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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

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Abstract

Background: A survival benefit was demonstrated for patients with low-volume metastatic prostate cancer (mPCa) when local radiotherapy was added to androgen deprivation therapy (ADT).
Objective: To determine the effect of ADT combined with external beam radiotherapy (EBRT) to the prostate on health-related quality of life (HRQoL) of patients with primary bone mPCa.
Design, setting, and participants: The HORRAD trial is a multicentre randomised controlled trial recruiting 432patients with primary bone mPCa between 2004 and 2014.
Intervention: Patients were randomised to ADT with EBRT or to ADT alone.
Outcome measurements and statistical analysis: Patients completed two validated HRQoL questionnaires (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core Module (QLQ-C30) and EORTC Quality of Life Questionnaire Prostate Module [QLQ-PR25]) at baseline and at 3, 6, 12, and24 mo after the initiation of treatment. The effect of both treatments was evaluated based on mixed-effect models.
Results and limitations: Patient characteristics and HRQoL scores at baseline were similar in both arms. At baseline, 98% of patients completed the questionnaires, compared with 58% at 24 mo. Patients reported significantly more diarrhoea (difference between the groups 10.8; 95% confidence interval [CI] 7.3–14.2), bowel symptoms (4.5; 95% CI 2.1–6.8), and urinary symptoms (11.9; 95% CI 8.9–14.8) after EBRT and ADT compared with ADT alone (all between-arm difference $p < 0.001$). Urinary complaints

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levelled at 6 mo. At 2 yr, only bowel symptom scores were significantly different (8.0; 95% CI 4.8–11.1, $p \leq 0.001$), but 68% of patients in the radiotherapy group did not report clinically relevant worsening of their bowel symptom scores.
Conclusions: Patients with bone mPCa reported temporary modest urinary and bowel symptoms after combined treatment with EBRT of the prostate and ADT compared with ADT alone. For some patients (22%), deterioration of bowel functions remains at 2 yr, whereas general HRQoL does not deteriorate..
Patient summary: This study investigated the effect of radiotherapy to the prostate added to hormonal therapy on patient-reported health-related quality of life (HRQoL) in patients with primary bone metastatic prostate cancer. Most patients reported only temporary urinary and bowel symptoms. In 22% of patients, bowel symptoms remained at 2 yr, whereas general HRQoL did not deteriorate.

1. Introduction

Despite the widespread use of prostate-specific antigen testing and therefore earlier detection of prostate cancer (PCa), a Dutch national registration database (PROZIB) showed that in 2015, 15.8% of patients with PCa in the Netherlands still presented with metastatic disease at diagnosis. When initiating the HORRAD trial in 2004, treatment of the primary prostatic tumour in patients with metastatic prostate cancer (mPCa) was controversial. Recently, survival data of the HORRAD trial and of arm H of the STAMPEDE trial were published [1,2]. Both trials examined the effect on overall survival of treating the primary prostatic tumour with external beam radiation therapy (EBRT) and androgen deprivation therapy (ADT) in patients with mPCa. A meta-analysis of the survival data showed that in patients with a low metastatic burden, addition of EBRT to ADT led to an improvement of overall survival [3]. The 3-yr overall survival improved with 7% in patients with fewer than five osseous metastases (hazard ratio = 0.73; 95% confidence interval [CI] 0.58–0.92; $p = 0.0071$).

Since these recent publications, the European Association of Urology (EAU) guidelines were altered so that prostate radiotherapy was advised to patients with low-volume mPCa at presentation in addition to ADT [4]. Low-volume mPCa was defined according to the CHAARTED criteria as no presence of visceral metastases and fewer than four bone lesions.

As local EBRT of the prostate is known to have a substantial impact on patients' health-related quality of life (HRQoL) potentially, the survival benefits of prostate radiotherapy added to ADT in those diagnosed with mPCa needs to be weighed against the potential negative side effects of local treatment [5–7]. In the HORRAD trial, patients in both randomisation arms had scrutinised follow-up that included handing out of standardised, validated HRQoL questionnaires at the time of randomisation and at set time points after treatment. These questionnaires contained the main domains of HRQoL and side-specific treatment-related complaints.

The objective of the present study is to assess the potential negative side effects of prostate EBRT on the HRQoL of patients with primary bone mPCa. We report on the HRQoL outcomes of patients with mPCa randomised to either ADT or ADT with local prostate radiotherapy. The results give insight into the potential incremental negative effects of HRQoL of additional local radiotherapy.

2. Patients and methods

2.1. Trial design and participants

The primary objective of the HORRAD trial was to assess whether adding local radiotherapy of the prostate to standard ADT prolonged overall survival as compared with ADT alone in patients with primary bone mPCa [1]. A secondary endpoint of the HORRAD trial was an assessment of HRQoL.

