (11.1)	–3.2 (9.1)	0.263

EBRT – external beam radiotherapy, HDR – high-dose-rate, SF-36 – medical outcomes study 36-item short form, PCS – physical component summary, MCS – mental component summary, FACT-G and FACT-P – Functional Assessment of Cancer Therapy (general and prostate module), EPIC – Expanded Prostate Cancer Index composite, IPSS – International Prostate Symptom Score. Data expressed as mean difference (standard deviation, SD)

alone group had significantly lower (worse) hormonal scores at 5-year follow-up. Moreover, the GEE model revealed greater worsening mainly in the FACT-P, FACT-G, SF-36, and bowel domain in the EBRT group in the fifth-year post-treatment. The greater deterioration of hormonal and sexual scores was most marked until the second year after the treatment. After this time point, there was a trend towards an improvement in these scores, probably due to the finalization of ADT and the consequent improvement in ADT-related side effects. This finding could be due to the slightly better (p = 0.135) baseline EPIC hormonal summary scores in the EBRT group.

Overall, findings of this study suggest that EBRT alone or combined with HDR-BT appear to have similar effects on HRQL. However, in our sample, patients in the BT boost group had fewer comorbidities at baseline, which could partially explain why we observed no major between-group differences. Indeed, this probably also explains why they were eligible for HDR-BT boost. Further studies with longer series and longer follow-up would provide more information about the impact of these radiotherapy modalities on HRQL.

Dose escalation with EBRT followed by brachytherapy boost have been shown to improve BRFS [5,15,25]. In the ASCENDE-RT trial [26], patients were randomized to dose-escalated EBRT (78 Gy) or EBRT plus low-dose-rate BT boost. The patients in the boost group were twice as likely to be free of biochemical failure at a median of 6.5 years of follow-up, without significant differences in OS. Theoretically, dose escalation with HDR allows for an increase in biologically-effective dose, improving tumor control and sparing organs at risk [22]. However, in our series, we found no statistical significance between-group differences in BRFS, OS, or CSS. Moreover, our BRFS results differ from those reported in randomized trials [22,23,25,26], probably because of the small number of patients. Certainly, the lack of significant differences in survival outcomes in our study may be due to the limited sample size, which was powered to detect differences in the main study variable (HRQL), but not for survival outcomes.

Other authors, such as Ferrer *et al*. [18], have reported that the addition of ADT causes temporary deterioration in some HRQL domains, a finding that is consistent with the worsening observed in our patients in the EPIC hormonal domain. Those authors observed that ADT was associated with worse results related to vitality, hormonal function, and sexuality. Only a few studies with long follow-up have been performed to assess HRQL in patients with high-risk PCa [22,27]. In this group of patients, it is necessary to achieve the most appropriate treatment to improve local control with the lowest toxicity and the best possible HRQL.

The main limitations of our study are the relatively small study population, the differences in group size, and the lack of randomization. Another limitation is the use of conformal 3D-RT rather than more advanced techniques, such as intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT). However, during the study period (2004-2006), neither of those techniques was available in the participating hospitals. Nevertheless, given the similar clinical characteristics at baseline in the two groups, the comparison can be considered valid. Study strengths include the prospective design and the fact that the same two trained interviewers administered all HRQL questionnaires during the entire period of study.

Conclusions

In the present study, EBRT administered alone or in combination with HDR-BT boost had a similar impact on

Table 3. Generalized estimating equation models of the association between treatment groups and clinical variables with specific HRQL scores at each year of follow-up. β coefficients (standard error)

