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) 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 compared to EBRT alone.

Methods:

HDR-BT boosts were given followed by 50 Gy conformal EBRT to the prostate and seminal vesicles. The HDR-BT/EBRT group (N:325) received Androgen Deprivation Therapy for median 2 years. The historical control group (N:296), received a median dose of 70 Gy to the prostate and seminal vesicles with lifelong Anti-Androgen Treatment. For each treatment

group, PCSM and OM were calculated using competing-risk and Kaplan-Meier analyses, respectively. Differences were assessed with the logrank test. OM and PCSM were computed using Cox and Fine & Grey regression. Significance level set to $p<0.05$. Patient-measured (PM) toxicity were assessed by EPIC-26 questionnaire at 5 years.

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.

Treatment modality (SHR=3.58, 95%CI 1.40-9.14) and Gleason score (SHR=2.58, 95%CI 1.15-5.78) 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). PM toxicity scores were acceptable and similar to the ProtecT study. A Gleason score of 8-10 was independently associated with increased risk of PCSM. Randomized studies in men with high-risk disease treated with dose-escalation are warranted.

Introduction

The concept of dose-escalation in radiotherapy of prostate cancer (PCa) was introduced in the 1990's 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 (2,3,4,5).

With continuing high risk of relapse following standard therapy, treatment intensification may improve biochemical and survival outcomes (6). Recently published data using HDR-BT as means of dose-escalation in combination with hormonal therapy and EBRT showed reduced biochemical failure and improved disease-free- and cause-specific survival, even for patients with high-risk PCa (7,8,9). However, few studies comparing HDR-BT/EBRT to EBRT alone with follow-up of more than 10 years have been published.

In addition, there is a lack of PM outcome studies in high-risk patients weighing the pros and cons central to the decision-making. Here, we report our long-term toxicity results after extreme dose-escalation with HDR-BT/EBRT.

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 (10,11).

In this case-control 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 (2004-2010) 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: cT3, Gleason score 8-10 or sPSA ≥20 ng/ml. All patients had life expectancy of minimum 10 years with good general health (including an Eastern Cooperative Oncology Group status of 0-1). The majority of patients were considered pN0 after pelvic lymph node dissection (obturator lymph node dissection). In the Control group patients with PSA level < 10 ng/ml were per protocol assumed to have no lymph node metastasis. 54 patients in the Cases group had Magnetic Resonance Imaging (MRI) for the assessment of pelvic lymph node involvement, however, 4 patients were considered Nx. No patients had metastatic disease. 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 (12). 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 (13). 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 ≥ 20 ng/ml.

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

Patient comorbidities for Cases were assessed using the Charlson Comorbidity Index (CCI) but due to the natural occurrence of the disease we used an unadjusted model for age (14). Comorbidities of the Controls group are not published but can be assumed to be low since inclusion criteria of the RCT was general good health with a life expectancy of at least 10 years (15).

Treatment

HDR-BT/EBRT cohort

The treatment of Cases commenced with Androgen Deprivation Treatment (ADT) with an oral antiandrogen daily for the first 30 days for a period of 3-6 months prior to the first of two HDR-BT boosts of 10 Gy given 2 weeks apart. A length of at least 2 years of ADT was intended.

The HDR-BT procedure has been described recently (11). Briefly, it is performed under general anaesthesia 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 ICRU 62 report (11). 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 (11).

EBRT-only cohort

Treatment consisted of total androgen blockade with an LHRH-agonist and an oral antiandrogen for three months. Patients continued using antiandrogen tablets until disease progression or death. After three months, patients received 3D conformal EBRT of 50 Gy (2 Gy x 25) to the prostate and seminal vesicles with a subsequent boost of 20 Gy (2 Gy x 10) to the prostate gland (3). 21 patients included after 2001 were treated with a total dose of 74 Gy (table 1). Assuming an α/β ratio of 3, the total equieffective dose (and BED) was 70 Gy.

Toxicity

All patients alive (n=323) with both intermediate- and high-risk PCa who received HDR-BT/EBRT between 2004-2011, including the HDR-BT/EBRT cohort described above, were invited to participate in the cross-sectional quality of life survey in 2016. We used the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire to assess patient toxicity after treatment (16). The scores were given on a scale of 0-100, with 100 being no problems. There is a paucity of long-term PM toxicity and our study design does not allow direct comparison to published data. However, descriptive comparisons were done to available published data from the EBRT arm of the ProtecT study (table 4), which used EPIC-26 (17). We did not compare PM toxicity data to the Controls in our study as these published results were obtained from a different questionnaire at different time points, impeding intergroup comparison (15).

