Does active surveillance for men with localized prostate cancer carry psychological morbidity?

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OBJECTIVES

To investigate, in a cross-sectional study, the prevalence of anxiety and depression in patients with localised prostate cancer managed by active surveillance, compared with those receiving immediate treatment, as active surveillance is a relatively new approach to managing this disease, designed to avoid ‘unnecessary’ treatment, but it is unclear whether the approach contributes to psychological distress, given that men are living with untreated cancer.

PATIENTS AND METHODS

A consecutive series of 764 patients with prostate cancer were approached in outpatient clinics. Of these, 329 men with localized disease (cT1/2, N0/NX, M0/MX) meeting the study entry criteria, completed the Hospital Anxiety and Depression Scale (HADS); 100 were on active surveillance, 81 were currently receiving radical treatment (radiotherapy + neoadjuvant hormone therapy) and 148 had previously received radical radiotherapy.

RESULTS

Overall, 16% (51/329) of patients met the HADS criteria for anxiety and 6% (20/329) for depression. Analyses indicated that higher anxiety scores were significantly associated with younger age (P < 0.01) and a longer interval since diagnosis (P < 0.01), but not with management by active surveillance (P = 0.38). Higher depression scores were significantly associated with a longer interval since diagnosis (P < 0.05), but not with management by active surveillance (P = 0.83).

CONCLUSION

Active surveillance for managing localized prostate cancer was not associated with greater psychological distress than more immediate treatment for prostate cancer.

KEYWORDS

anxiety, depression, coping, active surveillance, localized prostate cancer

INTRODUCTION

Active surveillance (AS) aims to individualize the management of early prostate cancer by selecting only men with significant cancers for curative treatment [1]. Patients on AS are closely monitored using PSA blood tests, and repeat prostate biopsies. The choice between curative treatment or continued AS is based on evidence of disease progression during this monitoring. It is possible that targeted radical treatment, based on an AS strategy, will be as effective, and considerably less morbid, than radical treatment for all cases. The most mature prospective study of AS was reported by Klotz [2]. Of 299 patients with favourable-risk, localized prostate cancer, 20% received radical treatment because of a rapid PSA doubling time, 10% because of ‘progression’ on repeat biopsy, and 10% because of patient preference, so that the remaining 60% avoided the risk of treatment-related morbidity. The 8-year disease-specific mortality was just 1%.

However, one potential concern about AS is that living with untreated prostate cancer might be expected to evoke psychological distress. For example, patients might feel helpless in terms of their cancer, feel that they are at a greater threat from their cancer, or be unsure about what the future holds in terms of prognosis and the potential need for treatment. Although there is much research reporting levels of depression and anxiety, assessed using the Hospital Anxiety and Depression Scale (HADS) in prostate cancer samples [3], and some studies compared various treatment groups [4] and other factors associated with anxiety and depression [5], the impact of AS on psychological functioning is unclear and unexplored.

Levels of anxiety and depression have been recorded in patients with prostate cancer, mainly using the HADS, with variable results [3]; e.g. the mean anxiety and depression scores were as low as 4.2 and 3.4 [6], and as high as 10.6 and 12.3 [7]. In terms of patients meeting the clinical criteria for anxiety or depression (using ≥ 8 as a standard threshold), the values were 14% and 9%, respectively [6]. Patients in that study mainly had localized disease (69%) and received radiotherapy and hormone therapy. Of 210 patients assessed, only 20% were currently on treatment and no patients were under AS.

Although the effect of disease stage on anxiety and depression levels has been considered [7], researchers often failed to explore any differences in anxiety and depression levels across different treatment strategies. One study [4] that considered the differences in psychosocial functioning across groups of patients with localized prostate cancer receiving different treatments, including radical prostatectomy, external beam radiotherapy or brachytherapy, found no significant differences in emotional functioning. However, patients managed by AS were not included.
In the present study we investigated whether patients on AS had different anxiety and depression levels from those undergoing radical treatment, or those being followed after radical treatment.