	FACT-P		EPIC urinary incontinence		EPIC urinary irritative/obstructive		EPIC bowel summary		EPIC sexual summary		EPIC hormonal summary	
	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
Intercept	41.9 (2.1)	< 0.0001	104.1 (9.5)	< 0.001	100.6 (8.6)	< 0.001	103.8 (5.4)	< 0.001	60.2 (6.8)	< 0.001	98.0 (7.4)	< 0.001
Age	0.0 (0.0)	0.004	0.0 (0.0)	0.019	–0.1 (0.0)	< 0.001	0.0 (0.0)	0.475	0.0 (0.0)	0.043	0.0 (0.0)	0.096
Gleason	–0.1 (0.3)	0.663	–1.2 (1.1)	0.268	–0.1 (1.2)	0.930	–0.6 (0.7)	0.352	–1.2 (0.8)	0.124	0.9 (0.9)	0.314
PSA	0.0 (0.0)	0.334	0.1 (0.0)	0.045	0.0 (0.0)	0.158	0.0 (0.0)	0.648	0.0 (0.0)	0.053	–0.1 (0.0)	0.001
Chronic conditions	–1.2 (0.3)	< 0.0001	–1.0 (1.1)	0.344	–1.7 (1.2)	0.149	–0.9 (0.7)	0.199	–4.3 (1.1)	< 0.001	–3.0 (0.8)	0.000
Treatment group (differences at baseline)												
Radiotherapy	(ref.)		(ref.)		(ref.)		(ref.)		(ref.)		(ref.)	
Radiotherapy + brachytherapy	0.7 (1.0)	0.437	2.1 (3.1)	0.485	0.0 (2.1)	0.991	0.4 (1.3)	0.745	–2.6 (4.4)	0.549	–4.0 (2.0)	0.047
Time (radiotherapy change from baseline)												
Baseline	(ref.)		(ref.)		(ref.)		(ref.)		(ref.)		(ref.)	
1 month	–4.2 (0.9)	< 0.0001	–4.2 (2.7)	0.129	–16.3 (3.4)	< 0.001	–8.5 (1.9)	< 0.001	–12.9 (3.8)	0.001	–7.6 (2.1)	0.000
3 months	–2.4 (0.7)	0.001	0.8 (3.3)	0.810	–6.3 (2.5)	0.013	–2.9 (1.4)	0.042	–11.8 (3.6)	0.001	–9.9 (1.9)	< 0.001
6 months	–1.8 (0.9)	0.037	–0.2 (2.3)	0.927	–1.9 (2.4)	0.424	–0.4 (1.6)	0.827	–12.3 (3.9)	0.002	–11.6 (2.5)	< 0.001
12 months (1 year)	–1.7 (0.8)	0.040	–5.2 (2.9)	0.073	–3.9 (2.3)	0.090	–0.7 (1.0)	0.465	–12.5 (3.9)	0.001	–17.1 (3.6)	< 0.001
24 months (2 years)	–4.1 (1.1)	< 0.0001	–7.5 (3.6)	0.036	–5.9 (2.8)	0.036	–3.3 (1.7)	0.052	–10.9 (4.4)	0.014	–18.0 (3.4)	< 0.001
36 months (3 years)	–2.7 (1.1)	0.017	–4.4 (3.6)	0.224	–11.4 (3.5)	0.001	–3.9 (2.4)	0.101	–4.2 (4.5)	0.354	–11.0 (3.2)	0.001
48 months (4 years)	–3.0 (1.2)	0.014	–6.8 (4.6)	0.140	–6.3 (3.1)	0.041	–4.3 (2.1)	0.035	1.0 (5.2)	0.840	–12.7 (3.4)	0.000
60 months (5 years)	–2.4 (1.2)	0.039	–6.9 (4.2)	0.100	–5.3 (4.1)	0.193	–3.1 (1.5)	0.045	4.6 (5.2)	0.372	–10.4 (3.1)	0.001
Interaction radiotherapy + brachytherapy * Time (difference from radiotherapy)												
Baseline	(ref.)		(ref.)		(ref.)		(ref.)		(ref.)		(ref.)	
1 month	0.1 (1.1)	0.960	2.2 (3.5)	0.542	–1.2 (4.6)	0.789	–8.5 (3.2)	0.007	1.9 (4.6)	0.682	2.0 (2.7)	0.470
3 months	–0.3 (0.9)	0.751	–3.6 (3.7)	0.333	–2.5 (3.1)	0.427	–4.6 (2.0)	0.025	0.9 (4.3)	0.836	2.5 (2.4)	0.296
6 months	–0.2 (1.0)	0.868	–0.1 (2.9)	0.959	–3.7 (2.9)	0.195	–5.7 (2.2)	0.010	3.0 (4.7)	0.527	3.3 (3.0)	0.270
12 months (1 year)	–1.3 (1.0)	0.200	–2.1 (3.5)	0.558	–4.6 (3.1)	0.147	–5.2 (1.8)	0.003	5.5 (4.8)	0.253	5.9 (4.2)	0.156
24 months (2 years)	1.7 (1.2)	0.157	–4.4 (4.5)	0.335	–3.8 (3.6)	0.288	–3.5 (2.4)	0.138	7.7 (5.5)	0.162	9.1 (4.0)	0.023
36 months (3 years)	–0.4 (1.3)	0.785	–9.6 (4.8)	0.048	–0.4 (4.4)	0.935	–6.2 (3.3)	0.057	5.5 (5.5)	0.318	5.5 (3.8)	0.148
48 months (4 years)	–0.1 (1.4)	0.969	–3.5 (5.5)	0.521	–4.8 (4.0)	0.228	–2.6 (2.7)	0.328	–1.0 (6.1)	0.873	7.8 (4.0)	0.049
60 months (5 years)	–0.3 (1.3)	0.815	–5.7 (5.1)	0.267	–2.7 (4.6)	0.565	–0.6 (2.1)	0.757	–4.6 (5.9)	0.434	8.1 (3.6)	0.025

