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Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial

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Abstract

Background: The cornerstone of standard treatment for patients with primary bone metastatic prostate cancer (mPCa) is androgen deprivation therapy (ADT). Retrospective studies suggest a survival benefit for treatment of the primary prostatic tumour in mPCa, but to date, no randomised-controlled-trials (RCTs) have been published addressing this issue.
Objective: To determine whether overall survival is prolonged by adding local treatment of the primary prostatic tumour with external beam radiation therapy (EBRT) to ADT.
Design, setting, and participants: The HORRAD trial is a multicentre RCT recruiting 432 patients with prostate-specific antigen (PSA) >20 ng/ml and primary bone mPCa on bone scan between 2004 and 2014.
Intervention: Patients were randomised to either ADT with EBRT (radiotherapy group) or ADT alone (control group).
Outcome measurements and statistical analysis: Primary endpoint was overall survival. Secondary endpoint was time to PSA progression. Crude and adjusted analyses were applied to evaluate treatment effect.
Results and limitations: Median PSA level was 142 ng/ml and 67% of patients had more than five osseous metastases. Median follow up was 47 mo. Median overall survival was 45 mo (95% confidence interval [CI], 40.4–49.6) in the radiotherapy group and 43 mo (95% CI: 32.6–53.4) in the control group ($p = 0.4$). No significant difference was found in overall survival (hazard ratio [HR]: 0.90; 95% CI: 0.70–1.14; $p = 0.4$). Median time to PSA

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progression in the radiotherapy group was 15 mo (95% CI: 11.8–18.2), compared with 12 mo (95% CI: 10.6–13.4) in the control group. The crude HR (0.78; 95% CI: 0.63–0.97) was statistically significant ($p = 0.02$).
Conclusions: The current RCT comparing ADT to ADT with EBRT to the prostate in patients with primary bone mPCa did not show a significant difference in overall survival, although the CI cannot exclude a substantial survival benefit. Further research is needed to confirm our findings.
Patient summary: This study investigated the effect of adding radiation therapy to the prostate to hormonal therapy in prostate cancer patients with metastasis to the bone at diagnosis. In our patient group, additional radiotherapy did not improve overall survival. Further research is needed to confirm our findings.
Twitter summary: Adding radiotherapy to the prostate in patients with bone metastatic prostate cancer does not improve overall survival.

1. Introduction

In western countries, prostate cancer (PCa) is the most common form of cancer among men of 50 yr and older, with a mortality-to-incidence ratio of 20% [1]. Worldwide, an estimated 1.1 million cases were diagnosed in 2012 [2]. Although the widespread use of prostate-specific antigen (PSA) testing has led to earlier detection of PCa, in 2015 still 16% of patients with PCa in The Netherlands presented with bone metastatic disease at first diagnosis. The current standard treatment for metastatic disease is systemic therapy with androgen deprivation therapy (ADT) that, at present, is frequently combined with docetaxel or abiraterone [3–5].

Treatment of the primary prostatic tumour is not standard practice in those with metastatic disease, although local therapy has been proven to prolong overall survival in other primary metastasised malignancies [6–9]. During the Advanced Prostate Cancer Consensus Conference 2017, however, 69% of panellists suggested that radical local treatment should be regarded as the appropriate type of treatment for patients with newly diagnosed oligometastatic prostate cancer [10]. In addition, 48% of panellists considered radical local treatment in men with de novo asymptomatic high-volume metastatic prostate cancer. To date, no randomised controlled trials (RCTs) have been published to address the potential benefits of simultaneous local treatment of the prostate complementary to ADT.

The current RCT was based on the hypothesis that in patients with primary bone metastatic PCa (mPCa), the oncological outcome might be improved by administrating radical radiotherapy (RT) to the primary tumour in addition to standard ADT. The HORRAD trial is a multicentre prospective RCT that studies the efficacy of external beam radiation therapy (EBRT) to the prostate in addition to standard ADT in patients with mPCa, with overall survival as the primary outcome.

2. Materials and methods

2.1. Trial design and participants

The HORRAD trial is a multicentre prospective RCT. Patients were recruited in 28 centres across The Netherlands. Patients were eligible if they had a previously untreated, histologically confirmed diagnosis of adenocarcinoma of the prostate with any number of bone metastases on bone scintigraphy. Tumours could be of any grade (Gleason score 6–10) and T stage (cT1-cT4; cN0-cN1; M1) [11].

