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Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: comparisons on long-term quality of life and symptom burden

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OBJECTIVE

To assess and identify factors associated with the long-term health-related quality of life (HRQL) of prostate cancer survivors managed expectantly, as patients with low-risk prostate cancer can be managed with active surveillance (AS), but research on associated long-term HRQL is scarce.

PATIENTS AND METHODS

From the population-based Eindhoven Cancer Registry, 71 men managed with AS were matched with 71 survivors who had similar demographic and clinical characteristics but treated with external beam radiotherapy (RT). All were diagnosed between 1994 and 1998. HRQL data were collected 5–10 years after diagnosis. Patients completed generic- (Short Form-36) and cancer-specific (Quality of Life – Cancer Survivors) HRQL instruments, and symptom burden (Expanded Prostate Cancer Index, Sexual Activity) questionnaires.

RESULTS

Patients on AS were comparable to those treated with RT for most generic- and disease-specific HRQL dimensions. Patients treated with RT had poorer mean (SD) bowel function scores, of 87.1 (13.1) vs 92.8 (10.7) ($P < 0.001$), more bother with bowel function, at 85.0 (16.4) vs 93.7 (10.1) ($P < 0.001$), and more problems with getting an erection (68% vs 47%, $P = 0.005$). Multivariate regression analyses (corrected for comorbidity and clinical disease progression) indicated that the management strategy independently predicted differences in physical functioning, bodily pain, spiritual and total well-being, and bowel function and bowel bother.

CONCLUSIONS

Patients managed expectantly at initial diagnosis (AS) have comparable HRQL and a lower symptom burden than patients treated with RT up to 10 years after the diagnosis.

KEYWORDS

active surveillance, disease progression, external beam radiotherapy, health-related quality of life, prostate cancer

INTRODUCTION

PSA testing has increased the early detection of low-risk localized prostate cancer, defined as tumour grade ≤T2a, a Gleason score of ≤6 and a PSA level of <10 ng/mL [1,2]. However, most of these low-risk prostate cancers are clinically insignificant and pose a minimal threat to health or life [1].

Low-risk prostate cancer can be treated with curative treatment or managed expectantly with active surveillance (AS) [3]. However, low-risk prostate cancers are often indolent; as such, patients could be over-treated with a curative procedure at diagnosis [2,4], and its associated complications could impair health-related quality of life (HRQL) [3,5]. AS is a less invasive alternative and refers to the systematic monitoring of men with low-risk prostate cancer for whom curative treatment is deferred at diagnosis, and who receive subsequent curative treatment when the tumour shows progression [6] or when patients decide to change the treatment [7]. AS is distinct from watchful waiting, which refers to the palliative treatment of men with prostate cancer for whom the tumour is too advanced for curative treatment at diagnosis [6].

Although associated with fewer treatment-induced side-effects, recommending AS for managing low-risk prostate cancer is controversial. Studies suggest that living with untreated cancer, and undergoing repeated PSA testing and prostate biopsy, increase the patients' feelings of anxiety and uncertainty compared with patients who received curative treatment at diagnosis [8–10]. In a study with a 3-year follow-up, patients under surveillance with greater anxiety were more likely to select treatment within the observation period independent of changes in PSA results [11]. By contrast, Burnet *et al.* found that patients under AS had no greater

psychological distress than those who received hormone therapy or radiotherapy (RT) [12].

However, studies of AS on long-term HRQL, symptoms and psychological morbidity compared with curative treatment are relatively scarce. The limitations of these studies include the qualitative nature, short follow-up from diagnosis, or poor sample definition with the inclusion of both low- and high-risk patients [5,8,10,12].

The objectives of the present study were to compare the HRQL and symptoms of a population-based sample of long-term prostate cancer survivors who opted for expectant management at diagnosis, with patients who had RT, and predict the effect of the management strategy at diagnosis on long-term HRQL and treatment-related symptom burden.