HRQL – health-related quality of life, FACT-G and FACT-P – Functional Assessment of Cancer Therapy (general and prostate module), EPIC – Expanded Prostate Cancer Index composite; SE – standard error. Time was included in the model as a categorical variable with six categories, so as not to assume a linear association: baseline (reference), month 12, month 24, month 36, month 48, and month 60. Interaction variables between each treatment group and time were included: for interaction with external beam radiotherapy, coefficients refer to changes from baseline, and for the external beam radiotherapy with HDR brachytherapy boost group, coefficients refer to difference from the external beam radiotherapy group (reference group) in the changes from baseline

Table 4. Generalized estimating equation models of the association between treatment groups and clinical variables with generic HRQL scores at each year of follow-up. β coefficients (standard error)

	SF-36 physical component summary		SF-36 mental component summary		FACT physical well-being		FACT social well-being		FACT emotional well-being		FACT functional well-being	
	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
Intercept	56.1 (3.6)	< 0.001	53.8 (3.8)	< 0.0001	27.9 (1.5)	< 0.0001	18.4 (1.3)	< 0.0001	22.3 (2.0)	< 0.0001	15.8 (2.0)	< 0.0001
Age	0.0 (0.0)	0.007	0.0 (0.0)	0.002	0.0 (0.0)	0.531	0.0 (0.0)	0.373	0.0 (0.0)	0.747	0.0 (0.0)	0.191
Gleason	0.1 (0.5)	0.844	0.4 (0.5)	0.350	0.1 (0.2)	0.760	–0.1 (0.2)	0.416	–0.2 (0.2)	0.371	0.3 (0.2)	0.214
PSA	0.0 (0.0)	0.373	0.0 (0.0)	0.235	0.0 (0.0)	0.318	0.0 (0.0)	0.001	0.0 (0.0)	0.056	0.0 (0.0)	0.597
Chronic conditions	–2.2 (0.4)	< 0.001	–0.5 (0.4)	0.223	–0.7 (0.2)	< 0.0001	–0.1 (0.2)	0.538	–0.6 (0.2)	0.007	–0.8 (0.2)	0.001
Treatment group (differences at baseline)												
Radiotherapy	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)
Radiotherapy + brachytherapy	1.7 (1.1)	0.130	–1.1 (1.0)	0.252	0.1 (0.4)	0.803	0.3 (0.7)	0.620	–0.5 (0.7)	0.478	–0.2 (0.7)	0.811
Time (radiotherapy change from baseline)												