Exclusion criteria were age >80 yr; PSA <20 ng/ml; previous treatment for prostate cancer; insufficient cognitive ability to understand the study or questionnaires; and concurrent malignancies, except for basal cell carcinoma of the skin. Patients needed to be randomised within 8 wk after diagnosis.

The HORRAD trial was performed in accordance with the Declaration of Helsinki, and the results are reported according to the CONSORT statement [12]. The trial protocol was approved by the local medical ethical review boards. All patients provided written informed consent. This trial was registered as ISRCTN06890529.

2.2. Randomisation

Randomisation was done centrally by an independent trial office (CuraTrial). Patients were assigned in a 1:1 ratio by using a restricted blockwise randomisation (block size 6 = 2 treatments × 3 patients per treatment). No stratification was performed. All patients and investigators were aware of study group assignments.

2.3. Intervention

Patients were randomly assigned to EBRT of the prostate combined with ADT (RT group) or ADT alone (control group). ADT in both groups consisted of an androgen receptor inhibitor (eg, bicalutamide, 50 mg once daily) for 4 wk as flare reduction and concurrent treatment with a luteinising hormone-releasing-hormone (LHRH) agonist. All patients started with an LHRH agonist 1–2 wk after randomisation. LHRH agonists were continued until death. In case of disease progression, further treatment was at the discretion of the treating clinician.

Within 3 mo of starting ADT, patients in the RT group commenced EBRT. The initial prescribed dose was 70 Gy in 35 fractions of 2 Gy, during an overall treatment time of 7 wk. During the study period, an optional schedule was added that was considered biologically equivalent and consisted of a dose schedule of 57.76 Gy in 19 fractions of 3.04 Gy, three times a week for 6 wk.

A computed tomography (CT) scan was performed to provide an accurate delineation of the prostate. Preferably, intensity-modulated radiation therapy was used for planning, but three-dimensional conformal RT was allowed. The clinical target volume (CTV) included the prostate with any apparent extraprostatic tumour extensions, including the base of the seminal vesicles. The planning target volume was the CTV including a 1-cm margin in all directions by using conventional RT. If a position verification protocol with implanted fiducial gold markers was used, the margin could be reduced to 8 mm. The pelvic lymph nodes were not included in the target area.

2.4. Data collection

All patient data were collected in a comprehensive database. Data collection was performed by an independent research centre (CuraTrial). Data were registered at baseline and thereafter once every 3 mo until death. At baseline, patient demographics were registered, as were World Health Organisation (WHO) performance status, comorbidity, WHO pain score, serum PSA level, alkaline phosphatase, and lactate dehydrogenase. The numbers of osseous metastases on bone scintigraphy were subdivided into three categories: <5 lesions, 5–15 lesions, and >15 lesions. Tumour characteristics were recorded. On follow-up, serum PSA, WHO performance status, WHO pain score, and adjuvant treatments were registered.

Two quality-of-life (QoL) questionnaires were administered at baseline and after 3, 6, 12, and 24 mo [13,14]. The questionnaires used were the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core Module (QLQ-C30) version 3.0 and the EORTC Quality-of-Life Questionnaire Prostate Module (QLQ-PR25). Results of the QoL analyses will be published elsewhere.

2.5. Primary and secondary study endpoints

The primary outcome of the HORRAD trial was overall survival, defined as time between date of diagnosis at prostatic biopsy and date of death. Secondary oncological endpoint was time to PSA progression, defined as time between diagnosis and a PSA increase after initiation of ADT of more than 50% of the lowest PSA value after start of treatment (PSA-nadir), with a minimum of 1 ng/ml. As serum testosterone levels were not assessed accordingly, PSA progression was only an indication for castration-resistant disease.

2.6. Statistical analyses

Calculation of the required sample size was carried out based on the assumption that a combination of ADT and EBRT will prolong median survival by 10 mo. When starting this trial in 2004, the median survival of patients with primary osseous metastases treated with ADT was 28 mo [15]. To detect the hypothesised difference with $\alpha = 0.05$ and a power of 0.80, 250 patients were needed in each study arm. In 2011, a planned interim analysis by an independent data management safety board was performed, leading to an adjustment of the sample size to 425 patients in total. Anticipating 5% violation of inclusion criteria, 446 patients were assessed for eligibility.

