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A longitudinal study on the impact of active surveillance for prostate cancer on anxiety and distress levels

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Abstract

***Objective*: Patients with potentially indolent prostate cancer (PC) can be managed with active surveillance (AS). Our objective was to analyse how anxiety and distress develop in men with untreated PC and whether highly anxious men quit AS.**

***Methods*: One hundred and fifty Dutch patients who opted for AS in the Prostate cancer Research International: Active Surveillance Study were invited to participate in an additional prospective, longitudinal quality of life (QoL) study within 6 months after diagnosis. Participants completed questionnaires with validated measures on anxiety and distress at inclusion ($t = 0$), 9 ($t = 9$) and 18 ($t = 18$) months after diagnosis. We assessed changes in scores on depression (Center for Epidemiologic Studies Depression (CES-D) scale), generic anxiety (State–Trait Anxiety Inventory (STAI-6)), PC-specific anxiety (Memorial Anxiety Scale for Prostate Cancer (MAX-PC)) and decisional conflict (Decisional Conflict Scale (DCS)) about patients' treatment choice between $t = 0$, $t = 9$ and $t = 18$ using repeated measures analysis.**

***Results*: Response rates for patients still on AS at $t = 0$, $t = 9$ and $t = 18$ assessments were 86%, 90% and 96%, respectively. Nine patients (7%, 9/129) between $t = 0$ and $t = 9$ and 33 of 108 patients (31%) between $t = 9$ and $t = 18$ stopped AS, mostly (86%) because of protocol-based reasons. CES-D, total MAX-PC and DCS scores did not change significantly ($p > 0.05$) when comparing $t = 18$ with $t = 9$ and $t = 0$ scores, but generic anxiety (STAI-6; $p = 0.033$) and fear of disease progression (sub-score of the MAX-PC; $p = 0.007$) decreased significantly. These differences, however, were clinically modest (0.089 SD and 0.281 SD). Overall, six of 129 men (5%) discontinued AS because of anxiety and distress.**

***Conclusions*: When men with low-risk PC are managed with AS, fear of disease progression and general anxiety decreased, and only few may discontinue AS because of anxiety and distress. This suggests that negative QoL effects are limited in men with favourable clinical characteristics who opted for AS. (Registered trial number, NTR1718)**

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Introduction

Screening and more intensive diagnostic work-ups lead to an increase in the detection of small, localized, well-differentiated prostate cancers (PCs). Therefore, the ratio between men dying with and from PC is increasing. In many developed countries, detection and treatment are tightly linked; most patients with PC receive radical treatment despite the favourable natural history of many tumours [1–3]. Treatment of small, localized, well-differentiated PC tumours should ideally be selective, reflecting each patient's individual characteristics [4]. Active surveillance (AS), in that context, is considered a realistic initial alternative for curative therapy.

Active surveillance aims at selecting low-risk PC with a likely favourable prognosis and strictly monitoring these tumours over time. If risk reclassification or disease progression occurs, men can opt for curative therapy. The aim of AS is to safely delay or even completely avoid side effects of active therapy [5].

From the moment low-risk PC is diagnosed, anxiety, distress, beliefs and expectations may play a role in a patient's treatment decision-making [5], affecting the patient's quality of life (QoL). The choice between an AS management strategy or active therapy potentially affects various QoL aspects. Although active therapy may provide patients with a feeling of certainty and being in control of their disease, the trade-off might be the potential worsening of sexual, urinary and bowel functions. Choosing AS spares these functions because active therapy is delayed or, potentially, completely avoided, but comes at the trade-off of continued uncertainty, anxiousness and distress. For patients who choose AS, there is always the possibility of missing the 'window of curability' or waiting too long before starting active therapy, which might lead to worse outcomes when compared with those with immediate

treatment. It is hypothesized that such possibilities might have an unfavourable effect on sexual, urinary and bowel function as well as on anxiety and distress levels [6,7]. It is therefore recommended that these potential negative effects are thoroughly considered before choosing AS.

