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Original Article

Ten-year survival after High-Dose-Rate Brachytherapy combined with External Beam Radiation Therapy in high-risk prostate cancer: A comparison with the Norwegian SPCG-7 cohort

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ABSTRACT

Background: The survival benefit of dose-escalation with High-Dose-Rate brachytherapy (HDR-BT) boost combined with External Beam Radiotherapy (EBRT) for the treatment of high-risk prostate cancer (PCa) remains debatable. We investigated 10-year PCa-specific mortality (PCSM) and overall mortality (OM) in high-risk patients treated with HDR-BT/EBRT (calculated EQD2 = 102 Gy) compared to EBRT alone (70 Gy).

Methods: HDR-BT boosts (10 Gy × 2) were given 2 weeks apart followed by 50 Gy conformal EBRT (2 Gy × 25) to the prostate and seminal vesicles. The HDR-BT/EBRT group (N:325) received Androgen Deprivation Therapy for a median duration of 2 years. The historical control group (N:296), received a median dose of 70 Gy (2 Gy × 35) to the prostate and seminal vesicles with lifelong Anti-Androgen Treatment. For each treatment group PCSM and OM were established by competing-risk analyses and Kaplan–Meier analyses respectively. Differences were evaluated by the logrank test. Independent associations were established by Cox regression analyses. Significance level set to $p < 0.05$.

Results: Median follow-up was 104 and 120 months for the HDR-BT/EBRT and the EBRT group respectively. A 3.6-fold decreased risk of PCSM ($p < 0.01$) and a 1.6-fold decreased risk of OM ($p = 0.02$) in the HDR-BT/EBRT cohort compared to the EBRT-only group were revealed. Ten-year OM and PCSM rates were 16% and 2.5% in the HDR-BT/EBRT group versus 23% and 8.2% in the EBRT-only group respectively.

Both treatment modality (HR = 3.59, 95%CI 1.50–8.59) and Gleason score (HR = 2.48, 95%CI 1.18–5.21) were associated with PCSM. Only treatment modality (HR = 1.63, 95%CI = 1.08–2.44) was significantly associated with OM.

Conclusions: Men with high-risk PCa have a significantly reduced PCSM and OM rates when treated with dose-escalated radiotherapy achieved by HDR-BT/EBRT compared to EBRT alone (70 Gy). A Gleason score of 8–10 was independently associated with increased risk of PCSM. Randomized studies are warranted.

Summary: Observational study of 10-year survival in high-risk Prostate Cancer (PCa) after High-Dose-Rate brachytherapy combined with External Beam Radiation Therapy (HDR-BT/EBRT) compared to EBRT alone. The combined HDR-BT/EBRT treatment was found to give a 3.6-fold decrease in Prostate Cancer Specific Mortality (PCSM) and a 1.6-fold decrease in Overall Mortality (OM). Gleason score and type of treatment strongly influenced PCSM whereas only treatment modality was associated with OM. The observed benefits of dose-escalation warrant future randomized trials.

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The concept of dose-escalation in radiotherapy of prostate cancer (PCa) was introduced in the 1990s after showing reduced biochemical recurrence, while maintaining acceptable acute and long-term toxicity [1]. Over the last decade, combined endocrine treatment and radiotherapy with doses exceeding 70 Gy have become the standard in radiotherapy in men with high-risk PCa [2–5]

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Patients with high-risk PCa are currently offered prostatectomy or Radiotherapy as equal standard treatment options [6]. Despite advances in technology, continuing high risk of relapse persists following such standard therapy. Treatment intensification may improve biochemical and survival outcomes [7,8]. Recently published data using HDR-BT as means of dose-escalation in combination with hormonal therapy and External Beam Radiation Therapy (EBRT) showed reduced biochemical failure and improved disease-free and cause-specific survival, even for patients with high-risk PCa [9,10]. However, few studies comparing HDR-BT/EBRT to EBRT alone with follow-up of more than 10 years have been published.

HDR-BT/EBRT was introduced in Norway in 2004 after favorable reports by Borghede et al. and has gradually become a standard treatment option in our unit for patients with intermediate- and high-risk PCa [11,12].

