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Original Article

Prostate Cancer–related Events in Patients with Synchronous Metastatic Hormone-sensitive Prostate Cancer Treated with Androgen Deprivation Therapy with and Without Concurrent Radiation Therapy to the Prostate; Data from the HORRAD Trial

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Abstract

Background and objective: A survival benefit was demonstrated for patients with low-volume synchronous metastatic hormone-sensitive prostate cancer (mHSPCa) when local radiotherapy to the prostate was added to androgen deprivation therapy. This study aims to determine the incidence of prostate cancer–related events and treatments in those who received and those who did not receive external beam radiotherapy for mHSPCa.

Methods: The HORRAD trial is a multicentre randomised controlled trial recruiting originally 432 patients with mHSPCa diagnosed between 2004 and 2014. In a second updated analysis, 328 patients were studied retrospectively for local and nonlocal prostate cancer–related events and treatments. Outcome measurements included the incidence and treatment of local (bladder outlet or ureter obstruction, catheterisation, surgical intervention, ureteric stents, and nephrostomy tubes) and nonlocal (blood transfusions, hospitalisations, and treatment for painful bone metastases) events. Differences between groups were compared using crude and adjusted logistic regression, while time to occurrence of local events was assessed with Kaplan-Meier curves and Cox regression analysis.

Key findings and limitations: A significant difference in the incidence of local events was observed: 30 events in the radiotherapy group versus 50 in the nonradiotherapy group ($p = 0.04$). Time to occurrence of local interventions was significantly longer in the radiotherapy group (hazard ratio 0.61, 95% confidence interval 0.37–0.99, $p = 0.04$). The study's limitations include its retrospective nature.

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Conclusions and clinical implications: Local radiotherapy to the prostate prolongs local event–free survival significantly and reduces local prostate cancer–related interventions in patients with mHSPCa.

ADVANCING PRACTICE

What does this study add?
This study demonstrates that adding local radiotherapy to androgen deprivation therapy reduces the incidence of local prostate cancer–related events significantly and prolongs the time to local interventions in patients with synchronous metastatic hormone-sensitive prostate cancer. These findings provide a new rationale for considering local radiotherapy in these patients.

Clinical Relevance
The combination of radiation therapy to the prostate and androgen deprivation therapy offers potential benefits for patients with synchronous metastatic hormone-sensitive prostate cancer. This updated analysis from the HORRAD trial reveals that local radiation therapy does not significantly improve overall survival in unselected patients, but does reduce the occurrence of adverse events caused by local prostate cancer progression, such as bladder outlet obstruction and hydronephrosis, while delaying the need for related interventions. These findings highlight the role of radiation therapy in enhancing local disease control. When considered alongside recent evidence from other randomized controlled trials, like STAMPEDE and PEACE-1, they support the inclusion of radiation therapy to the prostate as a standard treatment option for select patients with metastatic hormone-sensitive disease. Further research is awaited to confirm whether these favourable data also apply to the contemporary paradigms of hormone treatment intensification and molecular staging. Associate Editor Gianluca Giannarini MD.

Patient Summary
Administrating radiotherapy to the prostate in unselected patients with newly diagnosed metastatic prostate cancer does not influence their overall survival, but prevents and delays the occurrence of obstructive prostate cancer–related local symptoms.

1. Introduction

The treatment of patients with synchronous metastatic hormone-sensitive prostate cancer (mHSPCa) has changed over the past decade. When the HORRAD trial was initiated in 2004, standard treatment for patients with mHSPCa consisted of androgen deprivation therapy (ADT) only. Following the publication of the survival data from the HORRAD study, the STAMPEDE trial, and a concurrent meta-analysis of both trials, external beam radiation therapy (EBRT) was advised to patients with low-volume mHSPCa in extension to ADT. Subsequently, the European Association of Urology prostate cancer guidelines were altered [1–4]. For the definition of low-volume metastatic disease, the CHAARTED criteria were used. According to these criteria, low-volume disease was defined as the absence of high-volume disease, that is, four or more bone metastases including one or more outside the vertebral column or pelvis and/or visceral metastasis [5].