**PATIENTS AND METHODS**

A consecutive series of 764 outpatients with prostate cancer attending the Royal Marsden NHS Foundation Trust, UK, was approached for anxiety and depression screening using the HADS; the study was approved by the Local Research Ethics Committee. After obtaining informed consent, patients were given the opportunity to complete the HADS in clinic or to take it home and complete it in their own time.

The HADS [8] is a 14-item self-reported scale, developed specifically to measure depression and anxiety in physically ill populations, with threshold scores of 8–10 on the depression and anxiety subscales indicating clinically significant distress, 11–14 indicating moderate distress and 15–21 indicating severe distress [9]. The scale largely excludes somatic variables that might overlap with physical symptoms.

Normative data for the HADS from a large non-clinical sample (1792) [10] found, using a threshold of ≥8, that 33% of participants met criteria for anxiety and 11% met criteria for depression. The mean (SD) score on the anxiety scale was 6.14 (3.76) and on the depression scale was 3.68 (3.07).

Of 764 patients approached for screening, 493 had early-stage prostate cancer; 72% (353/493) of patients completed the HADS and a further 24 were excluded because treatment decisions were undecided, resulting in a final sample of 329 patients. Three treatment groups were formed: those who were currently on AS (100); those who were currently undergoing radical treatment (hormone therapy or radiotherapy, 81); and those who were on follow-up after radical treatment (148).

**RESULTS**

The demographic and clinical characteristics of the patient cohort did not differ for the AS, on-treatment and after-treatment groups in ethnic origin, marital status, education, employment and occupation. One-way ANOVA indicated that the treatment groups differed in age (P < 0.01) and time since diagnosis (P < 0.01; Table 1). Least significant difference (LSD) comparisons showed that patients on AS were significantly younger (67.12 years) than both on-treatment (70.05) and after-treatment groups (69.30; P < 0.01), and the interval since diagnosis was significantly longer for the after-treatment (56.43 months) than the AS (28.61) and on-treatment groups (33.95; P < 0.01).

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**TABLE 1 Characteristics and clinical factors, according to treatment group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AS (100)</th>
<th>On-treatment (81)</th>
<th>After treatment (148)</th>
<th>P (chi-square) between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White British</td>
<td>95 (95)</td>
<td>75 (92.6)</td>
<td>137 (92.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (5)</td>
<td>6 (7.4)</td>
<td>11 (7.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/with partner</td>
<td>78 (78)</td>
<td>71 (87.7)</td>
<td>126 (85.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>22 (22)</td>
<td>10 (12.3)</td>
<td>22 (14.9)</td>
<td>0.17</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left school before age 15</td>
<td>14 (14)</td>
<td>18 (22.2)</td>
<td>29 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Secondary education</td>
<td>35 (35)</td>
<td>27 (33.3)</td>
<td>40 (27.0)</td>
<td></td>
</tr>
<tr>
<td>College or specialized training</td>
<td>19 (19)</td>
<td>20 (24.7)</td>
<td>30 (20.3)</td>
<td></td>
</tr>
<tr>
<td>University or equivalent</td>
<td>29 (29)</td>
<td>12 (14.8)</td>
<td>45 (30.4)</td>
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</tr>
<tr>
<td>Unknown</td>
<td>3 (3)</td>
<td>4 (4.9)</td>
<td>4 (2.7)</td>
<td>0.16 (318)*</td>
</tr>
<tr>
<td>Employment</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>24 (24)</td>
<td>14 (17.3)</td>
<td>28 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>76 (76)</td>
<td>67 (82.7)</td>
<td>120 (81.1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>13 (13)</td>
<td>11 (13.6)</td>
<td>23 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Non-manual</td>
<td>48 (48)</td>
<td>31 (38.3)</td>
<td>66 (44.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>39 (39)</td>
<td>39 (48.1)</td>
<td>59 (39.9)</td>
<td>0.67</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) [n]:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, years</td>
<td>67.12 (6.95)</td>
<td>70.05 (6.64)</td>
<td>69.30 (6.13)</td>
<td></td>
</tr>
<tr>
<td>time since diagnosis, months</td>
<td>28.61 (20.95)</td>
<td>33.95 (36.44)</td>
<td>56.43 (34.55)</td>
<td></td>
</tr>
<tr>
<td>most recent PSA level, ng/mL [329]</td>
<td>7.72 (5.36)</td>
<td>2.76 (5.08)</td>
<td>1.94 (5.00)</td>
<td></td>
</tr>
<tr>
<td>initial PSA level, ng/mL [329]</td>
<td>6.72 (4.76)</td>
<td>15.19 (16.10)</td>
<td>12.94 (15.66)</td>
<td></td>
</tr>
<tr>
<td>T stage, %, T1/T2/unknown [329]</td>
<td>83/17</td>
<td>26/68/6</td>
<td>34/62/4</td>
<td></td>
</tr>
<tr>
<td>Gleason grade, % ≤6/7/≥8 [321]</td>
<td>93/7/0</td>
<td>47/39/14</td>
<td>60/35/5</td>
<td></td>
</tr>
</tbody>
</table>