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 death of 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 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 modelled using the Fine 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 PCSM rate was modelled using the Cox proportional hazards and Fine & Grey regression models respectively (table 1,2,3). The results were expressed as hazard rates ratios (HR and SHR) with 95 % confidence intervals (CI).

Analysis of the adverse effect scores were done by clinical significance (> 10 points difference between the two groups) and by statistical significance. The latter was calculated by Student t-test (table 4).

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

This study was approved by the local hospital board, the Regional Committee for Medical and Health Research Ethics of South-East Norway and the Data Protection Agency.

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). In the HDR-BT/EBRT group the CCI scores (n=313) were: score 0: 254 patients (81.2%), score 1: 43 (13.7%), score 2: 14 (4.5%) and score 3: 2 (0.6%). 95% of the patients had score 0-1. There were 12 patients which did not have registered comorbidities. 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. An additional 15 (4.6%) patients had biochemical relapse during the follow-up period.

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), (figure 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, SHR=3.58 (95%CI 1.40-9.14), (figure 2). In addition, patients with Gleason score 8-10 had a 2.5-fold (SHR=2.58, 95%CI 1.15-5.78) increased risk of PCSM compared to patients with Gleason score 6-7 (table 3, figure 3).

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 ($p<0.01$) (figure 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 ($p=0.61$) (figure 2B).

Toxicity after treatment

In the HDR-BT/EBRT group, all patients (intermediate- and high-risk Pca) who had received HDR-BT/EBRT treatment were invited to participate in the patient reported survey. 271 patients responded to the questionnaire for PM adverse effects, of which 12 were excluded (3 lacked consent forms and 9 did not wish to participate), leaving 259 included patients. The total compliance rate was 84 %. In the ProtecT study, 545 men were included and 473 patients responded to the 5-year questionnaire (compliance rate 86.7%).

In our study, 88.4 % had high-risk disease whilst the ProtecT cohort consisted mostly of patients with low-risk disease.

EPIC-26 score for urinary incontinence was 89.0 in the HDR-BT/EBRT group and 89.4 in the EBRT-only group (table 4). Urinary irritation/obstruction score was 81.3 in the HDR-BT/EBRT group and 93.0 in the EBRT-only group. Total urinary summary score was 83.6 (excluding urinary bother) and 91.3 (including urinary bother) in the HDR-BT/EBRT and EBRT-only groups respectively (table 4). The EPIC-26 score for bowel function was 86.7 in the HDR-BT/EBRT group and 90.3 in the EBRT-only group (table 4). Sexual function score was 27.9 in the HDR-BT/EBRT group and 31.9 in the EBRT-only group (table 4).

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.

If a treatment improves survival, it is pertinent to ask if the treatment negatively affects patient-measured function. We addressed this question by investigating the PM toxicity for bowel, urinary and sexual function in the HDR-BT/EBRT group and report our findings with results of the landmark study ProtecT. Patients self-reported adverse effect scores were similar for urinary incontinence after HDR-BT/EBRT and EBRT-only, but the scores decreased for urinary irritation/obstruction. The bowel function score was slightly lower in the HDR-BT/EBRT group than the EBRT-only group. Sexual function score was low in both groups.

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 $\geq$ 74 Gy compared to lower doses, leading to the current treatment recommendation of dose $>$ 75.6 Gy (23). The finding of the present study supports that a dose above EQD2 >76 Gy results in a decrease of 10-year mortality in high-risk patients. One way of achieving sufficient dose-escalation and precise delivery is to combine external radiation treatment with interstitial HDR-BT (7, 24).

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 (7,9). 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 (25). 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 % (20). 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, an 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 (3,4,5). ADT might work as a radiosensitizer and inhibitor of clonal proliferation leading to eradication of clonal cells (26,27). 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 (28). 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 (29). On the other hand, Martinez et al found that 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 (30,31). 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 of a short course (<6 months) of neoadjuvant/concurrent ADT (7).

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 (32). Long-term complications to the gastrointestinal and genitourinary tract are significantly higher with increasing dose of EBRT, as demonstrated in the RTOG 94-06 study (33). Dose-escalation by intraprostatic HDR-BT aims to deliver safe dosages to patients with acceptable toxicity and complications. To our knowledge, there are no published studies using EPIC-26 questionnaire to assess patient toxicity after 5 years for patients with high-risk Pca treated with HDR-BT/EBRT. We compared our results to the EBRT arm of the ProtecT study but statistical comparison cannot be done as the two cohorts are too different. This is among other factors due to age, T-stage (T3 versus T1), median PSA (20 versus 4.7) and duration of hormonal treatment. Median age in the ProtecT study was 62 years and 66 years in the HDR-BT/EBRT group respectively. Increasing age also effects sexual function (34). In the HDR-BT/EBRT group 90% of the patients received hormonal treatment for more than 1 year and 75% for at least 2 years compared to 3-6 months of neoadjuvant treatment in the ProtecT study. The length of hormonal treatment influences sexual function and is a major cause of impaired sexual function seen in our patients. In summary, our results show only moderate loss of function with little clinical relevant difference compared to the ProtecT cohort in the urinary and bowel domains measured by EPIC-26. Comprehensive results from our PM outcome study for the HDR-BT/EBRT cohort will be published in a separate article.