In this observational study, we primarily explored the difference in 10-year survival in men with high-risk PCa who had been treated with HDR-BT/EBRT or EBRT alone. Secondarily, we investigated the prognostic impact of clinical factors on 10-year mortality.

Materials and methods

Eligibility criteria

The present comparative study consists of two cohorts: Cases who received HDR-BT/EBRT (2004–2009) and Controls who received EBRT alone, the latter representing the patients from Norway, Scandinavian Prostate Cancer Group-7 (SPCG-7, 1996–2002 [3].

All patients met at least one criterium for the generally recommended definition of high-risk PCa according to the National Comprehensive Cancer Network (NCCN) criteria: cT3, Gleason score 8–10 or serum PSA (sPSA) $\geq$20 ng/ml [13]. All patients had life expectancy of minimum 10 years with good general health (including an Eastern Cooperative Oncology Group status of 0–1). Clinical T-stage was established by digital rectal examination. All patients also underwent ultrasound and ultrasound-guided biopsy of the prostate gland. The majority of patients in both groups underwent pelvic lymph node dissection (obturator lymph node dissection) as per protocol as method of exclusion of lymph node metastasis [12,14]. In the Control group, patients with sPSA level <10 ng/ml were assumed to have low risk of lymph node metastases and therefore did not undergo mandatory lymph node dissection. After 2001, Magnetic Resonance Imaging (MRI) for the assessment of pelvic lymph node involvement was used as the preferred method of assessing lymph node involvement and 54 patients in the Cases group were radiological N0 disease. Four patients were considered Nx. Distant metastasis to the skeleton was assessed scintigraphically by bone scan and/or MRI. All patients with metastatic disease to either lymph nodes or other organs were excluded.

Patients were followed-up according to National guidelines at the time of patient treatment. For Cases, sPSA measurements were done every third month for the first year, every six months for the second and third year, and afterward yearly. Controls had similar schedule of follow-up.

Exclusion criteria for Cases were sPSA levels >50 ng/ml, prostate volume >60 ml, tumor stage T3b/T4 and unfavorable anatomical conditions for HDR-BT, such as adipositas or large adenomas in the median lobe [15]. In the Controls group, patients with sPSA levels >70 ng/ml were excluded.

Both T1 and T2 tumors were grouped together as intra-prostatic disease and compared to extra-prostatic disease (T3 tumors)

In the SPCG-7 trial tumor grading was based on the World Health Organization (WHO) grading system (grade 1, 2 and 3) while the prostatic tumors in the HDR-BT/EBRT group were scored by the Gleason grading system [16]. To achieve conformity WHO 1 was viewed as Gleason grade 6, WHO 2 as Gleason grade 7 (without separating 7a and 7b) and WHO 3 as Gleason grade 8–10.

The sPSA levels were divided into three subgroups: <10 ng/ml, 10–19.9 ng/ml and $\geq$20 ng/ml.

On clinical basis, age was divided into two groups of <65 and $\geq$65 years at time of inclusion. Age was analyzed as a categorical, not a continuous variable, to correct for age and not estimate the effect of age.

Treatment

HDR-BT/EBRT cohort

To reduce the risk of tumor flare-up when commencing hormonal treatment, Cases were given an oral antiandrogen tablet (bicalutamide 50 mg once daily) for 30 days. After at least one week they started Androgen Deprivation Treatment (ADT) for a total intended length of treatment for at least 2 years in accordance with the European Association of Urology guidelines [6]. Radiotherapy was started after 3–6 months of ADT.

The HDR-BT procedure has been described recently [12]. Briefly, it is performed under general anesthesia with the patient lying in the lithotomy position. Iridium-192 was inserted by use of steel needles under ultrasound guidance through the perineum and into the prostate gland. The ultrasound images were transferred electronically to the treatment planning system.

All patients received EBRT (15 MV photon energy) defined by a 3-dimensional CT planning system. The target dose included the prostate and seminal vesicles to 50 Gy with optimized treatment plans according to the International Commission on Radiation Units and Measurements (ICRU) 62 report [12]. Assuming an α/β ratio of 3, the total equieffective dose if given with 2 Gy fractions (EQD2) was 102 Gy and Biological Effective Dose (BED) was 170 Gy [12]. Patients were followed-up according to National guidelines at the time of patient inclusion in the respective protocols. For Cases, clinical examination, sPSA and testosterone measurements were done every third month for the first year, every six months for the second and third year and afterward yearly.