Baseline	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)
1 month	–2.0 (1.1)	0.073	–0.4 (1.1)	0.702	–1.9 (0.5)	0.000	–1.5 (0.5)	0.003	1.0 (0.5)	0.042	–2.0 (0.5)	0.000
3 months	–2.6 (0.9)	0.005	0.0 (0.8)	0.968	–1.3 (0.4)	0.002	–1.3 (0.6)	0.037	1.5 (0.5)	0.003	–0.9 (0.5)	0.061
6 months	–3.2 (1.5)	0.033	–0.2 (1.3)	0.867	–1.4 (0.6)	0.030	–1.3 (0.6)	0.023	1.1 (0.8)	0.146	–1.3 (0.7)	0.056
12 months (1 year)	–4.7 (1.0)	< 0.001	–2.6 (1.6)	0.103	–2.0 (0.6)	0.001	–1.8 (0.6)	0.003	–0.7 (0.6)	0.270	–0.8 (0.7)	0.256
24 months (2 years)	–6.6 (1.3)	< 0.001	–3.6 (2.1)	0.082	–2.3 (0.6)	0.000	–1.4 (0.5)	0.007	–2.0 (0.8)	0.011	–1.4 (0.8)	0.076
36 months (3 years)	–6.6 (1.1)	< 0.001	–5.7 (2.1)	0.006	–2.8 (0.9)	0.002	–0.8 (0.7)	0.234	–2.8 (0.7)	< 0.0001	–0.4 (0.8)	0.600
48 months (4 years)	–8.1 (1.6)	< 0.001	–5.7 (2.3)	0.013	–3.2 (1.1)	0.004	–1.7 (0.7)	0.020	–2.6 (0.8)	0.002	–0.8 (1.0)	0.445
60 months (5 years)	–9.8 (1.6)	< 0.001	–7.1 (2.0)	0.001	–2.6 (0.8)	0.001	–1.5 (0.7)	0.032	–2.5 (0.7)	0.000	–1.2 (0.9)	0.155
Interaction radiotherapy + brachytherapy * Time (difference from radiotherapy)												
Baseline	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)	(ref.)
1 month	–0.7 (1.4)	0.602	0.0 (1.3)	0.977	–0.1 (0.7)	0.854	1.2 (0.7)	0.092	–0.4 (0.6)	0.544	0.1 (0.8)	0.923
3 months	–0.5 (1.2)	0.669	0.6 (1.1)	0.565	–0.3 (0.5)	0.617	0.8 (0.7)	0.279	–0.6 (0.6)	0.321	1.0 (0.7)	0.118
6 months	0.0 (1.7)	0.994	0.9 (1.4)	0.542	0.2 (0.7)	0.810	0.4 (0.7)	0.613	0.1 (0.8)	0.939	1.0 (0.8)	0.201
12 months (1 year)	–0.2 (1.2)	0.859	3.1 (1.8)	0.089	–0.1 (0.7)	0.939	0.7 (0.7)	0.287	0.5 (0.7)	0.436	0.6 (0.8)	0.471
24 months (2 years)	1.8 (1.5)	0.235	0.3 (2.5)	0.887	0.2 (0.8)	0.806	0.4 (0.6)	0.574	0.9 (0.9)	0.319	1.1 (1.0)	0.265
36 months (3 years)	–1.1 (1.6)	0.500	3.9 (2.4)	0.111	0.2 (1.0)	0.859	0.5 (0.8)	0.495	0.4 (0.9)	0.649	0.9 (1.0)	0.360
48 months (4 years)	0.6 (1.9)	0.740	2.2 (2.7)	0.415	0.5 (1.2)	0.666	0.3 (0.8)	0.719	0.3 (1.0)	0.790	1.0 (1.2)	0.412
60 months (5 years)	2.3 (1.9)	0.220	3.9 (2.4)	0.101	0.6 (0.9)	0.527	0.1 (0.8)	0.918	0.8 (0.8)	0.341	2.0 (1.0)	0.052