Eligible patients within the HORRAD trial had a previously untreated, histologically confirmed diagnosis of adenocarcinoma of the prostate and any number of bone metastases on bone scan (M1b). Tumours could be of any grade (Gleason score 6–10) and stage (cT1-cT4, cN0-cN1, or M1b-c).

The trial protocol was approved by the local medical ethical review board of all participating centres. All patients provided written informed consent.

2.2. Intervention

Patients were randomly assigned to EBRT of the prostate in combination with ADT (radiotherapy group) or to ADT alone (control group). Randomisation and data monitoring (including HRQoL data) were performed centrally by an independent trial office. No stratification was performed. ADT in both groups consisted of an androgen-receptor inhibitor (eg, bicalutamide o.d. 50 mg) for 4 wk as testosterone flare reduction, and concurrent treatment with a luteinising hormone-releasing hormone agonist. ADT was administered lifelong. In case of disease progression, further treatment was at the discretion of the treating clinician according to the actual standard of care.

Within 3 mo of starting ADT, patients assigned to the radiotherapy group commenced radiation therapy of the prostate. The administered dose was 70 Gy in 35 fractions of 2 Gy or its biological equivalence in fraction doses of 2.0–3.4 Gy. Target volume was the prostate and base of vesiculae and eventual prostate tumour extension plus a margin of 8–10 mm. Patients should be treated with at least a conformal technique. Use of prostate fiducials, volumetric modulated arc therapy (VMAT)intensity-modulated radiation therapy

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(IMRT), and cone beam verification were allowed but not mandated. Potential pathological pelvic lymph nodes were not included in the target area.

2.3. HRQoL assessment

Two validated quality of life (QoL) questionnaires were administered at baseline and at 3, 6, 12, and 24 mo after the initiation of treatment. Questionnaires were handed out on paper by the treating physicians at the outpatient departments. Patients were asked to report their symptoms during the week that preceded the completion of the questionnaires. The European Organization for Research and Treatment of Cancer(EORTC) Quality of Life Questionnaire Core Module (QLQ-C30) version 3.0 was used, which is a validated cancer-specific questionnaire assessing patients' overall HRQoL [8]. This questionnaire measures the functional aspects and symptoms commonly occurring in cancer patients in general. It contains 30 items distributed over five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and six additional symptom items (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea, and financial effect). These questions have four-point Likert response scales. Furthermore, there is a global health or QoL scale, which has a seven-point Likert response scale.

The EORTC Quality of Life Questionnaire Prostate Module (QLQ-PR25) was the second questionnaire provided, which is a validated PCa-specific questionnaire, specifically designed to address PCa-specific symptoms [9]. This questionnaire consists of 25 items, all of which have four-point response scales. It incorporates four symptom scales (urinary symptoms, bowel symptoms, hormonal treatment-related symptoms, and incontinence aid) and two functional scales (sexual activity and sexual functioning).

In both questionnaires, a higher score for a functional scale means better functioning, whereas a higher score for a symptom scale reflects more symptoms, so a worse condition. A clinically meaningful change was considered a change of $\geq$10 points compared with baseline.

2.4. Statistical analyses

All analyses were performed as per the intention-to-treat principle. Compliance was the proportion of patients who completed the questionnaire of those alive at that time point. In both questionnaires, all items and scale scores were linearly transformed to a 0–100 scale. The mean values and standard deviations of HRQoL scores in both arms were measured for all domains. The effect of both treatments on the QoL was evaluated based on mixed-effect models, whereby treatment arm, time of follow-up, and interaction between treatment and time were modelled. Mixed model analyses were also used to estimate the effect of any treatment over time on QoL and pain scores. All analyses were adjusted for baseline values of the outcomes. Adjustments were made for age, pain at baseline, World Health Organization (WHO) performance status, and demographic and socioeconomic status. A significance level of 0.05 was used.

Furthermore, for domains most relevant to treatment toxicity, percentages of patient scores that improved (ie, a change of $>$+10 points from baseline), became worse (ie, $>$−10 points), or remained stable (ie, between −10 and +10 points) were measured and displayed in bar graphs. In this, the baseline score is set at 0.

Missing values in multi-item scales were imputed, assuming that the missing items have values equal to the average of those items present, whenever at least half of the items of the scale were completed.

Analyses were performed with SPSS software (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

Between November 2004 and September 2014, 432 patients from 28 participating institutions were assigned randomly to ADT in combination with prostate radiotherapy (radiotherapy group, n = 216) or ADT alone (control group, n = 216). A detailed description of randomisation and participants has been published before [1].

Patient and tumour characteristics are summarised in Table 1. Most patients had a high metastatic burden, with almost 63% of patients having five or more osseous metastases. Clinical and pathological characteristics were well balanced between the two treatment groups.