EBRT-only cohort

Treatment consisted of total androgen blockade with a Luteinizing hormone-releasing hormone (LHRH)-agonist and an oral antiandrogen for three months followed by lifelong antiandrogen treatment. Radiotherapy was started three months after commencing hormonal therapy. Patients received 3D conformal EBRT of 50 Gy (2 Gy $\times$ 25) to the prostate and seminal vesicles with a subsequent boost of 20 Gy (2 Gy $\times$ 10) to the prostate gland [3]. 21 patients included after 2001 were treated with a total dose of 74 Gy (Table 1). Patient follow-up was followed according to national guidelines [17].

In both cohorts, patients' cause of death was obtained from the National Registry, a part of the Norwegian Institute of Public Health.

Statistical analysis

Continuous variables were described with median and range, categorical variables with counts and percentages. Differences between the treatment groups concerning categorical variables were assessed using the Chi-square test.

Time to event (death due to PCa or other causes) was defined as years (maximum 10 years) from the date of start of hormonal treatment to the date of death, or to the end of follow up (1st October 2016). Crude Overall Mortality (OM) was depicted using the Kaplan–Meier method. To account for the competing risk of dying of other causes, the cumulative incidences of both PCa specific mortality and death of other causes were modeled using the Fine

Table 1
Comparisons between the two cohorts.

	HDR-BT/EBRT cohort (Cases)	EBRT-only cohort (Controls)
Time of inclusion	2004–2010	1996–2002
Number of patients	325 (52.3%)	296 (47.7%)
Median age (years)	66 (45–80)	66 (49–75)
Risk group (modified)[‡]	High-risk	High-risk
Lymph node staging pN0, Nx rN0	267 pathological (82%)	208 pathological (70%)
	4 unknowns (1%)	88 unknown (30%)[‡‡]
	54 radiological (17%)	0 radiological
Hormonal treatment duration	ADT 2 years	AAT life-long
ECOG status	0–1	0–1
Median radiation dosage (Gy)	EQD2 102[*]	EQD2 70[*]
	BED 170[*]	BED 117[*]
Gleason score[**]		
6	25 (8%)	50 (17%)
7	177 (54%)	195 (66%)
8–10	123 (38%)	51 (17%)
cT category[**]		
1	26 (8%)	0
2	68 (21%)	29 (10%)
3	231 (71%)	267 (90%)
sPSA (ng/ml)		
0–10	69 (21%)	88 (30%)
11–19.9	99 (30.5%)	84 (28%)
≥20	157 (48.5%)	124 (42%)
Median observation time, in months (min–max)	104 (13–120)	120 (3–120)
Cause of death[**]		
PCa	7 (2%)	25 (8%)
Other cause	35 (11%)	44 (15%)
Total	42 (13%)	69 (23%)
PCSM[‡‡‡] *rate (95%CI)*		
5-year	1% (0.3–2.2)	3.1% (2.5–5.8)
10-year	2.5% (1.0–5.5)	8.2% (5.5–12.0)

[*] α/β ratio = 3.
[**] Statistically significant difference (Chi-square test), $p < 0.001$.
[‡] At least one of the following criteria met: T3 tumor, Gleason score ≥8, sPSA ≥20 ng/ml.
[‡‡] Patients with sPSA <10 ng/ml, lymph node dissection not performed.
[‡‡‡] Prostate Cancer Specific Mortality.

Table 2
Overall Mortality – Cox regression analyses of selected variables.

Variable	HR	95% CI	*p*-value
Treatment			
HDR-BT/EBRT	1 (ref)		
EBRT-only	1.63	1.08–2.44	**0.02**
Age (years)			
<65	1 (ref)		
≥65	1.35	0.92–2.00	0.12
cT-category			
T1 + T2	1 (ref)		
T3	1.32	0.77–2.26	0.31
PSA (ng/ml)			
<10	1 (ref)		
10–19.9	0.85	0.47–1.53	0.58
≥20	1.63	0.99–2.68	0.06
Gleason score			
6 + 7	1 (ref)		
8–10	1.29	0.84–1.99	0.25

Table 3
Cancer Specific Mortality Rate – Fine & Grey regression analyses of selected variables.