HRQL – health-related quality of life, SF-36 – medical outcomes study 36-item short form, FACT-G and FACT-P – Functional Assessment of Cancer Therapy (general and prostate module), SE – standard error. Time was included in the model as a categorical variable with six categories, so as not to assume a linear association: baseline (reference), month 12, month 24, month 36, month 48, and month 60. Interaction variables between each treatment group and time were included: for interaction with external beam radiotherapy, coefficients refer to changes from baseline, and for the external beam radiotherapy with HDR brachytherapy boost group, coefficients refer to difference from the external beam radiotherapy group (reference group) in the changes from baseline

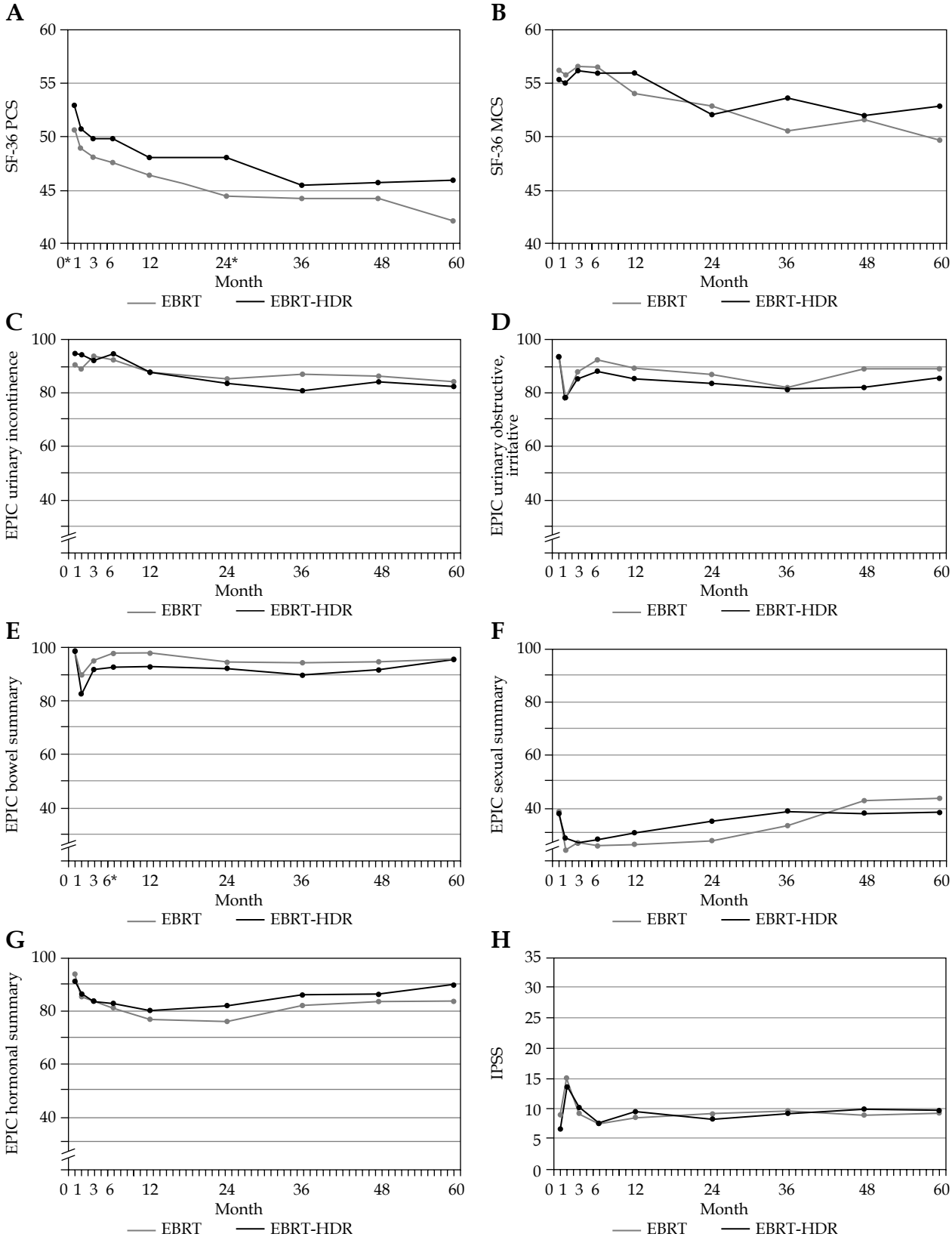

Fig. 1. Differences between EBRT alone and EBRT combined with HDR brachytherapy regarding the impact on mean scores of HRQL questionnaires during the 5 years of follow-up for short form-36 (SF-36) physical component score (PCS; **A**); SF-36 mental component score (MCS; **B**); expanded prostate cancer index composite (EPIC) urinary incontinence (**C**), urinary obstructive/irritative (**D**), bowel (**E**), sexual (**F**), hormonal domains (**G**), and international prostate symptom score (IPSS; **H**); one-way analysis of variance of QoL scores among the two treatment groups for each follow-up assessment; Tukey's studentized range pos-hoc comparisons: *$p < 0.05$ for external-beam radiotherapy (grey) vs. external-beam radiotherapy combined with HDR brachytherapy boost (black)