One of the secondary endpoints of the HORRAD trial was the effect of radiotherapy (RT) on the health-related quality of life (HRQoL) of patients treated for mHSPCa compared with the HRQoL of those who did not receive EBRT. An analysis of two validated HRQoL questionnaires showed that patients in the RT arm reported only a temporary modest increase in urinary and bowel symptoms after combined treatment [6]. In some patients, deterioration of bowel functions persisted after 2 yr. An analysis of patients' quality of life in the STAMPEDE study showed similar results [7].

The sequelae of local RT to the prostate on the incidence of events caused by local disease progression have been investigated only scarcely.

The objective of the present report is to compare the incidence of local prostate cancer–associated events and concurrent treatment within the two arms of the HORRAD trial. In addition, the nonlocal events and treatments related to prostate cancer progression are counted. For this, a second retrospective analysis was performed in which patient data and follow-up were updated. Furthermore, we will present the final analysis of overall survival (OS) in this study.

2. Patients and methods

2.1. Trial design and participants

The primary objective of the HORRAD study was to assess whether the combination of localised RT to the prostate

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with standard ADT extends OS in comparison with standard ADT alone in patients presenting with bone-metastatic mHSPCa [1]. A secondary endpoint involved the assessment of HRQoL based on patient-reported outcomes [6].

Participants in the HORRAD trial were patients diagnosed with previously untreated adenocarcinoma of the prostate, confirmed histologically and exhibiting bone metastases as detected by a bone scan (M1b). More details on the study design of the HORRAD trial can be found in previous publications [1,6].

The study protocol received approval from the ethical review board at each participating centre, and all patients provided written informed consent.

2.2. Intervention

Patients were assigned randomly to one of two groups: the RT group, receiving EBRT of the prostate in combination with ADT, or the non-RT group, receiving ADT alone. In the event of disease progression, subsequent treatment decisions were left to the discretion of the treating physician, as per the current standard of care.

Patients assigned to the RT group commenced RT to the prostate within 3 mo of initiating ADT. The dose administered was a biological equivalent to 70 Gy, applied in 35 daily fractions of 2 Gy. The details of the radiotherapeutic schemes are listed in the initial HORRAD paper [1].

2.3. Data collection

All patient data were stored into a comprehensive database, with baseline characteristics documented prospectively for all participants in the randomised controlled trial. In a second analysis conducted between 2022 and 2023, records of randomised patients were retrospectively retrieved from all participating hospitals and studied.

In this second analysis, additional data were collected with regard to disease progression and survival, successive life-extending treatments, and the incidence of local and nonlocal symptoms and treatments associated with prostate cancer progression.

2.4. Secondary analysis of study endpoints

Local events due to local progression of the prostate tumour are defined as either bladder outlet obstruction requiring temporary or permanent catheterisation or transurethral resection of the prostate (TURP), or obstruction of the ureters causing hydronephrosis requiring ureteral stent (JJ) placement or nephrostomy tubes, occurring after a minimum of 3 mo from the start of therapy with either RT (RT group) or ADT (non-RT group).

Nonlocal events due to progression of metastases are defined as symptoms related to bone metastases (pain, fractures, or spinal cord injury) requiring EBRT on metastases, surgical intervention or hospital admission for pain relief, or anaemia requiring blood transfusion.

Time to occurrence of local events was defined as the time between the date of start of therapy to the date of intervention. Patients were censored when an event did not occur at the time of last contact.

The primary outcome of the HORRAD trial was OS, defined as the time between the date of diagnosis at prostatic biopsy to the date of death. This report will give an update on this primary endpoint.

2.5. Statistical analyses

Time-to-event and time-to-mortality outcomes were compared between treatment arms with Kaplan-Meier curves and log-rank tests. Both crude and adjusted Cox regression analyses were used to obtain effect estimates with 95% confidence intervals (CIs). For all analyses, adjustments were made for the number of bone metastases (fewer than five lesions and five of more lesions), Gleason sum score (<8 and ≥8), and T stage (cT1, T2, T3, or T4). All analyses were performed according to the intention to treat, and additionally per-protocol analyses were performed.

Analyses were conducted with SPSS statistical software version 29 (IBM, Armonk, NY, USA). All tests were two sided, and a significance level of 0.05 was used.

3. Results

3.1. Patients

Between November 2004 and September 2014, 432 patients with synchronous mHSPCa from 28 participating hospitals were assigned randomly to ADT in combination with EBRT of the prostate (RT group) or to ADT alone (non-RT group). A detailed outline of the randomisation and baseline characteristics of participants within the larger trial has been published previously [1]. In the current second updated analysis, the follow-up data of 328 patients could be obtained.