Variable	SHR	95% CI	*p-value*
Treatment			
HDR-BT/EBRT	1 (ref)		
EBRT-only	3.58	1.40–9.14	**<0.01**
Age (years)			
<65	1 (ref)		
≥65	0.99	0.93–1.05	0.77
cT-category			
T1 + T2	1 (ref)		
T3	2.99	0.66–13.60	0.15
PSA (ng/ml)			
<10	1 (ref)		
10–19.99	0.65	0.25–1.67	0.37
≥20	0.83	0.36–1.91	0.66
Gleason score			
6 + 7	1 (ref)		
8–10	2.58	1.15–5.78	**0.02**

and Grey method. A Kaplan–Meier plot was performed to assess the cumulative probability of OM stratified by Gleason score and the two groups.

The impact of selected covariates on both OM rate and Prostate Cancer Specific Mortality (PCSM) rate was modeled using the Cox proportional hazards models (Tables 1–3). The results were expressed as hazard rates ratios (HR) with 95% confidence intervals (CI).

All tests were two-sided. *P*-values <0.05 were considered statistically significant. All analyses were performed using SPSS version 24 and Stata version 9.

Ethical considerations

The study was approved by the regional committee for medical ethics and the Norwegian Data Inspectorate. Signed informed consent was obtained for all patients.

Results

Overall, 621 patients were included in the study. The median follow-up was 104 months (range 13–120) and 120 months (range 3–120) for the HDR-BT/EBRT group and EBRT-only group, respectively (Table 1).

In total 325 patients were included in the HDR-BT/EBRT group from 2004 to 2010 with a median age of 66 years (range 45–80). Of these, 267 patients had pathological N0 (pN0) lymph node status, 4 Nx and 54 radiological N0 (radN0). Seven patients (2%) died from PCa whereas 35 (11%) died from other causes. The total number of deaths was 42 (13%). The 10-year OM and PCSM rate was 16.1% (95%CI = 78.6–88.1) and 2.5% (95%CI = 1.0–5.5) respectively.

In the EBRT-only group, 296 patients were included from 1996 to 2002 with a median age of 66 years (range 49–75). Of these, 88 were Nx, but had sPSA levels <10 ng/ml. Twenty-five patients (8%) died from PCa and 44 (15%) from other causes. The total number of deaths was 69 (23%). The 10-year OM and PCSM rate was 23.3% (95%CI = 71.4–81.1) and 8.2% (95%CI = 5.5–12.0) respectively.

Overall mortality rate

When adjusted for treatment modality, sPSA, age, T-category and Gleason score, only type of treatment (HDR/BT/EBRT versus EBRT only) remained significantly associated with higher OM rate (Table 2). Patients who received EBRT-only had a 1.6-fold higher OM rate compared to the HDR-BT/EBRT group, HR = 1.63 (95% CI 1.08–2.44), (Fig. 1).

Prostate cancer-specific mortality rate

When adjusted for treatment modality, sPSA, age, T-category and Gleason score, both type of treatment and Gleason score remained independent predictors of PCSM rate. Patients treated with EBRT-only had a 3.6-fold higher PCSM rate compared to patients treated with HDR-BT/EBRT, HR = 3.59 (95%CI 1.50–8.59), (Fig. 2). In addition, patients with Gleason score 8–10 had a 2.5-fold (HR = 2.48, 95%CI 1.18–5.21) increased risk of PCSM compared to patients with Gleason score 6–7 (Table 3, Fig. 3).