Intention-to-treat analysis was performed for all eligible randomised patients, including patients with a protocol violation.

We calculated Kaplan-Meier curves with time to mortality and time to PSA progression as outcomes and used log rank tests to compare curves between treatment arms. For mortality and PSA progression, Cox proportional hazard regression analyses were applied to evaluate the treatment effect, both crude and adjusted, for several covariates: age at diagnosis, performance status, initial pain score, initial PSA, number of bone metastases (<5 lesions, 5–15 lesions, >15 lesions), Gleason sum score (≤7, 8, ≥9), and T stage (cT1-cT3).

To determine whether the treatment effect differed between subgroups, the interaction of treatment and the subgroup-defining covariate was tested using the Cox regression model, including treatment and the covariate as main effects in the Cox model. We evaluated the proportional hazards assumption first by examining the Kaplan-Meier curve and second by performing a Cox regression analysis with a time-dependent covariate.

Analyses were performed with SPSS 22.0 (IBM, Armonk, NY, USA). All tests were two sided, and a significance level of 0.05 was used.

3. Results

3.1. Patients characteristics

Between November 2004 and September 2014, 446 patients diagnosed with mPCa were assessed for eligibility in 28 participating centres. Six patients were excluded because of either a second malignancy ($n = 2$), absence of osseous metastases ($n = 2$), or unknown screening failure ($n = 2$). Eight patients declined to participate, despite having previously given informed consent. The remaining 432 patients were randomly assigned to either ADT with EBRT (RT group, $n = 216$) or ADT alone (control group, $n = 216$). The patient inclusion and exclusion diagram is depicted in Figure 1.

There were some protocol violations. Three patients >80 yr old were accepted. Twenty-five patients had an untreated PSA <20 ng/ml, but they all had osseous metastases on bone scintigraphy.

Patient and tumour characteristics are summarised in Table 1. Clinical characteristics were well balanced between treatment groups. The salvage treatments patients received were also similar (Table 2).

3.2. Follow-up

At the time of final analysis, the median duration of follow-up for all patients alive was 47 mo (interquartile range, 36–68). Of the 216 patients in the RT group, 131 had died and 157patients demonstrated progression of their PSA level. In the control group, 139 of the 216 patients had died and 175 patients had PSA progression.

3.3. Endpoints

3.3.1. Overall survival

Median overall survival was 45 mo (95% CI: 40.4–49.6) in the RT group and 43 mo (95% CI: 32.6–53.4) in the control group: the difference of the median survival is 2 mo (95% CI:–9.2 to +13.2). A Kaplan-Meier plot comparing overall survival is shown in Figure 2 (log rank test, $p = 0.4$). The Cox proportional hazards regression analyses showed no significant difference in overall survival between randomisation arms for crude (HR: 0.90; 95% CI: 0.70–1.14) or adjusted (HR: 1.11, 95% CI: 0.87–1.43; $p = 0.4$).

Excluding the three patients over 80 yr of age and the 25 patients with untreated PSA <20 ng/ml, we found essentially the same HRs.

Additional analyses did not indicate that the treatment effect varied significantly over the follow-up period, and none of the interactions were statistically significant. A forest plot of the HRs based on different subgroups is depicted in Figure 3.

3.3.2. PSA recurrence-free survival

The median time to PSA progression in the RT group was 15 mo (95% CI: 11.8–18.2) compared with 12 mo (95% CI: 10.6–13.4) in the control group. The Kaplan-Meier curves differed significantly from each other (log rank test,