Five patients allocated to the RT arm of the HORRAD trial did not undergo local treatment due to various reasons, described earlier [1]. One patient in the RT cohort discontinued therapy after one session because a secondary brain tumour was found. In the per-protocol analysis, therefore, six patients in the RT arm were allocated to the ADT-alone arm. None of the patients allocated to ADT alone received primary EBRT.

Patient and basic tumour characteristics are summarised in Table 1. The median follow-up time for patients who are still alive (66/328) is 75 mo (interquartile range [IQR] 63–109). The median follow-up time for patients without a local event (248/328) is 43 mo (IQR 18–68). Most patients had a high-volume metastatic disease burden. The overall median prostate-specific antigen level was 149 ng/ml (54–473 ng/ml), and 215 patients (66%) had five or more bone metastases on staging bone scintigraphy.

3.2. Prostate cancer–related events and treatment

3.2.1. Local prostate cancer–related events and treatments

In the intention-to-treat analysis, not only fewer patients in the RT arm experienced symptoms and treatment of local events (30 vs 50 events), but also the time to occurrence of the local events is significantly longer in the group that received RT than in those who did not receive RT (hazard ratio [HR] 0.56, 95% CI 0.35–0.88, p = 0.01; Tables 2 and 3,

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Table 1 – Baseline clinical and tumour characteristics of patients with synchronous bone metastatic hormone-sensitive prostate cancer randomised to androgen deprivation therapy (ADT) with or without external beam radiotherapy of the prostate

	ADT + radiotherapy (*N* = 163)	ADT alone, nonradiotherapy (*N* = 165)
Age (yr), median (IQR).	67 (62–71)	67 (62–72)
Follow-up (mo), median (IQR)	46 (23–72)	39 (21–69)
PSA at start of ADT (ng/ml), median (IQR).	145 (54–450)	150 (50–501)
Gleason sum score, *n* (%)		
6–7.	49 (30)	55 (33)
8	35 (21)	51 (31)
9–10	78 (48)	58 (35)
Missing data	1 (1)	1 (1)
T stage, *n* (%)		
T1–2.	27 (17)	20 (12)
T3–4.	136 (83)	143 (87)
Missing data.	0.	2 (1)
Osseous metastases, *n* (%)		
<5 lesions.	65 (40)	48 (29)
5–10. lesions	41 (25)	52 (32)
>15. lesions	57 (35)	65 (39).
Any second-line systemic treatment, *n* (%)	86 (53)	95 (57)
Type of second-line systemic treatment, *n* (%)		
Docetaxel	67 (43)	56 (34)
Abiraterone	34 (22)	38 (24)
Enzalutamide	33 (21)	27 (16)
Cabazitaxel	15 (10)	13 (8)
Radium-223	14 (9)	13 (8)
Any other second-line systemic treatment	17 (10)	7 (4)

IQR =interquartile range; PSA = prostate-specific antigen.
Any other second-line systemic therapy included treatment with Estracyt, mitoxantrone, orteronel, cabozantinib, cisplatinum, olaparib, pembrolizumab, or carboplatin in different phases of disease.

and Fig. 1). When adjusted for baseline characteristics, this difference remains statistically significant (HR 0.61, 95% CI 0.37–0.99, $p = 0.04$).

3.2.2. *Nonlocal prostate cancer–related events and treatments*

In the intention-to-treat analysis, there were 96 hospitalisations for prostate cancer–related events in patients who received local RT compared with 116 admissions in patients who did not receive RT (Tables 2 and 3).The incidence of metastasis-directed palliative RT to symptomatic bone metastases was similar in both groups. The incidence of metastasis-directed treatment of painful osseous metastases was high throughout the cohort, with more than half of all cases in each group. Furthermore, the incidence of bone fractures, spinal cord injury, and blood transfusions was comparable between the groups. The per-protocol analysis showed similar results for all above-mentioned outcomes (Supplementary Tables 1 and 2).

Table 3 – Nonlocal prostate cancer–related events and treatments

	ADT + radiotherapy (*N* = 163)	ADT alone, nonradiotherapy (*N* = 165)
Any distant prostate cancer–related event	115	119
Prostate cancer–related hospitalisation	96	116
Palliative radiation therapy	90	96
Unknown	1	0
Bone fracture/spinal cord injury	35	41
Bladder outlet obstruction due to spinal cord injury	3	3
Blood transfusion	50	62

ADT = androgen deprivation therapy.