Ten patients allocated to the radiotherapy group did not undergo treatment; two patients refused radiation therapy after randomisation, two patients died before therapy started, one patient had previous palliative radiation therapy to the pelvis and was therefore not able to receive the prescribed radiation dose, two patients revoked informed consent, and two patients were ineligible for other reasons.

Furthermore, two patients discontinued the radiation intervention, one due to rapid progression of PCa and the other because of a second primary tumour in the brain. None of the patients allocated to the control group received EBRT.

3.2. Compliance rates

Table 2 shows the compliance rates for patients at each time point. At baseline, 98% of patients completed the questionnaires, whereas this figure declined to 58% at 2 yr of follow-up.

3.3. HRQoL scores at baseline

Table 3 reflects the mean HRQoL scores of all domains for both groups. At baseline, patients from both groups report low bowel symptom scores (3.5–4.6) and moderate urinary symptoms (19.6–20.7), fatigue (21.9–25.7), and pain scores (22.6–25.6) compared with a healthy reference group [10].

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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)	ADT alone (*N* = 216)
Age (yr)	67 (62–71).	66.5 (61–71)
PSA concentration at the start of ADT (ng/mL)		
Median	125	149
Q1	48	50
Q3	433	483
Missing data, *n* (%)	3 (1)	5(2)
Gleason sum score, *n* (%)		
6–7.	73 (34)	71 (32.8)
8	48 (22)	65 (30.1)
9–10	94 (44)	79 (35.4)
Missing data	0	1 (0.5)
T stage, *n* (%)		
T3–4.	176 (81)	187 (87)
Missing data.	0.	4 (2)
Osseous metastases, *n* (%)		
<5 lesions.	89 (41)	71 (33)
5–10 lesions	53 (25)	65 (30)
>15 lesions.	74 (34)	80 (37).
WHO performance status, *n* (%)		
0.	187 (87)	176 (82)
1.	22 (10)	31 (14)
2.	4 (2)	6 (3)
3.	3 (1)	3 (1)
Pain score, *n* (%)		
0.	140 (65)	139 (64)
1.	39 (18)	34 (16)
2.	18 (8)	18 (8)
3.	3 (2)	3 (2)
4.	16 (7)	22 (10)
Marital status, *n* (%)		
Single	35 (16)	31 (14)
Married/cohabitant	176 (82)	178 (83)
Unknown	5 (2)	7 (3)
Education level, *n* (%)		
<Compulsory education.	20 (9.)	20 (9)
Compulsory education	78 (37)	74 (35)
Post-compulsory education below university level	55 (26)	50 (23)
University level	49 (23)	59 (28)
Unknown	10 (5)	10 (5)

ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate-specific antigen; Q1 = lower bound of IQR; Q3 = upper bound of IQR; WHO = World Health Organization.
Data are median (IQR) or number of patients (%).
Gleason scores range from 6 to 10, with higher scores indicating more aggressive disease, less differentiated tumour, and worse prognosis.
WHO performance status: 0, asymptomatic; 1, symptomatic but completely ambulatory; 2, symptomatic and <50% in bed during the day; 3, symptomatic and >50% in bed but not bedbound; and 4, bedbound.
Pain score: 0, no pain; 1, pain occasionally, requiring non-narcotics; 2, pain regularly, requiring non-narcotics; 3, pain occasionally, requiring narcotics; and 4 pain regularly, requiring narcotics.

Table 2 – Compliance rates for questionnaires at each time point.

	Before treatment	Follow-up (mo)			
		3	6	12	24
No. of patients	432	429	420	391	311
Radiotherapy group	216	213	212	192	162
Control group	216	216	208	199	149
No. of patients who completed the questionnaire	423	375	327	303	181
Compliance (% of total)					
Radiotherapy group	98	87	78	77	58
Control group	209	177	150	151	94
	214	198	177	152	87

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Table 3 – HRQoL scores for EORTC C-30 and PR-25 questionnaires at baseline and at 3, 6, 12, and 24 mo.