PATIENTS AND METHODS

All eligible patients diagnosed with prostate cancer between 1994 and 1998 were identified from the Eindhoven Cancer Registry (ECR). The ECR records data on all patients newly diagnosed with cancer in the south of the Netherlands, an area with 2.3 million inhabitants, 10 hospitals with 18 locations and two large RT institutes [13]. After excluding all persons who had died before 1 November 2004 (according to the Central Bureau for Genealogy, which collects information on all deceased Dutch citizens via the civil municipal registries), data collection started in November 2004. Approval for this study was obtained from a local certified Medical Ethics Committee. Additional details of the study methods were described elsewhere [14,15].

Between 1994 and 1998, AS was not yet a standard recommended management strategy for low-risk prostate cancer in the region covered by the ECR. As was done previously [16,17], we selected a sample of patients diagnosed with low-risk prostate cancer who would be suitable for management with AS according to contemporary practice. For the purpose of the present study, we termed this group 'AS' and included patients who had cancer stage ≤2 and a tumour grade of ≤2 as determined with a biopsy at diagnosis. These patients thereafter received either no active treatment or at most, a TURP after diagnosis. AS patients were matched with patients who had received external beam RT as a primary treatment at diagnosis on (a) cancer stage, (b) tumour grade, (c) age at diagnosis (± 2 years), and (d) number of years since diagnosis (± 2 years). Similarly, RT patients were initially diagnosed with a biopsy and subsequently had active treatment after diagnosis. To achieve adequate power for the study we limited our comparison to RT patients as they were similar to AS patients on the matching criteria of age and clinical characteristics.

Prostate cancer survivors were informed of the study via a letter from their urologist. The letter explained that by completing and returning the enclosed questionnaire, patients had consented to participate in the study and agreed to the linkage of the questionnaire data with their disease history in the ECR. Patients were reassured that not participating had no consequences on their follow-up care or treatment. A reminder letter was sent within 2 months to those not responding.

The Dutch version of the Short-Form-36 (SF-36) questionnaire was used to assess generic HRQL [18]. The eight subscales: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to mental health problems, and general mental health were further combined into the physical (PCS) and mental (MCS) component summary scores. All scales were linearly converted to a 0–100 scale according to standard scoring procedures, with higher scores indicating better HRQL. For the SF-36, differences of ≥5 points (the general health domain) [19], 6.5 points (the physical domain) and 7.9 points (the mental health domain) [20] were considered clinically significant or minimal important differences (MID). MID for other subscales were determined with Norman's 'rule of thumb', whereby an ≈0.5 SD indicates a threshold of discriminant change in HRQL scores of a chronic illness [21]. The internal consistency and reliability of all scales were above the 0.70 criteria recommended for group comparisons.

HRQL issues specific to cancer survivors were assessed with the Dutch validated Quality of Life – Cancer Survivors (QOL-CS) questionnaire [22]. The QOL-CS includes 45 visual analogue scales, each ranging from 0 (worst outcome) to 10 (best outcome); these 45 scales are grouped into four multi-item subscales on well-being, i.e. physical, psychological, social and spiritual. Norman's rule of thumb was used to determine MID [21].

Four urinary and bowel modules of the Expanded Prostate Cancer Index (EPIC) were used to assess urinary and bowel functioning, and urinary and bowel bother [23]. All scores were linearly transformed, with a range of 0–100, with 100 indicating the best level of functioning or experiencing no bother. MID was determined with Norman's rule of thumb [21].

Sexual functioning was assessed with a Dutch 'sexual activities module' (SAc) to allow comparison with the Dutch general population. The SAc consists of 12 single items which do not add up to a scale [24]. Aspects assessed include interest in sexual activity, getting and maintaining an erection, and the use of erectile dysfunction treatments. There are three to five possible answer categories for each item.

Besides patients' sociodemographics, clinical information available from the ECR was included. The ECR routinely collects data on tumour characteristics, including date of diagnosis, tumour grade according to the TNM clinical classification [25], clinical stage [25], treatment, and patient background characteristics, including date of birth and comorbidity at the time of diagnosis (adapted from the Charlson comorbidity index) [26].