3.3. *Update on OS of the HORRAD trial*

For the 328 patients included in the second analysis, the median OS time was 46 mo in the ADT plus RT group ($n = 163$) and 39 mo in the ADT-only (non-RT) group ($n = 165$). There was no statistically significant difference between randomisation arms, both crude (HR 0.87, 95% CI 0.69–1.11; $p = 0.27$; Fig. 2) and adjusted (HR 0.98, 95% CI 0.75–1.28, $p = 0.89$).

3.4. *Adjuvant treatment in case of progression of the disease*

Of the 328 patients, 181 received additional second-line life-extending treatment in the form of chemotherapy (docetaxel, cabazitaxel, or other), second-line hormonal treatment (abiraterone or enzalutamide), or radium-223, ranging from one to up to five different types. Of the patients who received adjuvant systemic treatment, 85% needed a hospital admission, 71% received palliative RT, 30% had bone fractures, and 41% needed blood transfusions.

4. Discussion

In this second update of the HORRAD trial, we present the data of the incidence of events associated with local and nonlocal prostate cancer progression in synchronous mHSPCa patients. Previous articles from our study group have shown that in an unselected group of patients with

Table 2 – Local prostate cancer–related events and treatments; intention to treat analysis (Cox regression analysis)

Any local obstruction [a]	ADT + radiotherapy (*N* = 163)	ADT alone, nonradiotherapy (*N* = 165)	Adjusted HR (95% CI)	*p* value
Yes	30 (18%)	50 (30%)	0.61 (0.37–0.99) [b]	0.04
Urinary retention requiring catheter	23 (14%)	33 (20%)		
TURP	4 (2%)	8 (5%)		
Ureter obstruction requiring JJ or nephrostomy	4 (2%)	9 (6%)		

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; JJ = double J ureteral stent; TURP = transurethral resection of the prostate.
[a] Patients can have an indication for TURP or catheter, and a JJ or nephrostomy at the same time.
[b] Cox regression analysis with HR, adjusted for the number of bone metastases (fewer than five or five or more), T stage (T1, T2, T3, or T4), and Gleason sum score (<8 or ≥8).

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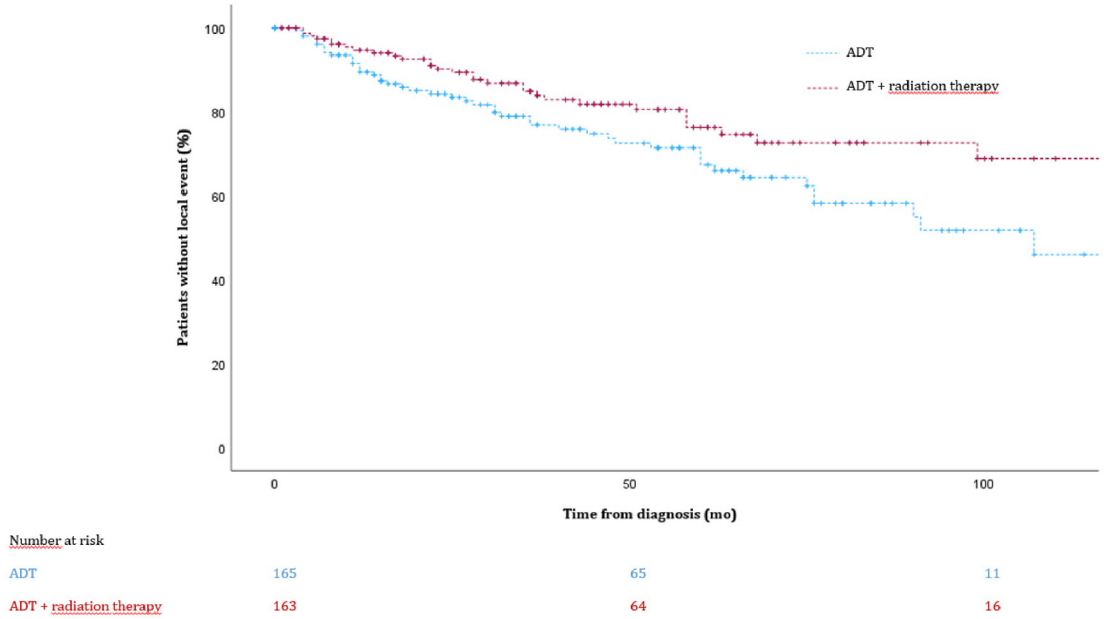

Fig. 1 – Kaplan-Meier estimates of the time to local event (intention to treat, Cox regression analysis $p = 0.01$). ADT = androgen deprivation therapy.