In our study of HDR-BT/EBRT compared to EBRT-only, competing risk analysis did not reveal any statistically significant difference between the two groups in the risk of dying from other causes than PCa, thereby supporting the persistent homogeneity of the patients included in the two cohorts. This is in agreement with Rajan et al who recently found that clinically

significant comorbidity influences OM but not PCSM (35). In our study, most patients had CCI 0-2, a group in whom active treatment is particularly beneficial (36).

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 (37,38). For men with Gleason score 8-10, cancer mortality rises significantly, as shown in our study. Even though not a 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 be 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 (39). 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 (40).

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. *Lack of data for biochemical relapse and distant metastasis for control group*: In the HDR-BT/EBRT there were a total of 22 patients who had biochemical relapse (including patients who died from Pca). Michalsky et al recently published findings that dose-escalation by EBRT

gave improvements to biochemical failure and distant metastasis but not on Overall Survival (41). Thus, an increase in PSA levels should pose little threat to longevity in many patients.

3. *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.

4. *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.

5. *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. However, published studies comparing ADT to Anti-Androgen Treatment show no clinical differences (42, 43). We have therefore assumed that despite the different types of hormonal treatment this does not disqualify for comparisons.

6. *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 end-points (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 ≤ 7 proved to be a strong predicator for PCSM in high-risk PCa. The patient-measured bowel and urinary scores after 5 years in the HDR-BT/EBRT cohort confirmed that this treatment is generally well tolerated. When compared against the EBRT arm of the ProtecT study there was no clinical relevant difference (< 10 points) for the summary score for the different domains.

Low sexual function score is a composite of long-term hormonal treatment, EBRT and age. Thus, dose-escalation by means of HDR-BT/EBRT in men with high-risk PCa seems to be a good treatment option in appropriately counselled and informed patients. The potential benefit on mortality seen in our study and the paucity of PM outcome in high-risk PCa warrants further studies, preferentially RCTs, comparing HDR-BT/EBRT to dose-escalated EBRT.

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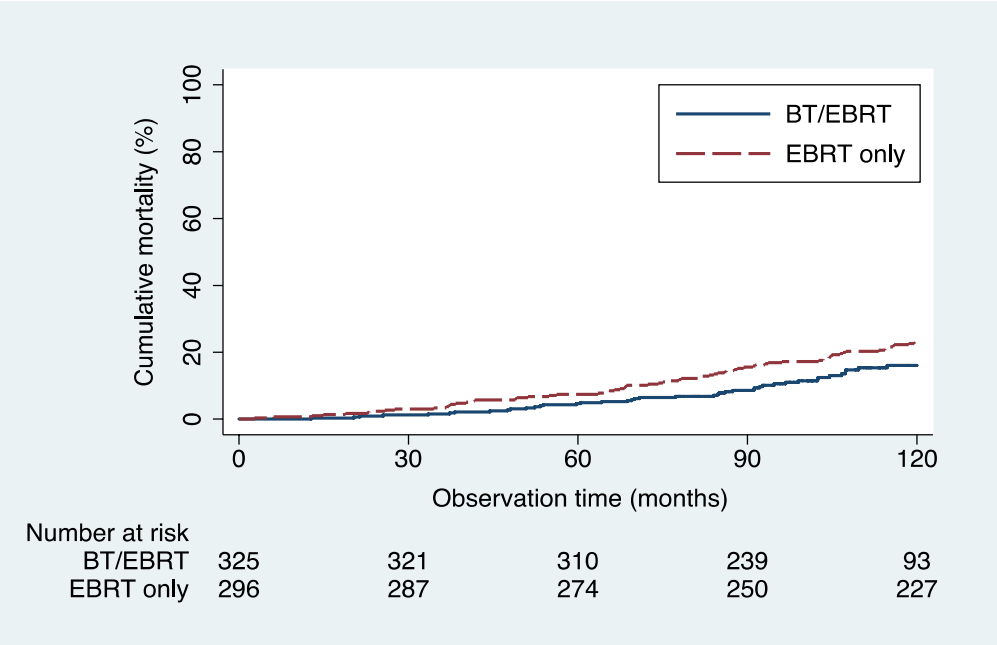
Figure Captions:

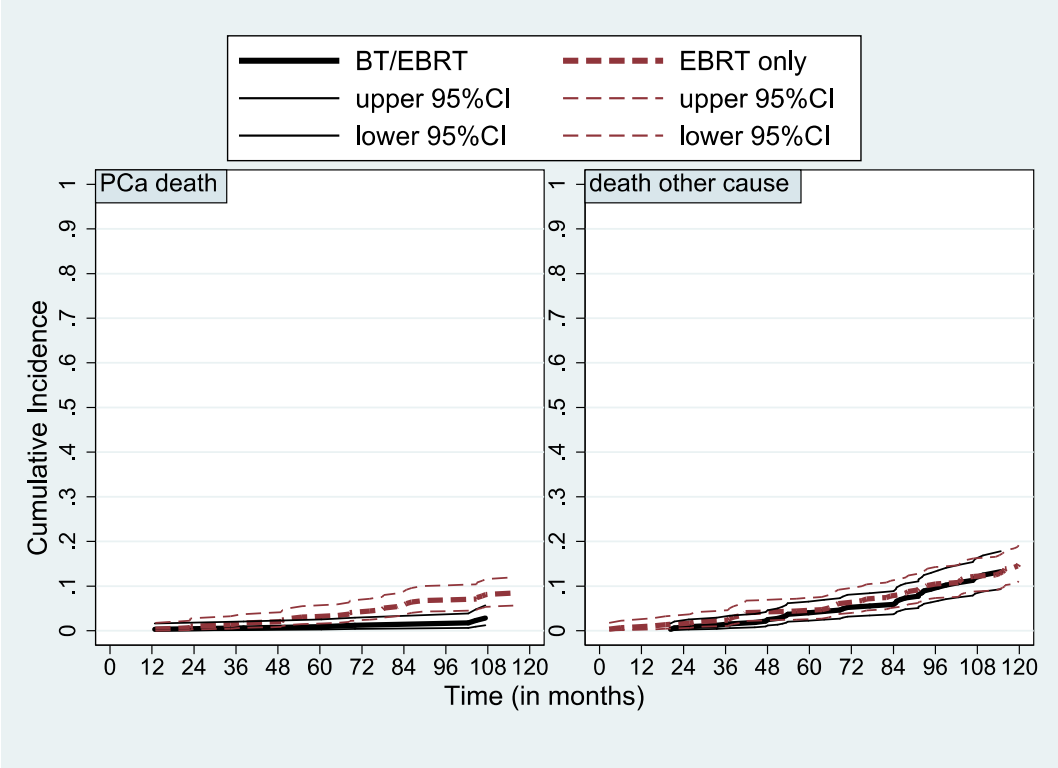
Figure 1: Kaplan-Meier plot Overall Mortality



Title: Kaplan-Meier plot Overall Mortality

Legend: 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.

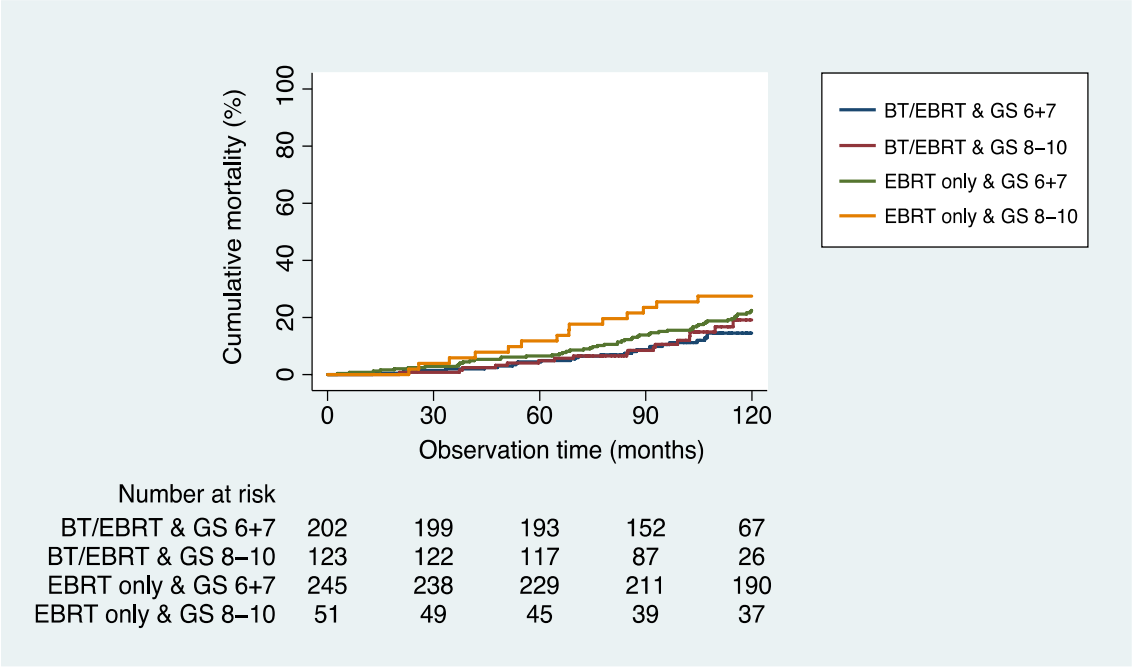
Figure 2:
A: cumulative incidences (competing risk regression PCSM), B: other causes