QoL among men on AS has been studied before [2,8–10]. Results showed that short-term anxiety and distress levels were favourably low for men on AS compared with QoL of men choosing active therapy. Up to now, few studies reported longer-term QoL. With this longitudinal study, we report on the 18-month QoL of a cohort of men who agreed to participate in a well-defined, globally accepted AS protocol, the Prostate cancer Research International: Active Surveillance (PRIAS) study, and who accepted to follow the PRIAS protocol for an 18-month period. Of specific interest is how levels of anxiety and distress develop during follow-up. We hypothesize that anxiety and distress levels remain favourable for men who continue AS for an 18-month period and that anxious men will discontinue AS early on.

Materials and methods

Patients included in this prospective QoL study were participants in the protocol-based, multicentre, prospective, observational PRIAS study [2,8,11]. PRIAS inclusion criteria are as follows: PC diagnosis with a prostate-specific antigen (PSA) of ≤10.0 ng/mL; a PSA-density (PSA/prostate volume) of <0.2 ng/mL/mL; (≤T2); one or two positive prostate needle-biopsy cores, with a Gleason score of $\leq 3+3=6$. The follow-up protocol included PSA measurements every 3 months for the first 2 years and every 6 months thereafter. Digital rectal examination was scheduled every 6 months for the first 2 years and once a year thereafter. Repeat biopsies were scheduled after 1, 4 and 7 years, and in the case of a PSA-doubling time between 3 and 10 years, yearly repeat biopsies were advised. Risk reclassification at repeat biopsy triggered a recommendation for active therapy and was defined as ≥3 positive biopsy cores and/or Gleason score of >6. A PSA-doubling time, which can only be reliably calculated after a minimum of one baseline and four follow-up measurements, of less than 3 years was also used as a trigger to initiate active therapy [11]. Men in our study thus have had several PSA measurements and underwent a repeat biopsy at 1 year post-diagnosis, that is, in between the t9 and t18 measurement. Participation in PRIAS requires informed consent.

The inclusion period May 2007–May 2008 determined the sample size [12]. All Dutch PRIAS participants who were diagnosed with PC (at most 6 months earlier) in that year were invited to be included in an additional QoL study ($n=150$). Besides the above-mentioned PRIAS inclusion criteria, no additional inclusion or exclusion criteria were applied. Through regular mail, those who consented received a first QoL questionnaire at their home address ($t=0$). If they had not returned their questionnaire within 1 month, they were reminded once by telephone. All patients who returned the first questionnaire received a second questionnaire 9 months after diagnosis ($t=9$). Patients who returned the second questionnaire received a third and final questionnaire 18 months after diagnosis ($t=18$).

The PRIAS study and its QoL study were approved by the Institutional Review Board of the Erasmus University Medical Centre (MEC number 2004-339) and by the Institutional Review Boards of peripheral hospitals, taking local regulations into account. (Registered trial number, NTR1718)

Measures included in the questionnaire

With the use of validated questionnaires, we evaluated levels of anxiety and distress of men on AS for low-risk PC. We defined distress as 'occurring when an individual cannot adapt to stress' [13]. Distress was measured through the Decisional Conflict Scale (DCS), Center for Epidemiologic Studies Depression (CES-D) scale and the self-estimated risk of progression scale.

We assessed potential decisional conflict regarding the choice for AS, using the DCS. This scale consists of 16 items with five response options each (score range per item is 0–4). Scale scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict). DCS scores ≤25 tend to be associated with implementing decisions, while scores ≥37.5 are associated with decision delay or feeling unsure about implementation of a decision [2,14,15]. Subscales of the DCS were not analysed in this study.

Symptoms of depression were assessed with the CES-D. The scale consists of 20 items with four response options each (score range per item is 0–3). The total score ranges from 0 to 60; the higher the score, the more symptomatology of depression is present. An individual is considered to be at high risk of clinical depression with a score of ≥16 [2,16,17].