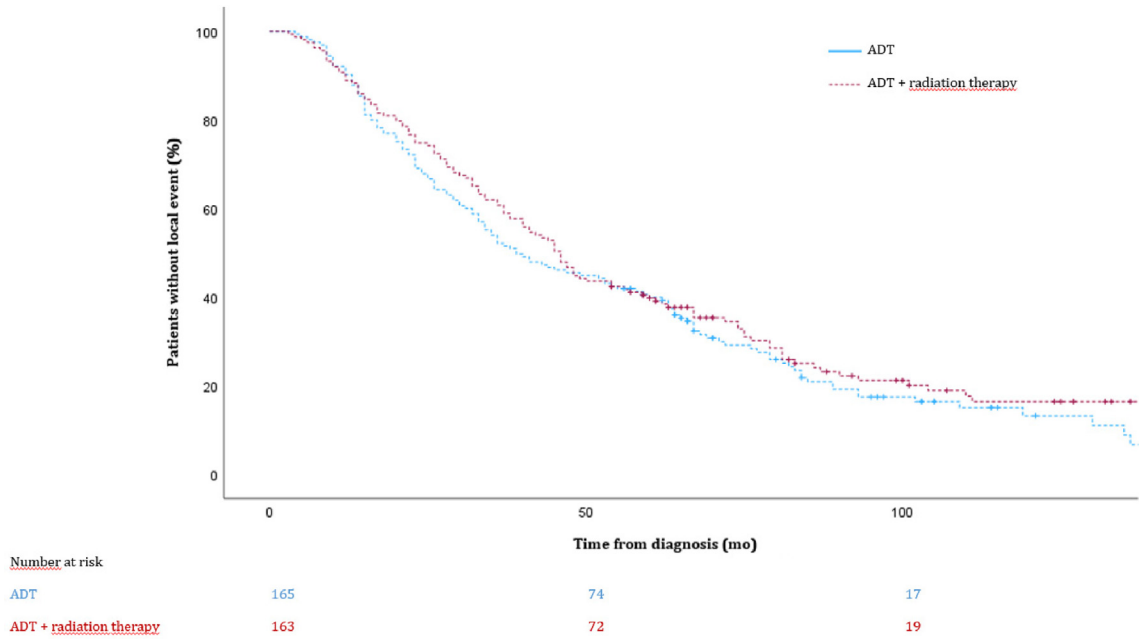

Fig. 2 – Kaplan-Meier estimates of overall survival (intention to treat, Cox regression analysis $p = 0.27$). ADT = androgen deprivation therapy.

synchronous mHSPCa, there is no OS advantage from local RT in adjunct to ADT alone. A subsequent meta-analysis showed that those with low-volume metastatic disease have a statistically significant benefit from the additional local RT [1–3]. We also demonstrated that the addition of RT to the prostate is well tolerated and not associated with permanent deterioration in HRQoL in these patients [6].

In the present study, we demonstrate that patients in the RT arm of the HORRAD trial show a better local control, resulting in fewer treatments for bladder outlet obstruction and hydronephrosis than in those in the non-RT arm (30 vs 50 events, adjusted HR 0.61, 95% CI 0.37–0.99, $p = 0.04$). In addition, the time to occurrence of these local events is significantly longer in the RT arm than in the non-RT arm ($p = 0.01$). Mortality in our cohort is high and is a competing risk for the occurrence of local events, but a competing risk analysis yielded results similar to those from the Cox regression model. The numbers of nonlocal events suggest that both groups are more or less equal, which is to be expected. However, due to a lack of information on the timing of occurrence of these nonlocal events, it was not possible to analyse these differences properly.

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As survival increases in metastatic prostate cancer patients due to new treatment options, and patients therefore run a higher risk to experience more events, insight into the incidence of those events and their possible prevention is increasingly important.