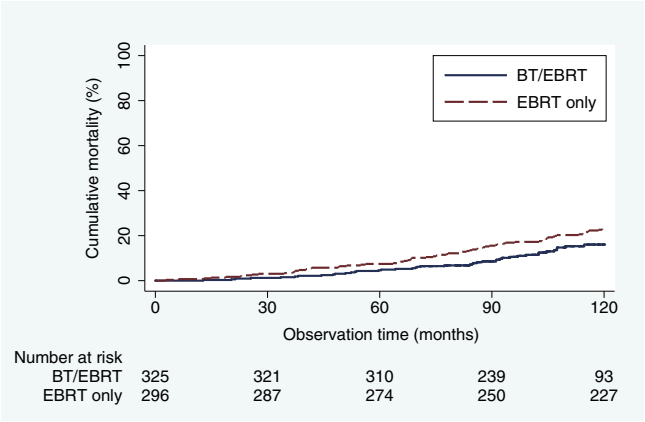

Fig. 1. Kaplan–Meier plot Overall Mortality. Kaplan–Meier Plot showing cumulative probability of Overall Mortality in the high-dose-rate brachytherapy/external beam radiotherapy (HDR-BT/EBRT) group compared to external beam radiotherapy (EBRT) alone.

Cumulative incidences of death by causes of death

When the competing risk of dying from other causes than PCa was taken into consideration, the cumulative incidence of dying from PCa was significantly higher in patients with EBRT only compared to patients treated with HDR-BT/EBRT ($p < 0.01$) (Fig. 2A). The cumulative incidence of dying of other causes was also higher for patients treated with EBRT-only compared to HDR-BT/EBRT. However, the difference was much smaller compared to the probability of dying of PCa and did not reach the level of statistical significance, likely due to a limited sample size and number of deaths ($p = 0.61$) (Fig. 2B).

Discussion

The results of our retrospective analysis of two high-risk cohorts demonstrate a significantly decreased risk of 3.6-fold for PCSM and 1.6-fold for OM in favor of HDR-BT combined with EBRT in patients with high-risk PCa compared to EBRT alone. 10-year OM was 16% in the HDR-BT/EBRT group and 23% in the EBRT-only group. 10-year PCSM was 2.5% in the HDR-BT/EBRT group versus 8.2% in the EBRT-only group. Regression models showed that type of treatment influenced both PCSM and OM, while a high Gleason score was associated with an increased risk of PCSM. We found no association between the risk of OM or PCSM and age, clinical T-category nor sPSA level.

Five RCTs have investigated the outcome of dose-escalation in a total of 2332 patients treated with conformal radiotherapy [18–22]. They have shown 10–20% improvement in biochemical control with a treatment dose ≥74 Gy compared to lower doses, leading to the current treatment recommendation of dose of 78 Gy [6]. The finding of the present study indicates that radiation doses >70 Gy results in decreased 10-year mortality in high-risk patient. One way of achieving sufficient dose-escalation and precise delivery is to combine external radiation treatment with interstitial HDR-BT [9,23].

Several studies have shown that dose-escalation with HDR-BT boost improves 10-year biochemical, disease-free and cancer-specific survival in men with high-risk prostate cancer [9,10]. Our observations support the above findings with a clear benefit of dose-escalation on hard end-points (PCSM and OM) with long-term follow-up (median 8.6 years). A systematic review by Zaorsky et al, including both prospective and retrospective studies of HDR-BT boost in combination with EBRT, reported the main outcome findings with a median follow-up of 4.5 years [24]. In the majority of these studies only biochemical free survival (BFS) was reported and the 10-year OS for all PCa risk groups was 80% [24]. This outcome seems inferior to our findings of 84% 10-year OS in a cohort restricted to high-risk patients. However, only a prospective study, or better, a Randomized Controlled Trial (RCT) can provide valid measures of the HDR-BT advantage.

Prospectively randomized trials with moderate radiation doses of 66–74 Gy have shown benefit of the addition of hormonal treatment to EBRT and hence have become the standard treatment of high-risk PCa [3–5]. ADT might work as a radiosensitizer and inhibitor of clonal proliferation leading to eradication of clonal cells [25,26]. However, there are conflicting findings concerning the duration of the addition of hormonal treatment and its true benefit. Hoskins et al found a significant reduction in the risk of recurrence when the combination of EBRT, HDR-BT and hormonal therapy was used [27]. In the systematic review by Keyes et al. of 52 studies (with approximately 43,000 patients of all risk groups), including both low-dose-rate and high-dose-rate BT, an improved biochemical progression-free survival of up to 15% was observed when adding 3–12 months of ADT for patients with high-risk PCa treated with BT/EBRT [28]. On the other hand, Martinez et al found that