Furthermore, we assessed the self-estimated risk of disease progression with a self-designed, non-validated, two-question measure (Question 1: 'Take in mind an average man with PC who has also chosen an AS management strategy. What is his chance of progression of his PC within the coming year?' – 'very unlikely, unlikely, average, likely, very likely'; Question 2: 'Now imagine your personal situation. Do you estimate your chance of deterioration of your PC in the coming year to become larger or smaller as compared to an average male on AS for PC?' – 'The chance of deterioration for me is "very unlikely-", "unlikely-", "average-", "likely-", "very likely" as compared to an average male'). The answering categories of both items are scored 1–5 (very unlikely = 1, very likely = 5). The total

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score of the self-estimated risk of progression scale ranges from −4 to 4 and is calculated by subtracting a man's own self-estimated risk of the self-estimated average risk that this man reported. This measure is based on earlier research by Essink-Bot *et al.* [18].

Anxiety was measured through the State–Trait Anxiety Inventory (STAI-6) and the Memorial Anxiety Scale for Prostate Cancer (MAX-PC).

Generic anxiety was assessed with the abridged STAI-6. This scale consists of six items with four response options each (score range per item is 1–4). The total score ranges from 20 to 80, with 80 indicating maximum generic anxiety. A STAI-6 score of ≥44 defines an individual as highly anxious [2,19,20].

The MAX-PC was used to assess PC specific anxiety. This scale consists of 18 items with four response options each (score range per item is 0–3). The total score ranges from 0 to 54, with 54 indicating maximum PC specific anxiety. In earlier studies, a MAX-PC score of 27 has been applied to identify individuals with clinically significant PC-specific anxiety [21]. The MAX-PC consists of three subscales that measure general anxiety related to PC and treatment, anxiety related to PSA levels in particular and fear of recurrence (fear of disease progression) [2,21,22]. The MAX-PC subscale 'fear of recurrence' was not originally designed to measure fear of disease progression; it was designed to measure fear of recurrence after one was treated for PC and the cancer was removed. With AS, it is not recurrence that men may be scared of, it is the progression of their cancer that they are worried about. Items of the subscale were structured in such a way that we consider them also applicable to fear of disease progression.

General physical health of participants was assessed at $t=0$ and $t=18$ with the short-form health-survey (SF-12). The total scale consists of 12 items with two to six response options each, with which two summary scores can be calculated: the mental component summary (MCS) and the physical component summary (PCS). All 12 items are necessary to calculate both the MCS and PCS. In calculating the MCS and PCS, the distributions of weights for each item differ. Because of the conceptual overlap of the MCS with the CES-D, STAI-6 and MAX-PC, in this study the MCS items were not included in the analyses. The total score of the PCS subscale can range from 0 to 100, with 100 indicating best overall health [23].

Validated Dutch translations of the DCS, CES-D, STAI-6, SF-12 and MAX-PC were used [24–28]. These measures had been validated in populations that are comparable to ours, that is, other cohorts of cancer patients, except for the CES-D, that had been validated in a cohort of older men from the general population. All measures were scored applying the official scoring system and regulations for missing values [14,19,21,23,29]. The Cronbach's alpha of the self-estimated risk of progression scale was 0.84, indicating that the two items in this scale measure the same construct. While validation was not the aim of our study, we will nevertheless look at some psychometric properties of the used validated Dutch measures.

Previously, we presented baseline QoL outcomes and outcomes after 9 months of follow-up [2,8]. In the current article, the differences between scores on DCS, MAX-PC, STAI-6 and CES-D between $t=0$, $t=9$ and $t=18$ were analysed using repeated measures analysis to assess changes over time. Differences in SF-12 (PCS) scores between $t=18$ and $t=0$ were analysed with paired samples t-test after log-transformation due to non-normal distribution. The clinical relevance of differences, that is, the smallest change in scores experienced as meaningful by patients, was determined using the minimal important difference, operationalized as half a standard deviation of the first measurement [30]. Differences ≥0.5 SD were considered as relevant. Men with STAI-6 scores >44 at baseline were considered as highly anxious [2,20]. We explored whether these men became less anxious during follow-up or whether these highly anxious men discontinued AS. Analyses were performed with SPSS, version 20 (IBM, Armonk, NY, USA), and SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The average age of participants at baseline was 64.6 years, and their average PSA level was 5.7 ng/mL (Table 1).