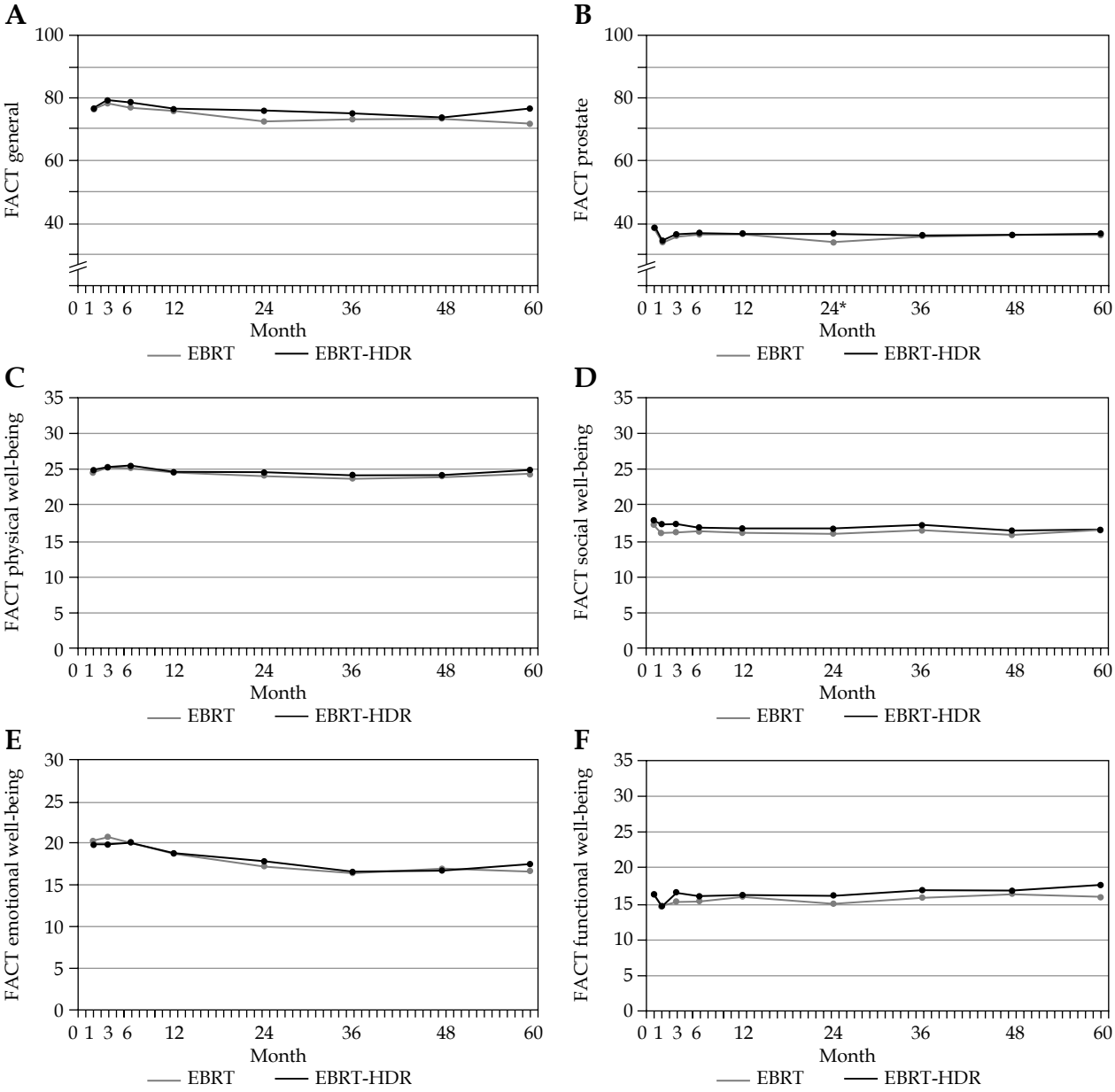

Fig. 2. Differences between EBRT alone and EBRT combined with HDR brachytherapy regarding the impact on mean scores in HRQL questionnaires during 5 years of follow-up for functional assessment cancer therapy-general (FACT-general; **A**) and prostate-specific (FACT-prostate; **B**); FACT physical well-being (**C**); FACT social well-being (**D**); FACT emotional well-being (**E**) and FACT functional well-being (**F**). One-way analysis of variance of QoL scores among the two treatment groups for each follow-up assessment. Tukey's studentized range post-hoc comparisons: $*p < 0.05$ for external-beam radiotherapy (grey) vs. external-beam radiotherapy combined with HDR brachytherapy boost (black)