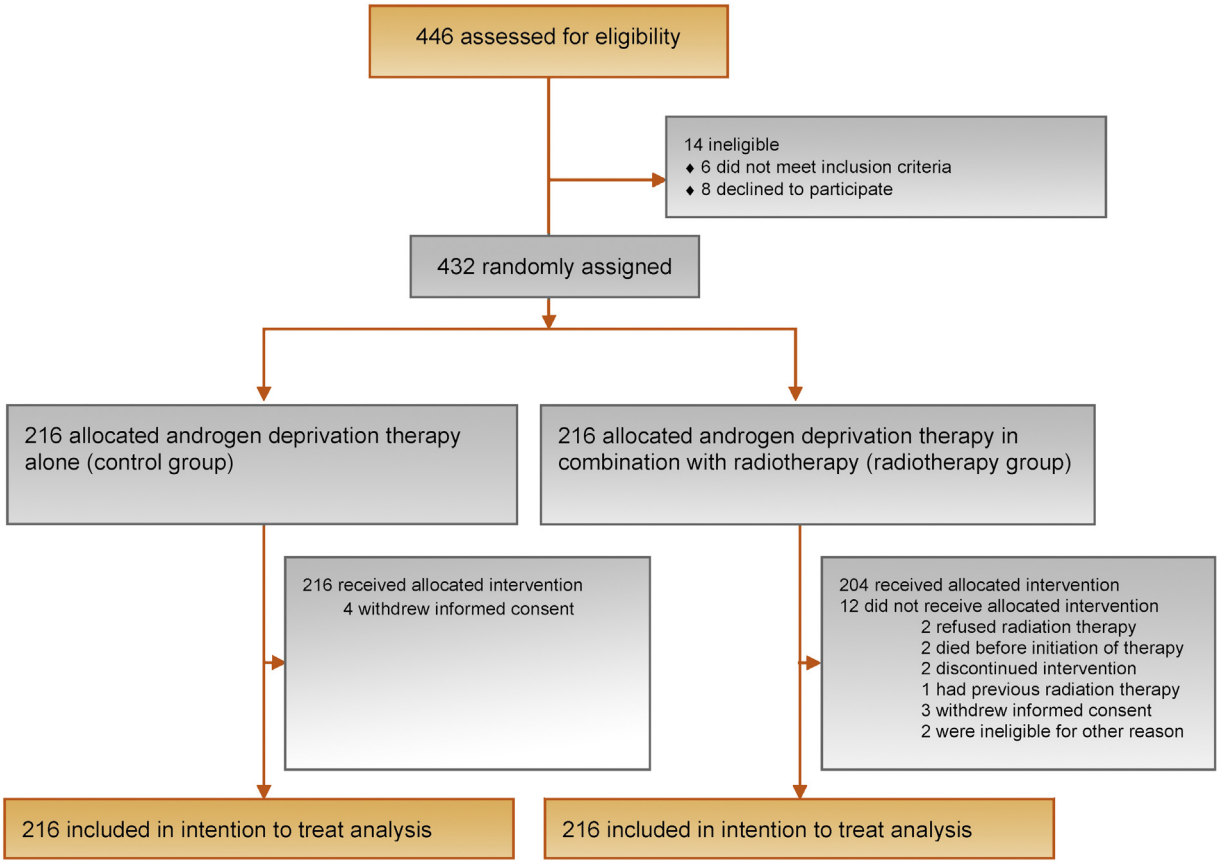

Fig. 1 – Trial profile.

$p = 0.02$; Fig. 4). Also, the crude HR of 0.78 (95% CI: 0.63–0.97) was statistically significant. After adjustment, the HR was slightly reduced and was no longer significant (HR: 0.86, 95% CI: 0.69–1.08; $p = 0.20$).

4. Discussion

This is the first RCT in patients with mPCa evaluating local treatment of the primary tumour along with ADT compared to ADT alone, with overall survival as the primary endpoint. No overall survival benefit was shown for concurrent local treatment after a median follow-up time of 47 mo. Median overall survival was 45 mo (95% CI: 40.4–49.6) in the RT group and 43 mo (95% CI: 32.6–53.4) in the control group ($p = 0.4$).

The results of our RCT differ from those in the recent literature, where various nonrandomised studies and patient cohort studies using national databases retrospectively evaluated the outcome of local treatment along ADT in patients with different extensiveness of mPCa [16–21]. In those studies, primary therapy consisted of either brachytherapy, RT, or radical prostatectomy (RP). Leyh-Bannurah et al. [20] performed a propensity score matched analysis on 13 692 patients with mPCa from the Surveillance Epidemiology and End Results (SEER) database, of whom 313 underwent RP and 161 received brachytherapy. The researchers found that both RP and brachytherapy yielded lower cancer-specific mortality rates when combined with ADT than when local treatment was not given. The other reports stated similar outcomes [16–19,21].