The $t=0$, $t=9$ and $t=18$ questionnaires were completed by 86% (129/150), 90% (108/120) and 96% (72/75) of participants still on AS (Figure 1). The questionnaires were completed at a median of 2.4 months (25–75p: 1.3–3.9), 9.2 months (25–75p: 9.0–9.6) and 18.2 months (25–75p: 17.6–18.6) after diagnosis. We compared the Cronbach's alphas we found for our measures to the Cronbach's alphas of Dutch validation studies: DCS 0.93 vs. 0.75–0.82 [24]; MAX-PC 0.77 vs. 0.77 [28]; STAI-6 0.77 vs. 0.83 [26]; CES-D 0.60 vs. 0.80–0.90 [25]; SF-12 0.72 vs. 0.81–0.91 [27]. Questionnaires contained low numbers of missing values, and respondents added no remarks about the questions.

Between the $t=0$ and $t=18$ questionnaire, 42 men switched to active therapy; six upon their own request (5%, 6/129) because of anxiety and distress and 36 (28%, 36/129) because of reclassification or progression of their PC. Treatments for these 42 men consisted of radical prostatectomy in 17 patients (40%), brachytherapy in 15 (36%), external beam radiation therapy in six (14%), High-Intensity Focused Ultrasound in one (2%), and an unknown treatment modality in three (7%).

Table 2 presents the mean, median and interquartile range of questionnaire scores at $t=0$, $t=9$ and $t=18$. Figure 2 shows a graphical overview of the mean questionnaire scores at $t=0$, $t=9$ and $t=18$. We noted non-

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significant decreases in the mean scores between $t=0$, $t=9$ and $t=18$ for the DCS ($p=0.336$), CES-D ($p=0.655$), total MAX-PC ($p=0.331$) and self-estimated risk of progression ($p=0.457$) scores. For the SF-12 (PCS), a non-significant ($p=0.428$) decrease was seen between $t=0$ and $t=18$. Generic anxiety (STAI-6) ($p=0.033$) and fear of disease progression (subscale of the MAX-PC) ($p=0.007$), however, decreased significantly when comparing $t=0$, $t=9$ and $t=18$. These differences, however, were clinically modest: 0.089 SD and 0.281 SD, respectively.

Twenty-six men presented with STAI-6 scores >44 at baseline. Eight of these 26 men (31%) became less anxious and remained on AS. Six (23%) men were highly anxious at $t=0$, $t=9$ and $t=18$ but remained on AS. Three men (12%) were highly anxious at baseline, their scores decreased to ≤44 at $t=9$ and at $t=18$ they quit AS because of tumour progression. Seven men (27%) were highly anxious at baseline and stopped AS because of reclassification of their PC at $t=9$. Two men (8%) were highly anxious and therefore stopped AS; these latter two belong to the group of six men who stopped AS upon their own request.

Table 1. Medical, demographic and other characteristics at the moment of diagnosis of the total study population ($N=129$) [2]

Total number of patients	129	
Medical		
PSA at diagnosis (median/25–75p[a])	5.7	4.6–7.0 ng/mL
Last known PSA before second questionnaire (median/25–75p[a])	5.6	3.8–7.0 ng/mL
Clinical stage at diagnosis		
Non-palpable	91	71%
Localized	38	29%
Number of positive biopsies at diagnosis		
1	79	61%
2	50	39%
Demographics		
Age at diagnosis (median/25–75p[a])	64.6	60.2–70.4 years
Education		
Low (primary, secondary)	86	67%
High (college, university)	42	33%
Missing	1	
Employed		
Yes	76	60%
No	50	40%
Missing	3	
Hospital		
University/specialized	68	53%
Other	61	47%
Civil status		
Married/living together	119	92%
Other	10	8%
Other		
Major life event before diagnosis other than PC		
Yes	15	12%
No	114	88%
Sexually active		
Yes	93	73%
No	35	27%

Total study population is $N=129$ [2]. PSA, prostate specific antigen; PC, prostate cancer.
[a]25–75p is 25–75th percentile.