Domain	Score range	Most reported score	Baseline score				3 mo				6 mo				12 mo				24 mo			
			ADT + RT		ADT		ADT + RT		ADT		ADT + RT		ADT		ADT + RT		ADT		ADT + RT		ADT	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
EORTC QLQ-C30																						
Global health-related QoL	0–100	83	70.2	22.8	70.0	22.6	77.8	17.2	76.1	19.4	76.2	17.4	73.5	20.4	75.6	19.1	74.2	19.5	79.2	17.8	76.6	19.2
Functional scales																						
Physical functioning	0–100	100	85.4	18.8	81.8	20.5	86.9	16.6	82.9	18.4	83.8	17.8	82.0	19.9	81.6	21.1	80.3	19.9	83.1	19.6	78.9	20.4
Role functioning	0–100	100	80.5	27.3	74.6	32.5	82.7	23.4	78.0	26.0	80.5	23.8	77.7	28.8	78.9	27.8	75.9	28.2	81.0	27.7	78.5	28.5
Emotional functioning	0–100	100	74.4	21.1	73.6	22.5	82.8	18.9	81.2	19.9	82.6	18.9	78.4	22.8	81.4	19.4	81.0	22.1	83.0	19.9	86.0	18.8
Cognitive functioning	0–100	100	90.3	16.5	88.1	18.4	90.1	17.7	86.4	20.5	88.8	17.1	86.4	19.9	88.4	16.8	85.3	20.5	87.8	19.1	87.6	17.5
Social functioning	0–100	100	87.3	20.0	84.6	22.1	89.9	17.5	88.2	21.1	89.7	17.9	85.0	22.9	87.9	20.3	86.4	20.6	88.4	20.2	86.6	22.7
Symptom scales																						
Fatigue	0–100	0	21.9	22.7	25.7	24.8	23.4	20.2	23.3	24.0	23.4	21.0	23.6	23.6	24.2	22.6	27.1	24.9	24.1	23.0	25.7	21.9
Nausea and vomiting	0–100	0	4.1	10.1	4.0	11.2	2.7	8.1	2.1	8.4	3.8	12.6	2.8	8.8	4.5	13.9	3.5	10.3	2.8	8.3	3.8	10.4
Pain	0–100	0	22.6	27.9	25.6	29.9	14.8	21.7	18.6	25.0	15.8	23.6	20.1	25.4	15.8	23.3	19.1	26.0	14.0	24.8	13.8	23.6
Dyspnoea	0–100	0	10.4	20.5	14.7	24.7	10.8	20.2	13.6	22.8	15.2	22.8	18.2	24.9	18.4	26.9	18.7	24.9	17.4	24.8	19.4	26.8
Insomnia	0–100	0	19.0	26.2	23.4	30.0	20.3	28.5	21.9	29.0	17.0	24.7	21.1	27.2	21.4	26.5	22.2	29.2	18.8	25.2	21.5	27.8
Appetite loss	0–100	0	11.2	23.0	11.1	24.8	4.7	16.6	4.7	15.8	4.7	16.0	5.3	16.6	4.6	13.4	5.7	17.1	6.0	17.6	8.1	20.3
Constipation	0–100	0	7.73	19.3	10.4	21.7	7.5	19.6	9.7	20.6	5.6	15.7	11.7	23.1	8.7	20.6	10.1	19.7	5.7	16.8	6.9	16.2
Diarrhoea	0–100	0	4.8	13.0	5.8	14.6	14.6	21.3	4.6	12.5	7.4	16.4	6.8	17.2	6.7	17.8	5.1	14.8	7.2	17.6	5.0	14.9
Financial difficulties	0–100	0	4.8	15.0	5.7	18.0	5.4	15.0	5.7	17.9	7.4	17.7	8.5	20.4	6.9	17.8	4.9	15.6	6.1	17.7	6.5	20.9
EORTC QLQ-PR25																						
Functional scale																						
Sexual activity	0–100	0	19.2	20.3	18.2	21.1	11.5	19.0	11.7	18.8	7.4	14.7	7.6	13.6	8.9	19.0	8.2	19.2	6.7	15.2	8.7	20.1
Sexual functioning	0–100	50	37.3	19.6	41.9	22.1	46.0	25.7	47.6	22.8	49.1	21.9	53.3	25.0	56.6	25.1	50.0	25.5	50.9	26.2	61.1	21.7
Symptom scales																						
Urinary symptoms	0–96	8	20.7	16.6	19.6	16.9	30.2	19.0	18.7	16.5	19.5	15.1	18.1	15.6	19.2	16.0	17.4	14.5	17.7	15.6	15.7	13.0
Bowel symptoms	0–92	0	3.5	6.7	4.6	9.2	7.6	11.3	6.9	8.7	6.9	10.8	5.7	12.3	8.3	13.5	4.8	9.2	10.0	15.0	1.7	4.3
Hormonal treatment-related symptoms	0–72	0	7.2	8.6	8.7	10.8	16.1	11.4	17.0	12.8	16.0	10.6	17.7	13.4	16.5	11.5	16.8	13.5	15.0	11.0	15.5	13.2

ADT = androgen deprivation therapy; EORTC = European Organization for Research and Treatment of Cancer; EORTC QLQ-C30 = EORTC Quality of Life Questionnaire Core Module; EORTC QLQ-PR25 = EORTC Quality of Life Questionnaire Prostate Module; HRQoL = heath-related QoL; QoL = quality of life; SD = standard deviation; RT = radiotherapy.

Table 4 – Estimated differences between the groups for the EORTC C-30 and PR-25 questionnaires at 3, 6, 12, and 24 mo.