In these retrospective studies, however, despite careful statistical modelling, pervasive selection bias towards healthier patients with lower tumour burden is still likely a meaningful source of confounding. This confounding effect is especially likely as patients treated locally represent a very small percentage of the entire cohort in these reports.

Data from several studies suggested that patients with metastatic disease derive most benefit from local treatment when having more favourable tumour characteristics [16–18,20,22,23]. Löppenberg et al. [18] reported from the National Cancer Database and included 15 501 patients with M1a-c mPCa. Of these patients, 1470 underwent local treatment (brachytherapy, EBRT, or RP). The researchers used predictors from a multivariable Cox regression analysis to predict overall mortality risk and found that the benefit of local treatment on mortality decreased progressively as the predicted overall mortality risk increased. They concluded that patients with a relatively low tumour burden and a good general health status appeared to benefit most.

Pompe et al. [23] recently published an update on the data of the SEER database that gave more insight in the

Table 1 – Baseline clinical and tumour characteristics of patients with bone metastatic prostate cancer randomised to androgen deprivation therapy with or without external beam radiotherapy of the prostate

	ADT + radiotherapy (n = 216)[a]	ADT alone (n = 216)[a]
Age (range), yr.	67 (62–71)	67 (61–71)
PSA concentration at start of ADT, ng/ml		
Median (range).	125 (8–14 000)	149 (4–6991)
Q1	48	50
Q3	433	483
Missing data	3 (1)	5 (2)
ALP		
≤ULN	133 (61)	141 (65)
>ULN	51 (24)	54 (25)
Missing data	32 (15)	21 (10)
LDH		
≤ULN	92 (43)	95 (44)
>ULN	65 (30)	69 (32)
Missing data	59 (27)	52 (24)
Gleason sum score[b]		
6	7 (3)	7 (3)
7	66 (31)	64 (30)
8	48 (22)	65 (30)
9	85 (39)	72 (33)
10	9 (4)	7 (3)
Missing data	1 (1)	1 (1)
T stage		
1	7 (3)	5 (3)
2	33 (15)	20 (9)
3	125 (58)	128 (59)
4	51 (24)	59 (27)
Missing data	0	4 (2)
Osseous metastases		
<5 lesions	89 (41)	71 (33)
5–15	53 (25)	65 (30)
>15	74 (34)	80 (37)
WHO performance status[c]		
0	187 (87)	176 (82)
1	22 (10)	31 (14)
2	4 (2)	6 (3)
3	3 (1)	3 (1)
Pain score[d]		
0	140 (65)	139 (65)
1	39 (18)	34 (16)
2	18 (8)	18 (8)
3	3 (1)	3 (1)
4	16 (8)	22 (10)

ADT = androgen deprivation therapy; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; Q = quartile; ULN = upper limit of the normal; WHO = World Health Organisation.
[a] Data are median (interquartile range [IQR]) and number of patients (%), unless otherwise stated. Q1 and Q3 are the lower and upper bounds of IQR, respectively. The ULN value of ALP is 115 IU/l and the ULN of LDH is 248 IU/l.
[b] Gleason scores range from 2 to 10, with higher scores indicating more aggressive disease, less differentiated tumour, and worse prognosis.
[c] WHO performance status: 0 = asymptomatic; 1 = symptomatic but completely ambulatory; 2 = symptomatic <50% in bed during the day; 3 = symptomatic >50% in bed but not bedbound; 4 = bedbound.
[d] Pain score: 0 = no pain; 1 = pain occasionally requiring non-narcotics' 2 = pain regularly requiring non-narcotics; 3 = pain occasionally requiring narcotics; 4 = pain regularly requiring narcotics.