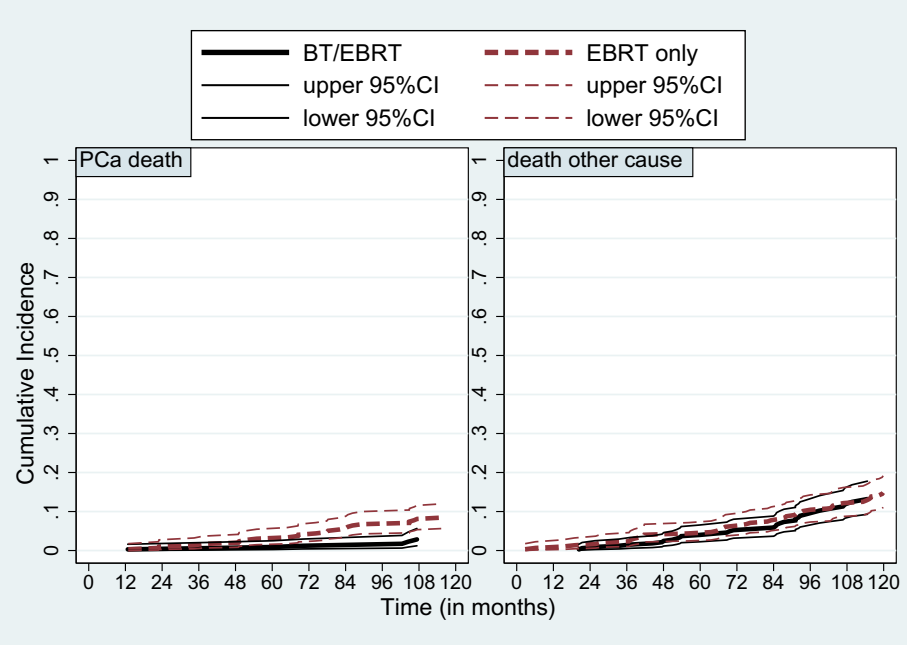

Fig. 2. (A) Cumulative incidences (competing risk regression PCSM), (B) Other causes. Fine and Grey competing risk regression curves for prostate cancer specific mortality (PCSM, graph A) and other causes (graph B).

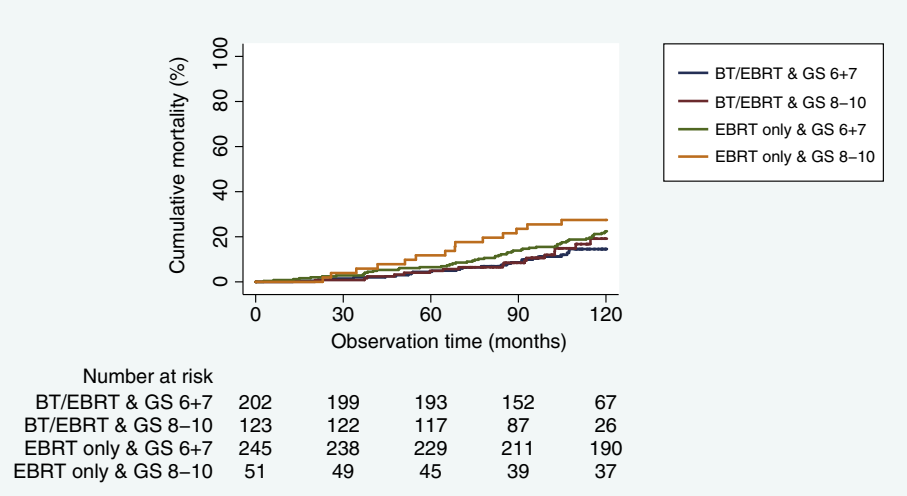

Fig. 3. Kaplan–Meier survival plots for Gleason score distribution for prostate-cancer specific survival. Kaplan–Meier plots showing cumulative probability of overall mortality (OM) stratified by Gleason score (GS) 6 + 7, GS 8–10 and treatment groups – combined high-dose rate brachytherapy/external beam radiotherapy (BT/EBRT) versus radiotherapy (EBRT only).

a short course of ADT (<6 months) in high-risk patients treated with HDR-BT/EBRT was not associated with improved tumor control, but instead added side-effects and increased costs [29,30]. Galalae et al. reported no gain in survival when the prostate was treated with a significantly higher BED (e.g. by HDR-BT) than standard doses, despite a short course (<6 months) of neoadjuvant/concurrent ADT [9].