Domain	3 mo			6 mo			12 mo			24 mo		
	Estimate difference	95% CI	*p* value [a]	Estimate difference	95% CI	*p* value [a]	Estimate difference	95% CI	*p* value [a]	Estimate difference	95% CI	*p* value [a]
EORTC QLQ-C30												
Global health-related QoL	1.6	−1.9 to 5.1	0.4	1.7	−1.9 to 5.4	0.4	0.9	−2.9 to 4.7	0.7	2.4	−2.2 to 7.1	0.3
Functional scales												
Physical functioning	−0.8	−2.6 to 4.1	0.7	−0.6	−4.1 to 2.9	0.7	−1.0	−4.6 to 2.6	0.6	0.7	−3.6 to 5.0	0.8
Role functioning	1.2	−3.7 to 6.1	0.6	−1.1	−6.3 to 4.0	0.7	−0.2	−5.5 to 5.1	>0.9	−2.1	−8.6 to 4.3	0.5
Emotional functioning	1.6	−1.9 to 5.2	0.4	4.1	0.4 to 7.8	0.029	0.8	−3.0 to 4.6	0.7	0.3	−4.3 to 4.8	0.9
Cognitive functioning	2.4	−1.0 to 5.8	0.2	1.7	−1.8 to 5.2	0.4	1.6	−2.0 to 5.2	0.4	0.2	−4.1 to 4.5	0.9
Social functioning	−1.0	−4.8 to 2.7	0.6	3.1	−0.8 to 7.0	0.1	−0.5	−4.5 to 3.6	0.8	−1.9	−7.0 to 3.1	0.5
Symptom scales												
Fatigue	3.0	−0.9 to 6.9	0.13	2.1	−1.9 to 6.2	0.3	−0.02	−4.2 to 4.2	>0.9	0.9	−4.2 to 5.9	0.7
Nausea and vomiting	0.6	−1.4 to 2.7	0.5	1.4	−0.8 to 3.5	0.2	0.9	−1.3 to 3.1	0.4	−1.1	−3.9 to 1.7	0.4
Pain	−2.7	−7.3 to 1.8	0.2	−3.4	−8.3 to 1.4	0.3	−2.8	−7.8 to 2.2	0.3	1.2	−5.1 to 7.4	0.7
Dyspnoea	1.3	−3.3 to 5.5	0.6	0.7	−3.8 to 5.2	0.8	3.4	−1.3 to 8.0	0.2	1.7	−4.1 to 7.4	0.6
Insomnia	−2.0	−7.4 to 3.4	0.5	−2.3	−8.0 to 3.4	0.4	−0.4	−6.2 to 5.4	0.9	−5.4	−12.4 to 1.6	0.1
Appetite loss	0.8	−2.5 to 4.2	0.6	0.8	−2.7 to 4.3	0.7	−0.1	−3.8 to 3.6	>0.9	−2.4	−6.9 to 2.2	0.3
Constipation	−1.6	−5.4 to 2.3	0.4	−4.5	−8.6 to 0.4	0.031	−0.3	−4.6 to 3.9	0.9	−0.1	−5.3 to 5.1	>0.9
Diarrhoea	10.8	7.3 to 14.1	<0.001	1.2	−2.4 to 4.8	0.5	0.7	−3.0 to 4.5	0.7	2.0	−2.3. to 6.7	0.4
Financial difficulties	0.9	−2.2 to 3.9	0.6	−1.2	−3.3 to 3.0	0.9	2.2	−1.1 to 5.4	0.19	−0.4	−4.5 to 3.6	0.9
EORTC QLQ-PR25												
Functional scale												
Sexual activity	−1.1	−4.6 to 2.3	0.5	−0.7	4.5 to 3.0	0.7	0.07	−3.8 to 3.9	>0.9	−2.7	−7.5 to 2.1	0.3
Sexual functioning	4.4	−4.9 to 13.7	0.4	1.1	−8.9 to 11.1	0.8	2.8	−8.3 to 13.8	0.6	0.4	−14.7 to 15.7	>0.9
Symptom scales												
Urinary symptoms	11.9	8.9–14.8	<0.001	1.2	−1.9 to 4.3	0.5	0.2	−3.0 to 3.4	0.9	0.1	−3.7 to 3.9	>0.9
Bowel symptoms	4.5	2.1 to 6.8	<0.001	2.2	−0.3 to 4.7	0.09	3.1	0.5 to 5.8	0.022	8.0	4.8 to 11.1	<0.001
Hormonal treatment-related symptoms	−0.9	−3.3 to 1.5	0.5	−0.7	−3.1 to 1.8	0.6	0.4	−2.2 to 3.0	0.8	0.3	−2.7 to 3.3	0.9

CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; EORTC QLQ-C30 = EORTC Quality of Life Questionnaire Core Module; EORTC QLQ-PR25 = EORTC Quality of Life Questionnaire Prostate Module; QoL = quality of life; WHO = World Health Organization.
Estimated differences are adjusted for age, pain at baseline, WHO performance status, and demographic and socioeconomic status.
[a] *p* values reflect between-treatment arm comparisons of mean scores for each time point.