Table 2 – Subsequent treatments in deceased patients (intention-to-treat population)

	ADT + radiotherapy (n = 131)[a]	ADT alone (n = 139)[a]
Time (range) to initiation of subsequent therapy, mo.	17 (12–25)	14 (10–30)
Any anticancer therapy	64 (49)	66 (48)
Missing data	2 (1)	2 (1)
Docetaxel	60 (46)	58 (42)
Cabazitaxel	12 (9)	9 (7)
Enzalutamide	11 (8)	18 (13)
Abiraterone	23 (18)	23 (17)
Other systemic treatment	13 (10)	8 (6)
Estracyt	2	2
Mitoxantrone	3	2
Orteronel	2	2
Carboplatin	2	0
Denosumab	1	0
Ipilimumab	0	1
Cabozantinib	0	1
Cisplatinum	1	0
Olaparib	1	0
Pembrolizumab	1	0
RA^{223}	4 (3)	4 (3)

ADT = androgen deprivation therapy; RA^{223} = radium-223.
[a] Data are median (interquartile range) and number of patients (%), unless otherwise stated.

influence of M1 substages and baseline PSA levels on the effect of local treatment in mPCa. They performed multivariable competing risk regression analyses after 1:2 propensity score matching and found a significant benefit for local treatment in M1a patients. In M1b patients, survival benefit was modulated by baseline PSA, where no improvement of cancer-specific survival was observed for M1b patients that underwent local treatment with a baseline PSA >60 ng/ml. Patients with M1c disease did not demonstrate a cancer-specific survival benefit, regardless of baseline PSA. We included the cut-off point of 60 ng/ml in our covariate analyses, but we did not find any differences between our treatment groups.

Although many recent retrospective studies indicate a beneficial effect of local treatment in patients with low metastatic burden, this was not found in every study. Steuber et al. [24] reported in a prospective case-control study of 83 patients that those with low-volume bone metastases and beneficial baseline characteristics undergoing RP did not have better overall survival than patients receiving best systemic therapy (p = 0.3). However, this study included only a small number of patients.

It remains to be established whether long-term outcome would be altered if a different type of local treatment was administered. Leyh-Bannurah et al. [20] compared RT with RP in patients with mPCa and concluded that patients gain most benefit from RP. It is important to consider that in their SEER database it was only possible to select patients who underwent brachytherapy, since there was a lack of EBRT organ site–specific codes. Therefore, the type of local treatment could not be determined in all cases, withholding us from drawing definite conclusions from this study.

There are some limitations of the present RCT. First, the protocol was developed more than a decade ago, and treatment techniques and doses have evolved. For instance, the applied radiation dose in the presented trial (70 Gy) is lower than that currently applied for localised prostate

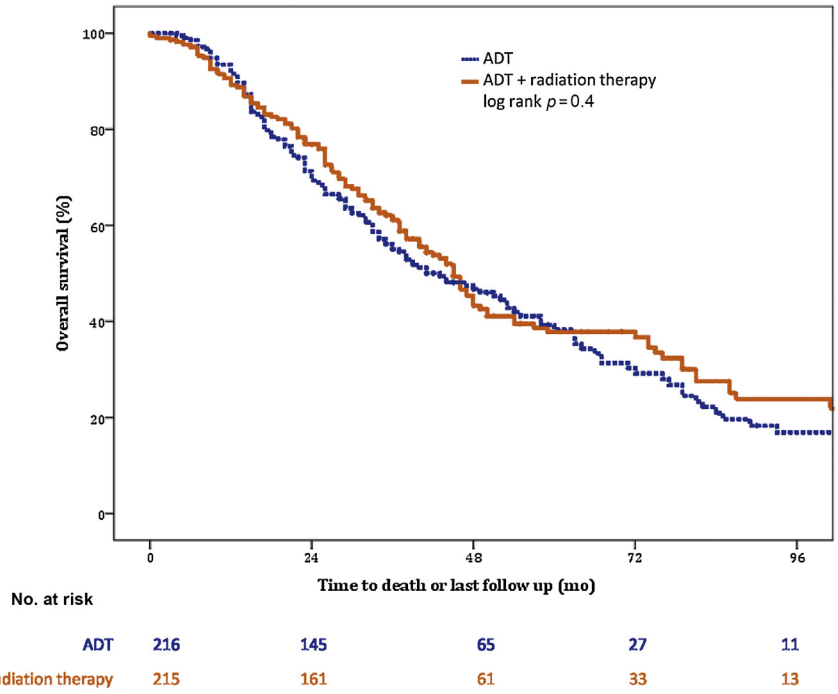

Fig. 2 – Kaplan-Meier estimates of overall survival (intention to treat).
ADT = androgen deprivation therapy.