It is acknowledged that treatment with HDR-BT combined with EBRT and ADT for 2–3 years gives increased risk for potentially life-altering long-term side-effects [31,32]. Long-term complications to the gastrointestinal and genitourinary tract are significantly higher with increasing dose of EBRT, as demonstrated in the Radiation Therapy Oncology Group (RTOG) 94-06 study [33]. Dose-escalation by intraprostatic HDR-BT aims to deliver safe dosages to patients with acceptable toxicity and complications. Patient-reported adverse effects for the HDR-BT/EBRT cohort compared to EBRT-only cohort will be published in a separate article.

Clinical T-category, sPSA and Gleason score are commonly used predictors of biochemical-free survival after prostatectomy and EBRT. Gleason score is an important component in nomogram reflecting prognosis [34,35]. For men with Gleason score 8–10, cancer mortality rises significantly, as shown in our study. Even though not a statistical significant finding, probably due to too few patients included, findings show better results for all Gleason score subgroups when treated with HDR-BT/EBRT compared to EBRT-only. Thus, patients with Gleason score 8–10 may in particular benefit from dose-escalated radiotherapy. Kishan et al. thus showed improved systemic control for patients with Gleason score 9 and 10 when treated with brachytherapy as means of dose-escalation compared to both EBRT and prostatectomy [8]. In the

review by Townsend et al. it was found that an altered Gleason score was common when biopsies were re-examined in a comprehensive cancer center, and that these changes would impact biochemical failure and change the treatment for up to 26% of patients [36].

Several limitations of this study must be acknowledged.

1. Use of a historical control group: The EBRT-only cohort was chosen due to the availability of data from the SPCG-7 trial and its long-term follow-up. The Controls were comparable to our Cases regarding inclusion criteria and co-morbidity indicated by the similar risk of dying from other causes than PCa.
2. Differences in the histology of the biopsies: Controls were graded by the WHO grading system and converted to the Gleason grading system. Hence, only 3 main groups were used without subgrouping Gleason score 7.
3. Sub-optimal dosage of the Controls: The EBRT-only group received a median dosage of 70 Gy which is an inferior dosage compared to todays' standard treatment. However, currently there is no RCT evidence that proves that high-risk patients benefit from dose-escalation regarding 10-year mortality. In this respect, the present study provides at least an indication of such benefit when adding HDR-BT as means of dose-escalation.
4. Different hormonal treatment: The effects and influence on outcome of the two different hormonal strategies could not be assessed as all patients within each group received the same length and type of hormonal treatment.
5. Bias: The HDR-BT/EBRT cohort was treated at one high-volume tertiary center whereas the Controls received their EBRT at multiple centers. This may have introduced bias regarding patient selection and the target volume included despite strict inclusion criteria and protocols of treatment given.

Strengths of this study are its restriction to patients with high-risk PCa, long observation time for both cohorts with hard endpoints (OM and PCSM).

Conclusion

Our findings of 10-year follow-up of high-risk patients with PCa shows a decrease in both OM and PCSM rates in patients treated with HDR-BT/EBRT compared to EBRT-only. Gleason score 8–10 as compared to Gleason score $\leq$7 proved to be a strong predicator for PCSM in high-risk PCa. The potential benefit on mortality seen warrants further studies in men with high-risk PCa, preferentially RCTs, comparing HDR-BT/EBRT to dose-escalated EBRT.

Conflict of interest

None.

Submission declaration and verification

The findings of this article were presented as poster presentation at ASCO June 2017 (abstract number 5059) in the format of an abstract. The article has not been published previously and is not under consideration elsewhere.

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