Information on disease progress (DP) was determined in a two-step approach. First, patients were asked to report on any DP, including the month/year. Affirmative answers were then confirmed by staff from the cancer registry against ECR records, together with information on the date of this diagnosis and subsequent radical treatment received. Therefore, we only included clinical DP which required active treatment in our current analysis.

Differences between demographic, clinical characteristics, HRQL scores, and symptoms function/bother scores between the groups were compared with the chi-square test or *t*-test, as appropriate. Nonparametric equivalents were applied when normality and homogeneity assumptions were violated. The SF-36 and EPIC mean scores of both groups were also compared to a Dutch normative population. Individual SAc items which showed significant differences in frequency

between AS and RT were compared to a male Dutch normative population [27]. The associations between treatment with HRQL and symptoms were investigated with linear regression models. Comorbidity and DP were controlled for in multivariate models. Statistical differences were indicated if $P < 0.05$ and reported P values are two-sided.

RESULTS

In all, 2348 patients identified from the ECR were eligible for the study. Details of the data collection process and baseline characteristics for the whole sample were reported elsewhere [14]. From the whole sample, 1543 were diagnosed with prostate cancer, stage 1 or 2. Of these patients, 128 (45%) on AS and 265 (40%) treated with RT were still alive at 1 November 2004 (data not shown).

Of the 128 AS survivors, 71 returned a completed questionnaire and were matched with 71 RT patients of similar age and comparable disease characteristics; Table 1 outlines the baseline characteristics of both groups. There were no differences on the relevant demographic and disease characteristics, indicating a successful match. Seventeen (24%) AS patients and 13 (18%) RT patients had DP. Of the 30 patients with DP, nine (six AS; three RT) had missing data on the time to DP. Among AS patients, the median (interquartile range, IQR) time to DP was 6.6 (1.5–8.3) years and for RT patients, 5.7 (4.0–6.4) years. Among 18 patients with DP from whom data on subsequent active treatment was available, one on AS had a radical prostatectomy (RP) and five RT, two had hormone therapy, one had both RT and hormone therapy. Among RT patients, five had RP, one had RT, two had hormone therapy, and one both RT and hormone therapy.

TABLE 1 The demographic and clinical characteristics of patients by the management strategy for low-risk prostate cancer

Variable	AS	RT	*P*
No. of patients	71	71	
Mean (SD)			
Years from diagnosis	7.9 (1.3)	7.7 (1.1)	0.33
Age at survey, years	75.8 (5.8)	75.9 (5.2)	0.98
Age at survey, %			
50–59	1	0	
60–69	10	10	0.46
70–79	39	46	
≥80	21	15	
Tumour stage, %			
1	48	49	0.86
2	23	22	
Tumour grade*, %			
1	57	57	1.00
2	14	14	
Marital status†, %			
Married	55	54	
Divorced	2	2	0.92
Widowed	12	14	
Educational level‡, %			
Low	27	36	
Medium	23	23	0.21
High	17	10	
Employment status, %			
Not working/retired	63	65	0.35
Working	5	5	
Comorbidity, %			
One	17	25	0.32
Two or more	54	46	
Most common comorbid conditions, %			
Hypertension	26	15	0.04
Arthritis	19	16	0.56
Asthma	12	16	0.40
DP, %			
Yes	17	13	0.41
Median (IQR) years to DP	6.6 (1.5–8.3)	5.7 (4.0–6.4)	

**Grade was based on the TNM clinical classification [16,25], where Grade 1 is comparable to a Gleason score of 2–4 and Grade 2 is comparable to a Gleason score of 5–7. †There were no single patients in our sample; ‡Low (no or primary school), medium (lower general secondary education or vocational training), high (pre-university education, high vocational training, university).*

The generic HRQL of the AS and RT groups were compared with those of a normative population, standardized for age and sex (Fig. 1); there were no significant differences in HRQL scores between the AS group and the normative population, but the RT patients had significantly lower physical role functioning scores than the normative population. Both the AS and RT groups had similar generic HRQL.