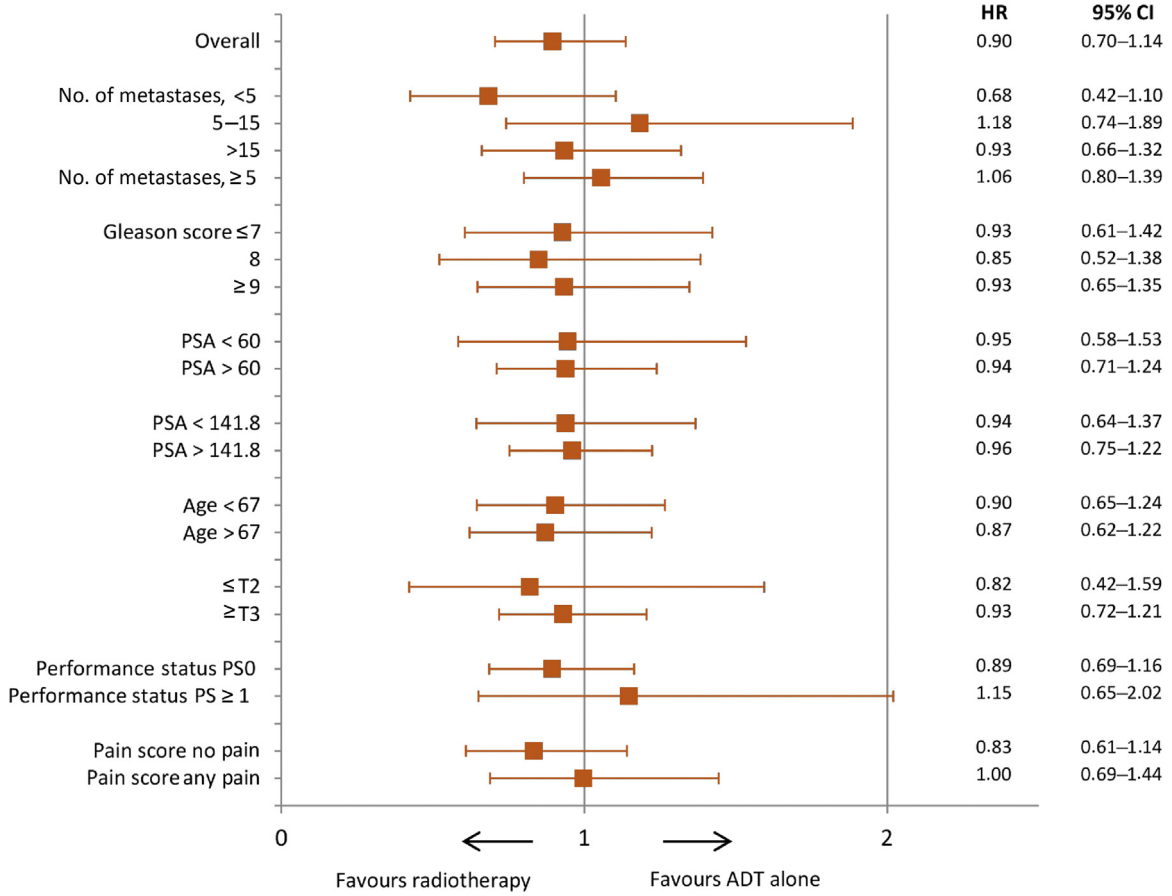

Fig. 3 – Forest plot of the crude HRs with 95% CIs based on different covariates.[a]
ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
[a] None of the subgroups defined by the different covariates showed a significant difference in hazard ratio ($p > 0.05$).