Discussion

In men with low-risk PC who were managed with AS for an 18-month period, average levels of anxiety and distress remained favourably low. Our findings suggested furthermore that generic anxiety and fear of disease progression tended to decrease in men remaining eligible for AS. Only six of 129 men (5%) discontinued AS because of anxiety or distress. Eight of 26 men who were highly anxious at baseline became less anxious while remaining on AS.

This study provides additional information on the effect of AS on longitudinal QoL scores. Anxiety and/or distress were uncommon reasons to stop AS and switch to active therapy. A significant trend towards lower scores of fear of disease progression was observed, which may be explained by the idea of stable disease providing confidence and tranquillity of mind during follow-up [31] or by an up-front selection of those patients who expect that they can mentally deal with the potential progression of their disease.

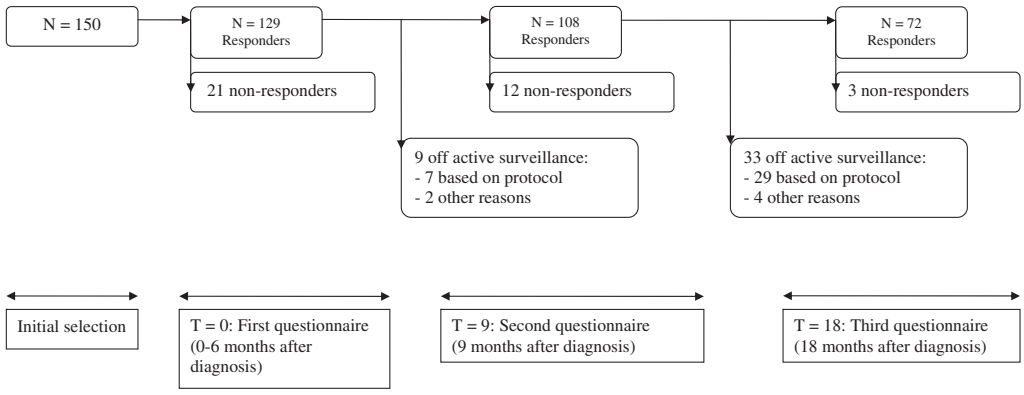

Figure 1. Patient cohort selection

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Table 2. Questionnaire scores at t0 (129 men), t9 (108 men) and t18 (72 men)

	Score range	Clinical threshold	Mean/median t0 (IQR) [2]	Mean/median t9 (IQR) [8]	Mean/median t18 (IQR)	*F*-value	*p*-value[a]
DCS	0–100	37.5	27.0/28.1 (17.2–36.3)	27.9/28.1 (17.2–36.3)	27.0/26.6 (15.6–35.9)	1.10	0.336
CES-D	0–60	16	5.4/4.0 (0.0–9.0)	5.3/3.0 (0.0–8.8)	5.4/3.0 (0.0–6.0)	0.42	0.655
STAI-6	20–80	44	35.2/33.3 (30.0–40.0)	33.4/33.3 (30.0–36.7)	34.4/33.3 (30.0–36.7)	3.48	0.033
Total MAX-PC	0–54	27	13.7/13.5 (6.3–20.0)	13.4/14.0 (7.0–18.0)	12.6/11.5 (6.0–18.0)	1.11	0.331
- PC anxiety	0–33	—	9.1/8.0 (3.0–14.0)	9.5/9.0 (4.0–13.0)	8.7/8.0 (3.8–13.3)	0.83	0.438
- PSA anxiety	0–9	—	0.3/0.0 (0.0–0.0)	0.3/0.0 (0.0–0.0)	0.5/0.0 (0.0–0.0)	1.02	0.364
- Progression fear	0–12	—	4.2/4.0 (2.0–6.0)	3.5/4.0 (2.0–5.0)	3.5/4.0 (2.0–5.0)	5.15	0.007
Self-estimated progression risk	−4–4	—	0.2/0.0 (0.0–1.0)	0.5/0.0 (0.7)	0.6/0.0 (0.0)	—	—[c]
SF-12 PCS	—	—	51.4/54.3 (48.9–55.9)	—	50.1/53.5 (47.9–54.3)	—	0.428[b]

IQR, interquartile range.
[a]*p*-value t0/t9/t18 (linear mixed model).
[b]*p*-value t0/t18 (paired *t*-test).
[c]No statistical testing applied; Cronbach's alpha was 0.84.