Title: A: cumulative incidences (competing risk regression PCSM), B: other causes

Legend: Fine and Grey competing risk regression curves for prostate cancer specific mortality (PCSM, graph A) and other causes (graph B).

Figure 3: Kaplan-Meier survival plots for Gleason score distribution for prostate-cancer specific survival



Title: Kaplan-Meier survival plots for Gleason score distribution for prostate-cancer specific survival

Legend: 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).

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%) 4 unknowns (1%) 54 radiological (17%)	208 pathological (70%) 88 unknown (30%) ‡‡ 0 radiological
Hormonal treatment duration		ADT 2 years	AAT life-long
ECOG status		0-1	0-1
Median radiation dosage (Gy)		EQD2 102* BED 170*	EQD2 70* BED 117*
Gleason score*	***6*** ***7*** ***8-10***	25 (8 %) 177 (54 %) 123 (38%)	50 (17%) 195 (66%) 51 (17%)
cT category*	***1*** ***2*** ***3***	26 (8%) 68 (21%) 231 (71%)	0 29 (10%) 267 (90%)
sPSA (ng/ml)	***0-10*** ***11-19.9*** ***≥20***	69 (21%) 99 (30.5%) 157 (48.5%)	88 (30%) 84 (28%) 124 (42%)
Median observation time, in months (min - max)		104 (13-120)	120 (3-120)
Cause of death*	***PCa*** ***Other cause*** ***Total***	7 (2%) 35 (11%) 42 (13%)	25 (8%) 44 (15%) 69 (23%)
PCSM‡‡‡ rate (95%CI)			
	5-year ***10-year***	1 % (0.3-2.2) 2.5 % (1.0-5.5)	3.1 % (2.5-5.8) 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**

Table 4: 5-year follow-up patient-measured toxicity measured by EPIC-26 questionnaire.

Variables	*HDR-BT/EBRT (102 Gy) (Mean (SD) Wedde et al 1 (ref)*	*EBRT (74 Gy) Mean (SD) Donovan et al ProtecT study*
Follow-up (months)	60	60
Patients included	323	545
Complete response to questionnaire (n)	259	455-473
Risk group (n)		
Low/Intermediate	30 (11.6%)	455 (97.4%)
High	229 (88.4%)	14 (2.6%)
Clinical T-stage (n)		
T1	24 (9.3%)	429 (78.7%)
T2	73 (28.2%)	116 (21.3%)
T3	162 (62.5%)	0
Gleason score (n)		
6	22 (8.5%)	423 (77.6%)
7	153 (59.1%)	108 (19.8%)
8-10	82 (31.7%)	14 (2.6%)
unknown	2 (0.7%)	0
PSA (median)	17	4.8
Length of hormonal treatment (n)		
>24 months	186 (71.8%)	0
12-24 months	35 (13.5%)	0
6-12 months	25 (9.7%)	0
3-6 months	0	*455 (83.5%)
None	1 (0.4%)	0
Unknown	12 (4.6%)	0
Urinary incontinence EPIC-26 score	89.0 (18.1)	89.4 (14.4) n=455 *p = 0.75*
Urinary irritation/obstruction EPIC-26 score	81.3 (19.6)	93.0 (8.3) n=469 *p < 0.001*
Urinary function EPIC-26 summary score	83.6 (18.0)	91.3 (9.6)** *p < 0.001*
Bowel function EPIC-26 score	86.7 (20.6)	90.3 (10.1) n=473 *p = 0.02*
Sexual function EPIC-26 score	27.9 (29.5) n=247	31.9 (24.8) n=463 *p = 0.06*

*Neoadjuvant Androgen Deprivation Therapy
**Summary score including urinary function and urinary bother