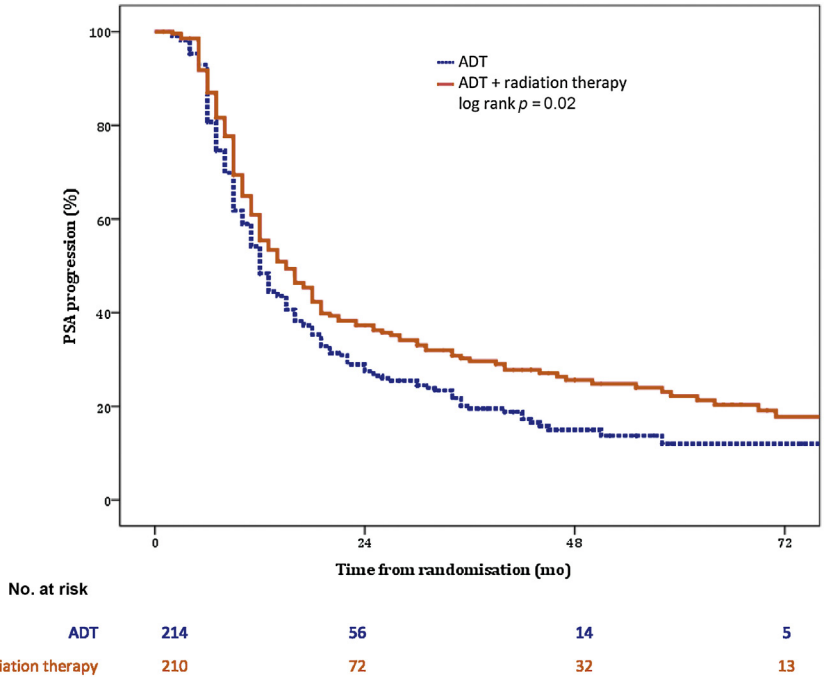

Fig. 4 – Kaplan-Meier time to PSA progression (intention to treat).
ADT = androgen deprivation therapy; PSA = prostate-specific antigen.

cancer (78–81 Gy), based on several randomised dose-escalating studies demonstrating an improved biochemical failure-free survival with higher doses [25]. However, overall survival was not improved with dose escalation; thus, it is not likely that higher doses would have affected our primary endpoint.

Second, we did not perform stratification in randomising patients. Also, in our patient series with bone mPCa, we were not informed on the presence of visceral metastases or of the extent of regional or distant lymph node metastatic disease, both of which might have affected our outcomes.

Furthermore, combined and adjuvant hormonal or chemotherapeutic treatments both in primary hormone-naïve mPCa and in castration-resistant disease have shown a substantial improvement in the survival of patients with mPCa [4,5,26–28]. This suggests that the outcome in our patients may have been influenced by the kind and timing of the systemic treatments that they received. However, patients in both groups received comparable rates of adjuvant treatments, but small differences in timing of these secondary treatments still potentially exist.

Based on the results of the current trial, treatment of the primary tumour is not recommended in patients with bone mPCa. The results of our trial do not rule out a possible benefit of treating the primary prostatic tumour in the current era where upfront systemic therapy is added to ADT in patients with metastatic disease, nor when treatment would be combined with salvage brachyradiotherapy. In patients with primary mPCa, especially those with high metastatic burden, it has been established that adjuvant systemic therapy achieves significantly higher rates of overall survival than ADT alone [5]. Certainly, the definition of high- (or low-) risk disease or disease with high (or low) metastatic potential remains to be established. Nowadays, the staging of patients with PCa increasingly relies on new imaging modalities such as prostate-specific membrane antigen positron-emission-tomography/CT scans [29]. It is assumed that using these modern imaging modalities, metastases and oligometastases will be detected earlier and more frequently than with previous imaging techniques. It is a question of further debate how the findings of these new imaging modalities relate to those of our RCT, in which staging was performed by bone scintigraphy only.

Considering the outcomes of the current trial and the retrospective literature, local treatment of the prostate in patients with primary bone mPCa should not be performed outside clinical trials. Future trials should evaluate the impact of local treatment in patients with oligometastatic disease and by use of modern imaging modalities.

5. Conclusions

The current randomised trial comparing ADT to ADT with EBRT to the prostate in patients with primary mPCa showed no significant difference in overall survival, although the CI cannot exclude a substantial survival benefit. Further research is needed to confirm our findings.

Author contributions: Liselotte M.S. Boevé had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hulshof, Zwinderman, Witjes, Verhagen, van Andel.

Acquisition of data: Boevé, Hulshof, Witjes, Delaere, van Moorselaar, Verhagen, van Andel.
Analysis and interpretation of data: Boevé, Zwinderman, Twisk.
Drafting of the manuscript: Boevé.
Critical revision of the manuscript for important intellectual content: Boevé, Hulshof, Vis, Zwinderman, Twisk, Witjes, Delaere,. van Moorselaar, Verhagen, van Andel.
Statistical analysis: Boevé, Zwinderman, Twisk.
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Supervision: van Andel.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.008.

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