*11 men whose education was unknown were excluded from this specific analysis.
One-way ANOVA showed that the three treatment groups differed in the most recent PSA reading (P < 0.01), which was significantly higher in the AS (7.72 ng/mL) than in the on-treatment (2.76) and after-treatment groups (1.94; P < 0.01). There was also a significant difference in initial PSA level between AS, on-treatment and after-treatment groups (P < 0.01); the level was significantly lower in the AS group (6.72 ng/mL) than in both the other groups (15.19 and 12.94 ng/mL, respectively; P < 0.01).

Patients on AS were significantly more likely to have T1 stage disease than T2 stage disease (P < 0.01) than were the other two groups. Kruskal–Wallis analysis of Gleason grade among the three treatment groups was statistically significant (P < 0.01), with significantly fewer patients on AS (7%) scoring above the median (six) than patients in the other two groups (53% and 40%, respectively).

The number of patients meeting the criteria for clinically significant anxiety (28) was 16% and for depression (28) was 6%. The mean (sd, range) for anxiety scores was 4.13 (3.49, 0–18) and for depression scores was 2.70 (2.60, 0–13).

Frequency analyses indicated a low prevalence of anxiety and depression, with 21 (21%) and 4 (4%) patients on AS scoring above the threshold (≥ 8) for anxiety and depression, respectively. Eight of 81 (10%) and three of 81 (4%) patients on-treatment scored above the threshold and 22/148 (15%) and 13/148 (9%) of those after treatment scored above the threshold for anxiety and depression, respectively. There were few clinical cases among the treatment groups, with the number of patients meeting clinical levels of anxiety and depression below that reported in a normative sample [7]. The median and distribution of anxiety and depression scores according to treatment group are presented in Fig. 1A,B.

Variables to be included as covariates in the between-group analysis were those that differed between treatment groups and were correlated with anxiety and depression scores. Bi-serial correlations indicated that T stage of either 1 or 2 was not significantly associated with anxiety (R = −0.02, P = 0.73) or depression (R = 0.03, P = 0.59) and therefore it was excluded in the subsequent between-group analyses. Gleason grade, recent PSA level and initial PSA level were also not significantly related to anxiety (R = −0.09, P = 0.11; R = 0, P = 0.96, R = −0.11, P = 0.06) or depression (R = −0.04, P = 0.54; R = −0.01, P = 0.93, R = −0.06, P = 0.31) and were therefore excluded.