Our outcomes are supported by the results of a study among Finnish PRIAS participants that showed no deterioration of QoL after 1 [32] and 3 years [33] of follow-up. Instead, in this cohort of men, statistically significant QoL increases were seen, although clinically insignificant.

Not all men with low-risk PC may be candidates for AS. It was found that men with more neurotic personalities tend to have a higher chance of anxiety or psychological distress, which may lead to not choosing AS at all or stopping AS early [2,34]. It has been hypothesized that such men could benefit from psychological support in making a treatment decision. Bellardita *et al.* found in multivariate logistic regression models that factors predicting poor QoL during AS were having no partner, impaired mental health, recent diagnosis, influence of clinicians and lower number of core samples taken at diagnostic biopsy [7]. They concluded that the assessment of such predictors at entrance in AS could be useful in identifying more vulnerable patients to prevent poor QoL by promoting educational support from physicians and emotional/social support. Such predictors can also help in designing and implementing educational psychosocial interventions to support patients and in promoting well-being and positive adjustment to cancer [7]. In the Finnish AS cohort, men newly diagnosed with PC were thoroughly informed about their treatment options by a urologist as well as by a specialized PC nurse [32,33]. Only patients who seemed to accept the idea of living with a possible clinically insignificant PC for which no immediate treatment was needed were offered AS as a primary management option. The support that was provided in making a treatment decision led to none of the patients discontinuing AS because of anxiety in this cohort [32]. In our cohort, men were informed about all possible treatment options by their treating urologist. Potential additional methods of counselling were not standardized and decided upon by the individual centres. Applying predictors of poor QoL upfront inclusion on AS to prevent poor QoL by promoting educational support by physicians, as suggested by Bellardita *et al.* [7], or offering counselling, as suggested by Vasarainen *et al.* [32], to the two men who presented with STAI scores of >44 could potentially have led to the continuation of AS.

The strengths of the present study are the prospective design and the availability of clinical parameters for all participants. The outcomes of our study provide support for AS as a management strategy for low-risk PC. Furthermore, we consider the use of validated measures in our cohort as a strength. The measures show similar Cronbach's alphas compared with Dutch validation studies, except for the CES-D, which is potentially due to differences in the populations in which the Dutch translation of the measure was validated. The low number of missing values on the questionnaires indicates that patients considered the questions acceptable and that the questions were well understood.

Limitations of our study are the unavailability of a baseline measurement of anxiety and distress, the rather limited sample size, and that we cannot compare 18 months follow-up data of men on AS to QoL data of men who initially chose an AS strategy but later opted for curative therapy.

The fact that we were unable to obtain a baseline measurement of anxiety and distress levels before men made a treatment decision may have led to an underrepresentation in our cohort of men who expected to experience feelings of anxiety and distress about living with untreated PC. It is therefore unknown how many men preferred active therapy over AS to avoid potential feelings of anxiety and distress of living with untreated PC.

As men switching to active therapy during follow-up were not included in this study, we recommend focusing future research on QoL of men who switched from AS to active therapy. We found that of the six men who stopped AS because of anxiety and distress, two had reported high anxiety scores. It would be interesting to know how their QoL evolved after their decision to opt