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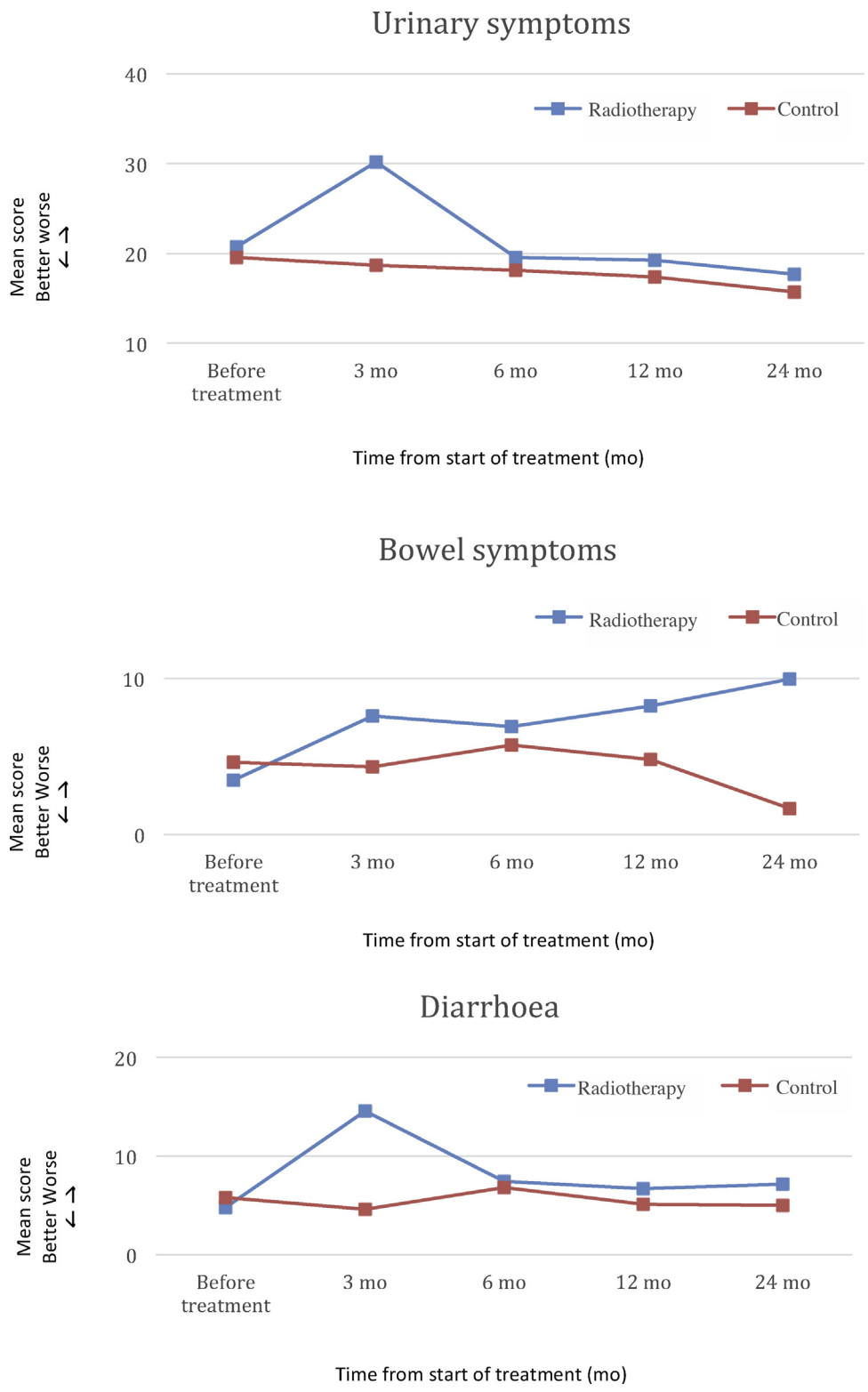

Fig. 1 – Mean scores over time for the symptoms most relevant to radiotherapy toxicity. Lower scores represent fewer symptoms.

3.4. *Effect of radiotherapy of the prostate on HRQoL scores*

Table 3 shows the mean scores for HRQoL outcome at 3, 6, 12, and 24 mo after the start of treatment for both treatment groups. Table 4 shows the estimated differences between the groups at different time points adjusted for age, pain at baseline, WHO performance status, and demographic and socioeconomic status.