HRQL in patients with high-risk localized PCa over 5-year follow-up. However, patients in the EBRT alone group experienced significantly greater worsening in hormonal symptoms (EPIC questionnaire) at 5-year follow-up, perhaps due to the higher EPIC hormonal summary scores at baseline in this group. Longer follow-up would be needed to minimize the effects of ADT on HRQL and to determine the best treatment in terms of HRQL.

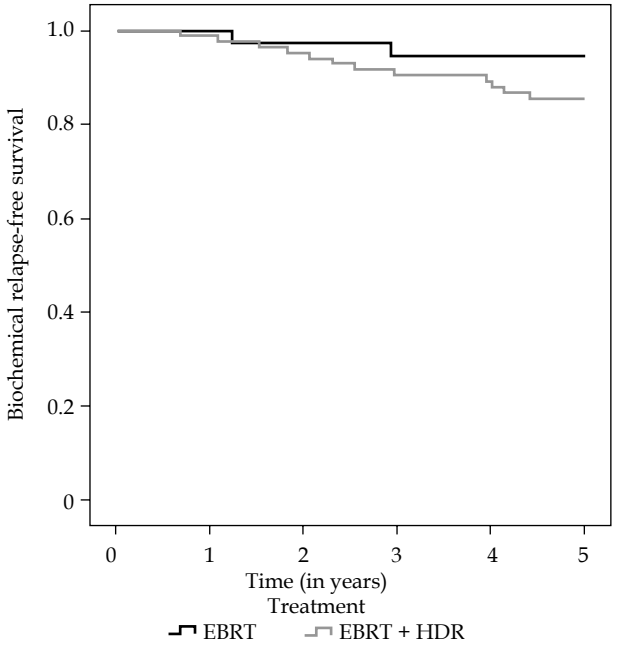

Fig. 3. Biochemical relapse-free survival curves in patients treated with EBRT alone and EBRT + HDR-BT. Kaplan-Meier method and log-rank test: *$p < 0.05$ for external-beam radiotherapy (black) vs. external-beam radiotherapy combined with HDR brachytherapy boost (grey)