There was no difference in HRQL between AS and RT as measured on the QOL-CS (data not shown). Further analyses examining the two individual items from the QOL-CS psychological well-being subscale assessing fear ('Do you feel fearful?') and depression ('How gloomy or depressed are you?') showed no differences between AS and RT patients (results not shown).

Compared with the AS group, the RT group had more symptom complaints. The RT patients reported significantly poorer bowel function, with scores of 87.1 (14.0) vs 92.80 (10.6) ($P < 0.001$) and were more bothered by their bowel function, at 85.0 (16.4) vs 93.7 (10.1) ($P < 0.001$) (Fig. 2). There were MID in bowel bother scores. There were no significant differences in urinary function and bother between the AS and RT groups. When compared with the normative

*FIG. 1. Comparison of SF-36 scores according to mode of management to the normal population standardized for age and sex. An asterisk above a subgroup indicates a difference in the mean score between that subgroup and the normal population. *P < 0.05*

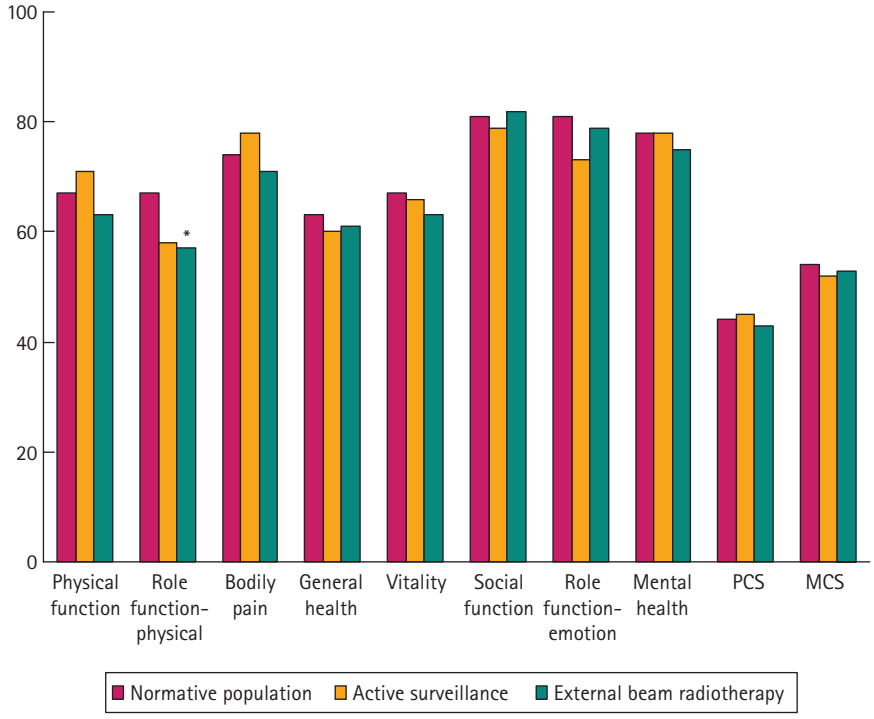
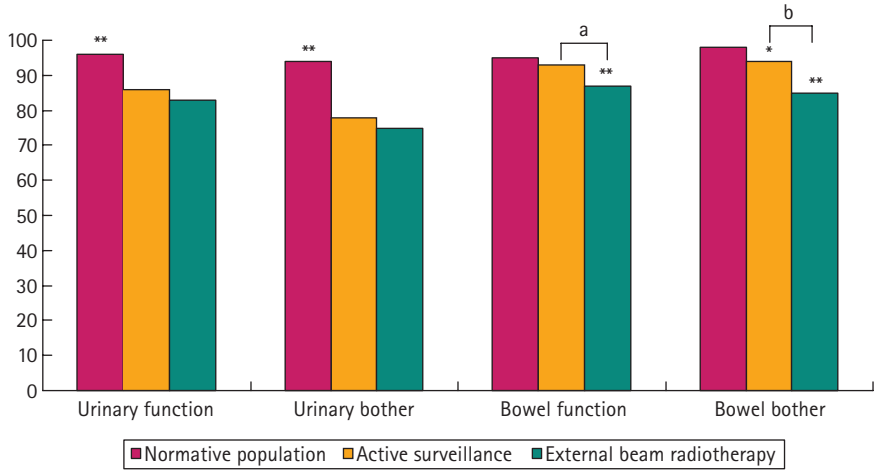