Anxiety was significantly associated with age (R = −0.18, P < 0.01) and time since diagnosis (R = 0.14, P < 0.01) and thus both variables were included as covariates in the between-group analysis. Depression was positively associated with time since diagnosis (R = 0.15, P < 0.01) but not with age (R = −0.04, P = 0.45) and therefore only time since diagnosis was included in the analysis for depression. Analysis of covariance indicated that there was no significant effect of treatment group on anxiety (P = 0.38) after controlling for age and time since diagnosis. Anxiety was significantly affected by age (P < 0.01) and time since diagnosis (P < 0.01). Younger men were significantly more anxious than older men, and the more months that had elapsed since diagnosis the more anxious men became. There was no significant effect of treatment group on depression (P = 0.83) after controlling for time since diagnosis. However, there was a significant association between depression and time since diagnosis (P < 0.05), with increased depression being associated with increased time since diagnosis.

In summary, the present study, with 98% power to detect an effect size of f = 0.25 [11] (based on an α level of 0.05 and a mean sample size of 110) showed there were no significant differences in anxiety and depression between the treatment groups.

DISCUSSION

We found no evidence to suggest that AS for localized prostate cancer, rather than immediate radical treatment, carries additional psychological morbidity, as measured by the HADS. There were no significant differences in anxiety or depression between patients on AS, on treatment or after treatment, after controlling for age and time since diagnosis. These findings support the feasibility and acceptability of AS as a strategy for managing favourable-risk localized disease.

The overall prevalence and level of anxiety and depression in the present study was low, with values comparable to those found in non-clinical populations [10,12]. This is in line with previous research in a similar cohort [6], which also reported low levels of anxiety in patients with prostate cancer.

The finding that age was inversely related to anxiety also supports previous research with a mixed group of patients with cancer [13], and research conducted specifically in men with prostate cancer [6,14]. Younger patients might be more at risk of anxiety because they feel more pressure associated with financial matters and sexual dysfunction than older men [6].

Although the increase in anxiety and depression with increased interval since diagnosis seems counterintuitive, previous research also found a trend for patients with localized prostate cancer to report more anxiety at the 6-month follow-up than at diagnosis [15]. Another study investigating psychological morbidity in women with ovarian cancer [16] also found that more patients met the criteria for anxiety on the
HADS after completing chemotherapy to the 3-month follow-up. It was suggested that in the absence of external safety signals such as hospital consultations, patients might attend more readily to internal bodily symptoms which are falsely believed to be indicative of disease progression, and thus lead to feelings of anxiety.

A further possible explanation for increased psychological distress with increased time since diagnosis might include the appraisal of cancer as a progressive, chronic disease rather than an acute disease which resolves after treatment [17]. Patients might feel more anxious and depressed about the possibility of having a protracted experience of cancer, including continuous follow-up appointments at outpatient units and possible fears of recurrence.

Although the present study provides some support for the use of AS, there are limitations that should be considered in future research. The study was not randomized, with each treatment group representing a self-selected population. It might be that other characteristics or variables not measured in the present study are also important in determining low anxiety levels reported by individuals in different groups. For example, it is plausible that men with a tendency towards anxiety might be more inclined to choose immediate radical treatment than AS. Also, the study was cross-sectional and further longitudinal research is required to determine whether there are significant differences over time in psychological distress between patients on AS and those on treatment.

The present study focused only on anxiety and depression, whereas measures of coping and quality of life might also be important indicators of how men with prostate cancer are functioning according to treatment type.

Another limitation of the present study is that participants were mainly White British, married and retired. Thus, the finding that AS is not significantly more distressing than immediate treatment so far only applies to a particular demographically homogeneous population of patients with prostate cancer. Finally, active treatment in the present study referred to radiotherapy and hormone therapy, and future research comparing psychological distress across treatment groups could include other treatment approaches, such as radical prostateectomy.

In conclusion, we found no evidence to support the hypothesis that AS of localized prostate cancer carries a psychological burden, compared to that of immediate treatment. Men on the AS programme reported similar levels of anxiety and depression to those on treatment or on follow-up after treatment. Although the null hypothesis that there is no difference between the treatment groups cannot be 'proved', the study had adequate power and we are confident that we have not missed a moderate effect, let alone a clinically significant effect.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: AS, active surveillance; HADS, Hospital Anxiety and Depression Scale.