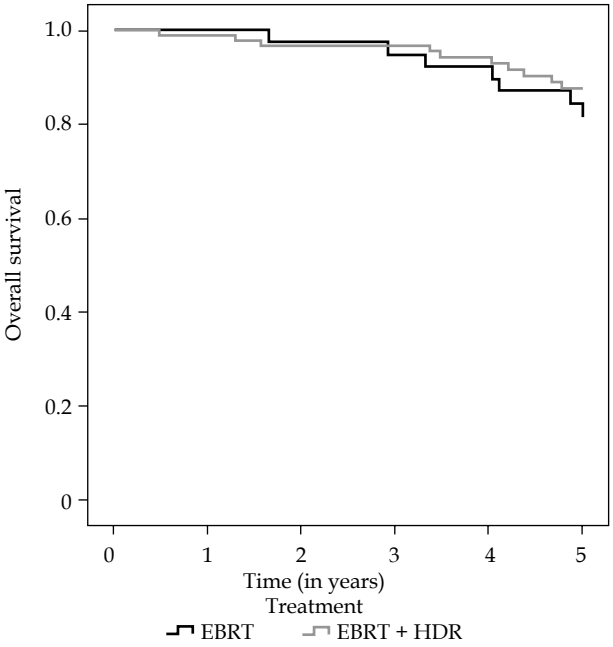

Fig. 4. Overall survival curves in patients treated with EBRT alone and EBRT + HDR-BT. Kaplan-Meier method and log-rank test: *$p < 0.05$ for external-beam radiotherapy (black) vs. external-beam radiotherapy combined with HDR brachytherapy boost (grey)

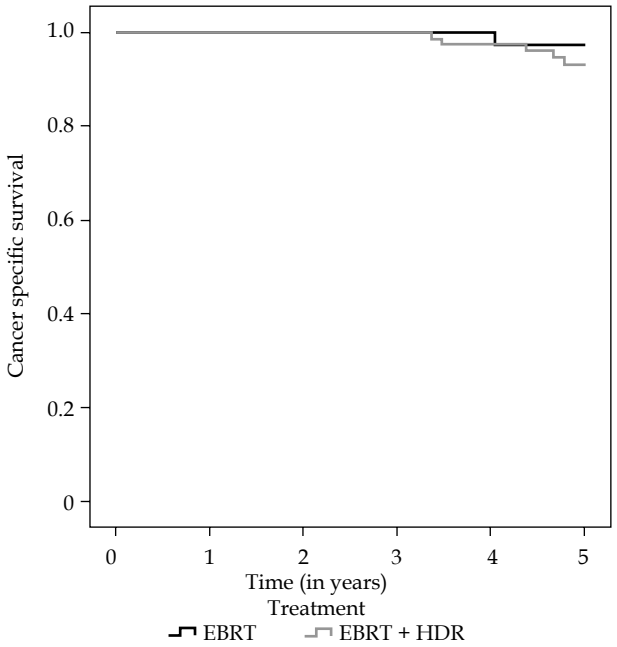

Fig. 5. Cancer-specific survival curves in patients treated with EBRT alone and EBRT + HDR-BT. Kaplan-Meier method and log-rank test: *$p < 0.05$ for external-beam radiotherapy (black) vs. external-beam radiotherapy combined with HDR brachytherapy boost (grey)

Acknowledgments

The authors would like to thank Marta Pulido, MD, and Bradley Londres for professional English language editing.

Disclosure

The authors report no conflict of interest.

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