*FIG. 2. Comparison of EPIC urinary functioning/bother and bowel functioning/bother scores according to mode of management compared to the normal population standardized for age and sex. An asterisk above a subgroup indicates a difference in the mean score between that subgroup and the normal population. **P < 0.001; *P < 0.05; a and b, P < 0.001.*



population, both the RT and AS groups reported significantly poorer urinary function, and higher urinary and bowel bother. For bowel function, RT patients had significantly lower scores than the normative population.

On the SAc items, patients treated with RT reported significantly more problems related to 'getting and maintaining an erection in the last 2 weeks' than the AS group and the normative population (Fig. 3). There were no significant differences between the groups on other items of the SAc.

To ensure that the above results were not reflective of DP, subanalyses comparing the HRQL and symptom burden of RT and AS patients without DP were conducted; the results remain unchanged (data not shown).

In multivariate regression analyses, management strategy was an independent predictor of differences in HRQL and symptom complaints experienced by low-risk prostate cancer survivors (Table 2). RT was negatively associated with physical functioning and bodily pain dimensions of the SF-36. There was also a negative association on the QOL-CS spiritual and total well-being scores of RT patients. On the EPIC assessments, there were significant negative associations only with bowel function and bowel bother among RT patients. Poorer scores on various HRQL domains of the SF-36 and QOL-CS were independently predicted by DP and comorbidity.

In subanalyses within the AS group, patients with DP had similar scores on most HRQL dimensions as those patients without DP at the time of survey (data not shown). The only HRQL dimensions in which AS patients with DP scored significantly and clinically poorer than stable patients were on the SF-36 role functioning emotional and MCS summary dimensions, and QOL-CS total well-being scale. There were no differences in urinary and bowel function/bother in both groups.

DISCUSSION

Our study showed that long-term survivors of localized low-risk prostate cancer managed expectantly (AS) had comparable HRQL to prostate cancer survivors of similar age and clinical manifestation treated with RT. Furthermore, AS patients reported fewer problems with getting an erection, had better bowel functioning, and were less bothered with their bowel function than RT patients. In addition, the HRQL of AS patients was comparable to that in the age- and sex-matched normative population up to 10 years after diagnosis.

The similarity of HRQL scores of AS and RT patients up to 10 years after diagnosis is comparable to other studies. A randomized trial reported no differences in HRQL except for social functioning among prostate cancer

survivors treated with RT compared with those who deferred treatment [5]. A Swedish randomized trial comparing RP with watchful waiting also found no differences in HRQL between the groups [28].

Both the AS and RT groups in the present study had comparable urinary function and bother, while only the RT group had significantly poorer bowel function and higher levels of bother with their bowel function. Likewise, patients in the RT arm in the study of Fransson *et al.* [5] had more bowel symptoms than the deferred treatment group.