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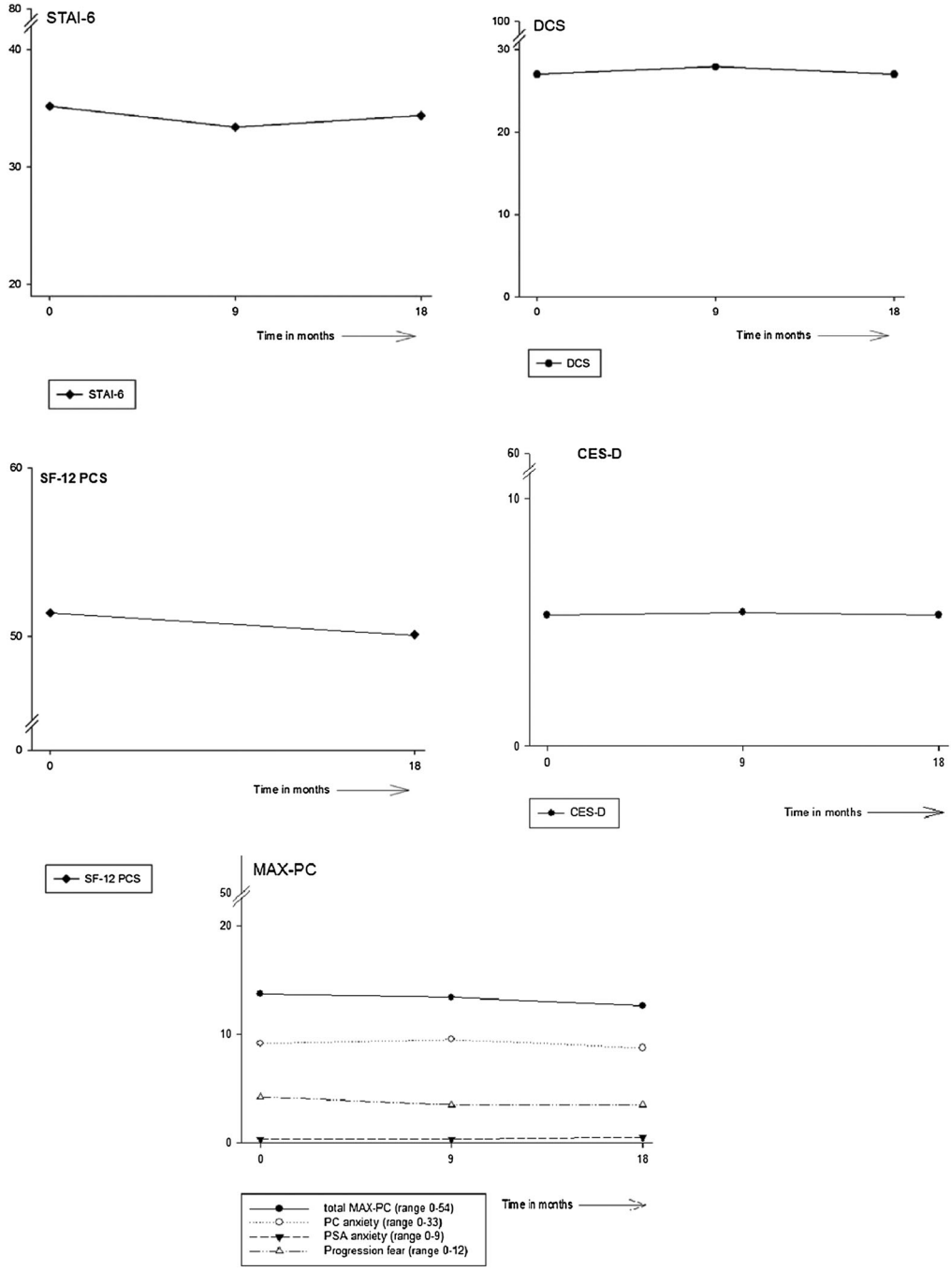

Figure 2. Mean questionnaire scores at $t = 0$, $t = 9$ and $t = 18$ (in accordance with Table 2)

for curative therapy and the initiation of treatment. Also, four men discontinued AS because of distress, but this was not reflected in their anxiety scores.

Conclusion

When men with low-risk PC are managed with AS, fear of disease progression and general anxiety decrease, and only few may discontinue AS because of anxiety and distress. This suggests that negative QoL effects are limited in men with favourable clinical characteristics who opted for AS. The sample size was small, however, and further research is needed to confirm our results.

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