Reporting in the literature of the benefits or downfalls of EBRT combined with ADT only with respect local tumour progression in patients with synchronous mHSPCa is limited. Some data have been published on local control in those undergoing local RT within the STAMPEDE trial. Parker et al [7] reported on the local intervention-free survival (LIFS), consisting of the time from randomisation to the first report of several medical and surgical outcome measures (including death), and on the symptomatic local event–free survival, comprising any of the LIFS events and other symptoms including urinary tract obstruction. Of the patients, 59% were reported as experiencing at least one symptomatic local event. They did not find a difference in time to the first symptomatic local event reported by treatment arm (HR 1.00, p = 0.931). Furthermore, 53% of patients had one or more local intervention events reported, but no difference existed between treatment arms (HR 0.94, p = 0.286). The fact that no difference in local control is reported in the STAMPEDE trial might be explained by the difference in definitions. In the STAMPEDE trial, in addition to the events due to local progression (ie, obstruction of bladder outlet and distal ureters), urinary tract infections and prostate cancer deaths are also classified as local events. In 65% of patients, prostate cancer death was the only event. During a recent congress, the ESMO 2023, the results of an analysis on interventions for upper urinary tract obstruction (including percutaneous nephrostomy and or ureteric stent insertion) in the STAMPEDE arm H cohort were presented [8]. The authors reported that prostate RT significantly reduced these interventions from 5% in the ADT group and 3% in the radiation group (p = 0.017).

In a lecture during the ASCO 2023, the findings of the PEACE 1 study, investigating the addition of abiraterone to ADT and docetaxel with or without prostate RT in synchronous mHSPCa, were presented [9]. The authors also reported that patients undergoing RT exhibited a significantly lower incidence of interventions in the urinary tract than the group that did not receive RT. The final publication of these results on local control of EBRT within the PEACE 1 trial is awaited eagerly.

In the current study, we collectively examined local events, considering all interventions related to obstructive local disease progression, due to uncertainty about the reasoning behind a practitioner's selection of one intervention over another. We cannot identify clinicians' medical reasoning for performing or not performing desobstructive surgery. Practitioners were not blinded to the treatments that patients underwent. To what extent these clinical decisions influenced the incidence of TURP in this article cannot be determined properly. We scored these interventions because these have the greatest impact (both on HRQoL and economically [cost]) and, in our opinion, are the only events that are truly caused by local progression.

Based on the results of our trial, no firm conclusion can be drawn regarding the optimal radiation dose schedule. Since positive effects were demonstrated in our population with doses equal to 70 Gy over 7 wk, which is lower than the doses used currently for curative RT in localised prostate cancer (≥78 Gy), dose escalation may not be necessary for symptom prevention.

In any case, given the fact that in newly diagnosed metastatic rectum cancer RT of the primary tumour also delivers a better local control, it is conceivable that this will also be the case with prostate cancer [10].

In addition, it is important for daily practice to realise that the negative impact (toxicity and duration of treatment) of modern RT is decreasing due to improved radiation techniques and shorter schedules [11].

We also showed that in the updated second analysis, the median OS of patients with synchronous mHSPCa treated by ADT only is 39 mo (95% CI 27.9–50), compared with 46 mo (95% CI 40.4–51.6) in the ADT plus RT group. This is comparable with the high-burden disease group reported by Parker et al [7] from the STAMPEDE trial, where OS is 41 mo in the standard of care (SOC) group and 39 mo in the SOC with RT (SOC + RT) group (adjusted HR 1.11, 95% CI 0.96–1.28, p = 0.164). It is considerably lower than the OS of the patients with a low metastatic burden: 64 mo in the SOC and 86 mo in the SOC + RT group (adjusted HR 0.64, 95% CI 0.52–0.79, p < 0.001). In this trial, 42% of patients had a low metastatic burden. In our trial, 34% of patients had fewer than five osseous metastases, but it can well be that some of them had visceral metastases that we did not detect by performing bone scintigraphy only.

This emphasises that the patient population in our trial had a significant disease burden. Nevertheless, adherence to prevailing treatment guidelines resulted in the administration of relatively less additional treatment to patients in this trial. Overall, 45% of patients did not receive any second-line treatment. It is plausible that increased survival with additional treatments leads to more prostate cancer–related events, and we demonstrated that the burden of progressive disease is high: 30% of patients receiving second-line therapies have bone fractures, 71% needed palliative RT, and 41% needed blood transfusion. This highlights the importance of preventing events as much as possible. Local radiation can play an important role in minimising local events.