Previous, mainly qualitative, studies suggest that being managed with AS could increase the patients' psychological morbidity due to the untreated cancer [9,10]. In our sample, patients managed with AS had equivalent levels of psychological well-being as RT patients up to 10 years after diagnosis, and responses on the individual items of fear and depression of the QOL-CS were within normal levels, even after considering DP. Similarly, the Swedish study comparing RP with watchful waiting found no psychological differences between the groups at 4 years after randomization [28]. It could be suggested that it is not the type of treatment *per se* that increases psychological morbidity but rather patients' psychological state that determines treatment selection. A patient with low-risk prostate cancer who chooses curative treatment such as RT over AS could have anxiety and fear about living with untreated cancer. Latini *et al.* [11] showed that anxiety and PSA velocity were independent predictors of receiving curative treatment in a group of localized prostate cancer survivors under surveillance. In another study where patients with localized prostate cancer were allowed to decide between a lower- or higher-dose RT, patients with higher anxiety or depression levels were more likely to choose more aggressive treatment [29]. However prostate cancer survivors who regretted their curative treatment have poorer HRQL and more symptom complaints than those who were not regretful [30]. Interestingly, that study, patients who had regrets about their treatment had lower median PSA levels and Gleason scores than those who were not regretful. Treatment objectives could differ between patients with prostate cancer and their physicians [31], and agreement was poor when physicians were asked to predict patients' treatment preferences [32]. These

FIG. 3. Comparison of sexual complaints (%) among prostate cancer survivors with a Dutch male normal population standardized for age and sex. a, P < 0.01 between normal and AS, normal and RT, AS and RT; b, P < 0.01 between normal and AS, normal and RT; c, P < 0.01 between normal and RT, AS and RT.

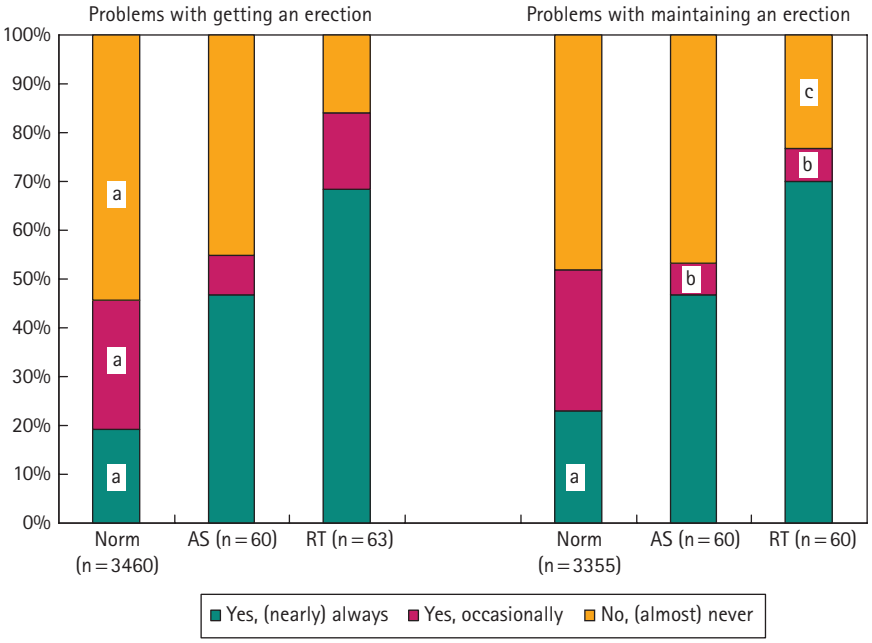


TABLE 2 Standardized β coefficients of multivariate analyses indicating the association of management strategy of low-risk prostate cancer on HRQL, and urinary/bowel function/bother

Instrument/domain	RT vs AS	DP, yes vs no	Comorbidity yes vs no
SF-36			
GH	ns	ns	−8.4*
PF	−9.4*	ns	−15.5*
RP	ns	−19.3*	−18.4*
RE	ns	−25.2*	ns
BP	−8.9*	ns	−12.9*
SF	ns	ns	ns
VT	ns	−9.2*	ns
MH	ns	−7.8*	−7.4*
PCS	ns	ns	−4.4*
MCS	ns	−6.2*	ns
QoL-CS			
Phy	ns	ns	−0.9*
Psy	ns	−0.9*	ns
Soc	ns	ns	−0.7*
Spi	−0.5*	ns	−0.6*
Tot	−0.5*	−0.6*	−0.6*
EPIC			
UF	ns	ns	ns
UB	ns	ns	ns
BF	−5.7*	ns	ns
BB	−8.8†	ns	ns