Patients in the radiotherapy group reported statistically significantly more diarrhoea (difference between the

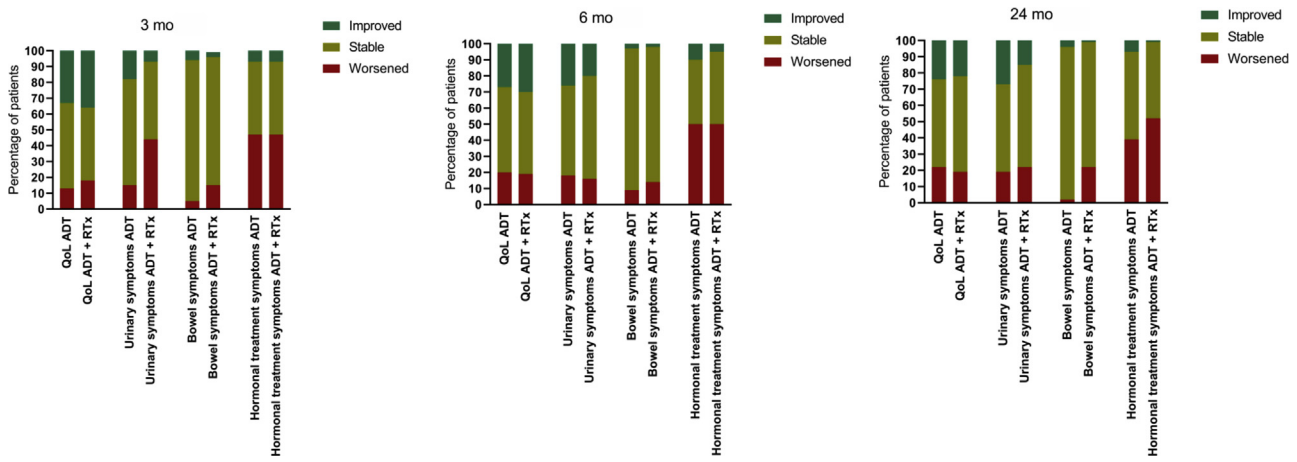

Fig. 2 – Percentage of patient scores improving (change of >+10 points from baseline), worsening (>–10 points), or remaining stable (–10 to +10 points) for the symptoms most relevant to treatment toxicity. ADT = androgen deprivation therapy; QoL = quality of life; RTx = radiotherapy.

groups 10.8; 95% CI 7.3–14.2), bowel symptoms (difference between the groups 4.5; 95% CI 2.1–6.8), and urinary symptoms (difference between the groups 11.9; 95% CI 8.9–14.8) at 3 mo than patients in the control group (all between-arm difference test $p < 0.001$). At 6 mo, patients in the radiotherapy group reported statistically better emotional functioning (difference between the groups 4.1; 95% CI 0.4–7.8, between-arm difference $p = 0.029$) and less constipation (difference between the groups -4.5; 95% CI –8.6 to –0.4, $p = 0.031$) than patients receiving ADT alone. There was no statistically significant difference from baseline in urinary symptom scores (difference between the groups 1.2; 95% CI –1.9 to 4.3, $p = 0.5$). Only few bowel symptoms remained in the radiotherapy group, but not statistically significant different compared with the ADT group (difference between the groups 2.2; 95% CI –0.3 to 4.7, $p = 0.09$). At 2 yr of follow-up, only bowel symptom scores (difference between the groups 8.0; 95% CI 4.8–11.1, between arm $p \leq 0.001$) were statistically significantly different between the radiotherapy and the control group. The only clinically significant changes (>10 points) between the radiotherapy and the ADT-only group were worsening of urinary function and diarrhoea at 3 mo, whereas all other variables at all other time points were not clinically relevant. The mean scores over time for the symptoms most relevant to radiotherapy toxicity are shown in Fig. 1. All residuals were more or less normally distributed.

Fig. 2 shows the percentage of patient scores who improved (ie, >+10 points change from baseline), got worse (>–10 points), or remained stable (–10 to +10 points) for the symptoms most relevant to treatment toxicity. Fig. 2 shows that at 3 mo of follow-up, almost half of all patients in the radiotherapy group reported worse urinary symptoms; however, these difficulties improved rapidly with time since <20% of patients reported worsening of urinary symptoms at 6 mo. This figure at 6 mo is comparable with that in the control group. Worsening of bowel symptoms in the radiotherapy group was reported by 14% of patients at 6 mo and by 22% of patients at 2 yr.