The present study is not devoid of limitations. Firstly, we were unable to reliably obtain additional data from all patients who initially participated in the study. Overall, data could be obtained from 328 of the 432 (76%) originally randomised patients. This lack of data may be explained by the difficulty of obtaining patient data from all separate participating hospitals using different electronic medical records and subsequent losses to follow-up. However, we did not find any differences in the baseline characteristics between those in the original study and those within the updated secondary analysis, so a selection bias is unlikely.

Secondly, in our cohort, we cannot reliably identify which patients had low-volume and high-volume disease according to the CHAARTED criteria. At the time this study recruited patients, it was common to perform a bone scan only. As a result, we are not informed of any lymph node burden or the presence of visceral metastases. Previous

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reports showed a survival advantage for patients with low-volume disease. As we cannot reliably identify this subgroup in our trial, we can neither comment on the survival of these specific patients, nor determine the effect of RT on local symptoms. However, we can report that RT is beneficial for preventing local symptoms in our entire cohort, which has a relatively high metastatic burden.

Furthermore, this is a retrospective analysis within a prospective trial, focussing on treatment interventions for local obstruction. Other symptoms of local progression such as pain, infections, or haematuria could not be reliably retrieved from the medical charts and were not taken into account. The current results could thus be an underestimation of the effects of radiation on the reduction of local events.

Lastly, the landscape of systemic treatment for metastatic prostate cancer has evolved considerably since the start of the trial. Presently, the standard treatment for men with synchronous mHSPCa typically incorporates one of the newer hormonal agents (ie, androgen receptor targeted agents such as abiraterone, apalutamide, or enzalutamide) along with ADT and docetaxel. The impact of these agents on local events and concurrent treatment as compared with EBRT and ADT remains uncertain and warrants further investigation.

5. Conclusions

The findings from this analysis provide compelling evidence that local RT to the prostate prolongs local event–free survival significantly and decreases the need for local prostate cancer–related interventions among patients with synchronous mHSPCa. There is no effect on nonlocal events.

***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: Van Andel, Hulshof.
Acquisition of data: Boevé, Hulshof, Verhagen, Witjes, de Vries, van Andel.
Analysis and interpretation of data: Boevé, Twisk.
Drafting of the manuscript: Boevé, Vis, Van Andel.
Critical revision of the manuscript for important intellectual content: Hulshof, Verhagen, Twisk, Witjes, de Vries, van Moorselaar.
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Supplementary material

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References

[1] Boeve LMS, Hulshof M, Vis AN, et al. 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. Eur Urol 2019;75:410–8.
[2] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353–66.
[3] Burdett S, Boeve LM, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. Eur Urol 2019;76:115–24.
[4] Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II—2020 update: treatment of relapsing and metastatic prostate cancer. Eur Urol 2021;79:263–82.
[5] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
[6] Boeve L, Hulshof M, Verhagen P, et al. Patient-reported quality of life in patients with primary metastatic prostate cancer treated with androgen deprivation therapy with and without concurrent radiation therapy to the prostate in a prospective randomised clinical trial; data from the HORRAD trial. Eur Urol 2021;79:188–97.
[7] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: long-term results from the STAMPEDE randomised controlled trial. PLoS Med 2022;19:e1003998.
[8] Jones C, Dutey-Magni P, Murphy L, et al. Prostate radiotherapy reduces long-term risk of obstructive uropathy in metastatic hormone sensitive prostate cancer (mHSPC): results from the STAMPEDE M1|RT comparison. Ann Oncol 2023;32:S954–S1000.
[9] Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet 2022;399:1695–707.
[10] Sager O, Dincoglan F, Demiral S, et al. A concise review of pelvic radiation therapy (RT) for rectal cancer with synchronous liver metastases. Int J Surg Oncol 2019;2019:5239042.
[11] Staffurth JN, Haviland JS, Wilkins A, et al. Impact of hypofractionated radiotherapy on patient-reported outcomes in prostate cancer: results up to 5 yr in the CHHiP trial (CRUK/06/016). Eur Urol Oncol 2021;4:980–92.

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