Manuscript title: Active Surveillance for Favourable-Risk Prostate Cancer: Is there a Greater Psychological Impact than Previously Thought? A Systematic, Mixed Studies Literature Review.

Running Head: The Psychological Impact of Active Surveillance for Prostate Cancer

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Author contribution

ER and GP were responsible for the design of this systematic review, data acquisition, analysis and interpretation. OS aided in this process, arbitrating any disagreement. SP and JO'S advised on design and evidence acquisition. ER drafted the article. GP, OS, SP and JO'S critically revised the manuscript. All authors approved the final submission.

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Abstract

Objective

Active Surveillance (AS) allows men with favourable-risk prostate cancer (PCa) to avoid or postpone active treatment and hence spares potential adverse side effects for a significant proportion of these patients. Active surveillance may create an additional emotional burden for these patients.

The aim of the review was to determine the psychological impact of AS to inform future study in this area and to provide recommendations for clinical practice.

Methods

Studies were identified through database searching from inception to September 2015. Quantitative or qualitative non-interventional studies published in English that assessed the psychological impact of AS were included. The Mixed Methods Appraisal Tool was used to assess methodological quality.

Results

Twenty-three papers were included (20 quantitative, 3 qualitative). Quantitatively, the majority of patients do not report psychological difficulties, however when appropriateness of study design is considered, the conclusion that AS has minimal impact on wellbeing, may not be accurate. This is due to small sample sizes, inappropriately timed baseline, and inappropriate/lack of comparison groups. In addition, a mismatch in outcome was noted between the outcome of quantitative and qualitative studies in uncertainty, with qualitative studies indicating a greater psychological impact.

Conclusions

Due to methodological concerns, many quantitative studies may not provide a true account of the burden of AS. Further mixed-methods studies are necessary to address the limitations

highlighted and to provide clarity on the impact of AS. Practitioners should be aware that despite findings of previous reviews, patients may require additional emotional support.

Keywords

Prostatic Neoplasms. Cancer. Oncology. Active Surveillance. Anxiety. Depression. Uncertainty.

Background

Active surveillance (AS) was developed in response to the increasing prevalence of lower risk prostate cancer (PCa) in older men [1]. AS allows the majority of patients with lower risk PCa to avoid active treatment and hence the side-effects associated with such therapy [2]. Although AS protocols may vary, they usually involve Prostate-Specific Antigen (PSA) tests and Digital Rectal Examinations (DRE) at regular intervals, and annual/biannual biopsies. In recent years, regular multi-parametric MRI scans of the prostate have become part of AS protocols [3]. Numerous studies have documented the appropriateness of AS from a medical perspective, however the psychological impact of AS remains understudied [4]. In spite of this, the assumption is that men undergoing AS do not require additional support, psychological or otherwise, throughout this monitoring period. This assumption can partly be attributed to results of systematic reviews in this area, for example: a recent exclusively quantitative systematic review [5] concluded that men on AS reported no major difficulties in quality of life (QoL) or psychological wellbeing. However, this review utilised narrow inclusion and exclusion criteria and excluded studies referring to Watchful Waiting (WW), a management approach that is palliative in nature but often incorrectly used interchangeably with AS. This omission may have led to the exclusion of some relevant papers. The lack of critical appraisal meant study quality was not taken into consideration in the interpretation of the results.

In a similar quantitative review [6], it was concluded that AS was unlikely to be associated with an adverse effect on general psychological wellbeing. In this instance, studies describing WW or 'no treatment' were included. However, no distinction was made between those studies describing AS versus true WW. Although the methodological quality of studies was assessed, this was not considered when interpreting the results of the review. In addition, neither of these reviews included qualitative studies, which meant that an important opportunity to better understand the experiences of patients was missed. It is our contention that a mixed methods review that includes both qualitative and quantitative studies would allow for richer experiential data to be included without compromising generalisability achieved using quantitative methods [7].

Aims

The aim of this systematic mixed studies review was to synthesise and appraise the quantitative and qualitative knowledge to develop a more comprehensive picture of published studies reporting the psychological impact of undergoing AS.

Evidence acquisition

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for the conduct and reporting of this systematic review [8].