4. Discussion

This is the first report on patient-reported QoL and the changes in HRQoL with time in patients with mPCa, randomised between standard of care (ADT) or a combination of ADT and EBRT to the prostate. A survival benefit for selected patients with mPCa treated with local radiotherapy has previously been demonstrated [3]. However, it is prudent to evaluate the QoL in patients with mPCa when a noncurative treatment with potentially harmful side effects is offered. We found that patients reported temporary modest urinary and bowel symptoms after combined treatment with prostate radiotherapy. Both treatments did not affect global HRQoL, and at 24 mo, no clinically relevant differences in urinary and bowel symptoms persisted.

The finding that a change in HRQoL scores is statistically significant does not necessarily imply that it also is clinically relevant. It is known that the degree of clinical relevance, or the minimally important difference (MID), can differ between questionnaires and across domains. Based on interdomain analyses of our data, 10 points appears to be a reasonable MID in which 60% of patients indicate that they are limited in their daily activity because of the bowel symptoms, whereas it is <20% in a five-point difference. Therefore, we considered changes in QoL scores of ≥10 points compared with baseline as clinically relevant.

In our trial, patients reported statistically significant worsening of bowel and urinary symptoms in the first 0–6 mo after treatment. In order not to confuse average effects with individual effects, we depicted the individual change scores per patient in Fig. 2. At 3 mo, 44% of patients treated with radiotherapy reported worsening of their urinary symptoms with ≥10 points, and 15% stated worsening of their bowel symptoms. The other patients were unaffected. At 6 mo, 16% of patients in the radiotherapy group reported worsening of urinary complaints, whereas the figure was still 18% of patients in the ADT-only group. Bowel symptoms persisted for longer periods of time. At 24 mo, 22% of patients still reported worsening of their bowel symptoms

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with >10 points in the radiotherapy group, compared with 2% in the ADT-only group. General HRQoL, however, was never deteriorated.

These HRQoL results are in line with those of other studies with comparable designs in a nonmetastatic setting. In a randomised controlled trial of 1028 patients with locally advanced PCa comparing between ADT with radiotherapy and ADT alone, Brundage et al [7] found that irradiated patients had statistically significant more bowel symptoms ($p = 0.02$), diarrhoea ($p < 0.001$), and urinary difficulties ($p = 0.003$) after 6 mo of treatment than those on ADT alone. At 3 yr, however, no significant differences between groups remained in any of the function scales. Donovan et al [11] also reported in their cohort of 545 patients receiving radiotherapy of the prostate combined with ADT that, at 6 mo, bowel functions were worse than in patients after radical prostatectomy or on active surveillance, but recovered quickly. The same holds true for urinary symptoms. At 6 mo, urinary symptoms were worse for radiotherapy, but were similar to the other treatment groups after 12 mo of treatment.

Some limitations to the interpretation of our findings are noteworthy. There are a relevant number of nonresponders for the long-term follow-up questionnaire. We have investigated whether nonresponse was related to earlier measurements, and we found that nonresponders at 24 mo had a significantly lower QoL score at 3 and 6 mo ($p = 0.008$ and $p \leq 0.001$, respectively) than responders. In addition, regarding urinary symptoms, nonresponders had statistically significantly more complaints at 6 mo, with a mean score of 21 versus 16 ($p = 0.006$). Therefore, the responders were slightly selective regarding better QoL and fewer urinary symptoms. This indicates that the nonresponse was partly related to earlier observations, which means that missing was at random. The use of mixed model analysis is one of the preferred methods to deal with this kind of missingness [12].

Furthermore, we imputed the missing data as the mean of the other items in that domain. Therefore, the items within the bowel domain are clearly correlated, while in general bowel domains tend to have lower Cronbach α levels than other health domains. This might have affected our outcomes.

Finally, the outcome of the HRQoL might be different or even improved at present, as the techniques and curative dose of local radiation therapy have developed further. Unfortunately, the number of patients who underwent modern radiation techniques such as IMRT/VMAT is not known.

The guidelines of the EAU have recently been adjusted, advising prostate radiotherapy with ADT in patients with low-volume mPCa. The results presented here are therefore important for shared decision making to properly inform patients about the choices of palliative treatments. Owing to the relatively mild and transient side effects of local radiotherapy in patients with metastatic disease, combined by a statistically significant improvement in overall survival, addition of EBRT to ADT is a well-balanced treatment option. Patients should be counselled that additional prostate radiotherapy can lead to more urinary symptoms that disappear after 12 mo and that in some patients (22%) bowel symptoms remain at 2 yr. The overall QoL experienced was never deteriorated.

5. Conclusions

In conclusion, there is only little and mostly transient deterioration of the important domains of HRQoL due to additional radiotherapy of the prostate in patients with mPCa opting for ADT. At 3 mo, significant worsening of urinary function, bowel function, and diarrhoea was reported by patients in the radiotherapy group, which then rapidly improved for most patients. For some patients (22%), deterioration of bowel functions remains at 2 yr, whereas general HRQoL does not deteriorate.

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

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