*†P < 0.001; *P < 0.05. GH, general health; PF, physical function; RP, role function, physical; RE, role function, emotional; BP, bodily pain; SF, social function; VT, vitality; MH, mental health; Phy, physical well-being; Psy, psychological well-being; Soc, social well-being; Spi, spiritual well-being; Tot, total well-being; UF, urinary function; UB, urinary bother; BF, bowel function; BB, bowel bother.*

results suggest that patients diagnosed with low-risk prostate cancer, besides having adequate and relevant information on the natural history of low-risk prostate cancer and its treatment options, could also benefit from psychological support in their decision-making.

Of interest is DP among the AS and RT patients in our study. Despite the assumption that undergoing RT decreases or eradicates possible DP, while AS patients live with untreated cancer and therefore risk DP, both groups had similar numbers of patients with DP. Among patients with a known time to DP, those in the AS group had a longer median time to progression than the RT group (Table 1). Furthermore, in a retrospective study of the survival time of men managed expectantly, the 10-year prostate cancer-specific survival was 100% [16]. We acknowledge that the psychological burden and treatment options after DP could differ for AS and RT patients, but the results remained similar when DP patients in both groups were excluded from the analyses. As such, these results, in addition to the increase in symptom burden for patients treated with RT, suggest these patients could be over-treated for their localized prostate cancer compared with AS patients with similar clinical characteristics.

There are several limitations to the current study; the inclusion of long-term AS survivors could indicate possible survival bias. However, as both the AS and RT groups had a similar mortality rate (data not shown), we conclude that survival bias is unlikely to be a problem. Second, although we included patients with low cancer stage and grade in the AS group, we cannot exclude the possibility of some misclassification, as we do not have data on Gleason scores and PSA values of these patients. We limited our comparison only to patients receiving RT. We acknowledge as such that we are not able to generalize our results to survivors who received other forms of curative treatment. Selection bias could explain the lack of difference in psychological well-being between the groups, as the anxiety levels might have decreased over time, or those more anxious patients were less likely to stay on the AS protocol. Furthermore, the cross-sectional design of our study limits the determination of a causal association between management strategy and HRQL, as baseline HRQL at diagnosis before the start of management is not known. Moreover, DP was established by patients' self-report and thereafter confirmed via the ECR. Therefore, under-representation of patients with DP is possible, as patients who had progression did not report this on the questionnaire. Despite these limitations, our current results are intriguing and would benefit from further investigation using a prospective longitudinal design with a long follow-up to detect possible clinical DP. Future studies could assess the HRQL of men with newly diagnosed low-risk localized prostate cancer before start of *any* form of management strategy, to establish a baseline against which follow-up assessments could be compared.

Nevertheless, the strong points of our study include the HRQL assessment of a population-based sample managed expectantly up to 10 years after diagnosis. Our study can therefore be considered unique in providing information on the long-term effect of expectant management on HRQL and symptom burden. Moreover, the inclusion of DP for consideration when assessing long-term HRQL in patients managed expectantly has, to our knowledge, not been previously reported.

In conclusion, patients diagnosed with localized low-risk prostate cancer are often faced with difficult decisions about their treatment options. In our study, patients managed expectantly had comparable HRQL and a lower symptom burden than RT patients up to 10 years after diagnosis, even after controlling for comorbidity and DP.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **AS**, active surveillance; **RT**, radiotherapy; **HRQL**, health-related quality of life; **ECR**, Eindhoven Cancer Registry; **PCS**, physical component summary; **MCS**, mental component summary; **SF-36**, Short-Form-36; **EPIC**, Expanded Prostate Cancer Index; **IQR**, interquartile range; **QOL-CS**, Quality of Life – Cancer Survivors; **MID**, minimal important differences; **SAc**, sexual activities module; **DP**, disease progress(ion); **RP**, radical prostatectomy.