Eligibility criteria

Inclusion criteria: non-interventional studies published in English assessing the psychological impact of AS in lower-risk PCa, including studies comparing AS with AT. Studies referring to WW were included when the definition was that of AS.

Exclusion criteria: review articles, editorials, comments, intervention studies (e.g. studies that included a psychosocial intervention), needs assessments and studies assessing quality of life (QoL). While QoL is an important factor, it was deemed inappropriate for the present review

due to the insensitivity of general QoL measures in assessing clinical change in psychological functioning [9].

Information sources

Medical and nursing databases were searched from inception between August and September 2015 with no limitations on time, using a predetermined search strategy (Fig.1.). Titles and abstracts were screened by ER and GP based on the inclusion/exclusion criteria, where there was doubt regarding the eligibility of a particular title or abstract the record was retained for full-text screening. OS arbitrated any disagreement at the full-text screening stage.

Search

Figure 1. PRISMA Flow Diagram

Study selection

Qualitative and quantitative findings related to the prevalence and predictive/protective factors of psychological variables were reported, namely depression, anxiety, and uncertainty. ER and GP extracted data from each article and applied the quality appraisal tool, OS arbitrated any disagreement.

Data collection process

The Mixed Methods Appraisal Tool (MMAT) [10], an appropriate, reliable and efficient tool for mixed studies reviews was used to assess study quality [11]. ER and GP completed the MMAT for each study, with OS arbitrating. This appraisal directly informed the interpretation of study findings.

Results

Synthesis of results

Twenty-three papers were included, 20 quantitative [12-31], and 3 qualitative [32-33]. Nine were longitudinal [15, 18-21, 23, 25-27] with a follow-up period ranging from 9 months [25] to 3 years [18]. Attrition in these studies varied, with response rates at follow-up time-points

ranging from 13% [21] to 89% [15]. Three studies did not report attrition [18, 20, 23]. Four of the 9 longitudinal studies had follow-up response rates of >70% [15, 19, 25, 27], whereas others reported more conservative follow-up response rates of <60% [21, 26]. Fourteen were cross-sectional [12-14, 16-17, 22, 24, 28-34], with time since diagnosis ranging from 2 months [23-24, 29] to 136 months [22]. Six papers referring to WW, yet providing definitions for AS, i.e. not palliative care, were included [17-18, 23, 32]. Seven papers included comparison groups; the majority compared AS patients with patients opting for AT [14, 15, 18, 21, 23, 26], one was a comparison of North American and Irish AS patients [17]. Breakdown of individual sample sizes and countries of origin are detailed in Table 1. The pooled number of AS patients across the twenty-three papers amounted to 1777 men.

Quality appraisal

Using the MMAT [11], papers were scored against four main criteria associated with the specific research design; four papers met 100% of criteria; 15 met 50-75%; and four met only 25% of the methodological quality criteria (Table 1). Failure to justify sample size, inappropriate/no comparison group, and lack of baseline measures were the most frequently observed methodological issues.

Depression

Twelve quantitative studies investigated depression in this population, reporting data for 1007 AS patients in total. Five studies included AT men as a comparison group [14, 15, 18, 23, 26]. Six different scales were used to assess depression (Table 2).

Quality appraisal

Eight of the 12 studies were considered high quality studies (75%-100% of methodological criteria was met). Two of the studies fulfilled 50% of the methodological criteria [15, 22]; with an insufficient response rate, failure to provide reasons for non-participation and an inability to determine if the sample was representative due to the authors failing to report

demographic information per treatment group included were limitations of these studies. Two studies met only 25% of the methodological quality criteria [16, 29]. The first [16] failed to justify sample size, provide reasons for non-participation and recruited from support groups, leading to a potential selection bias. Response rate was also not reported [16]. In the second [29], the HADS was used inappropriately to diagnose clinical depression. HADS does not include somatic symptoms that makes up the diagnostic criteria of clinical depression therefore the measure used does not address the aims of their study. Other methodological issues included lack of a representative sample, as despite the use of multiple sites 95% of the sample identified as white British. The authors' failure to include a control group also reduced the MMAT score attributed to the study. The study did however include a large number of participants (n=313) and their response rate was high (73.47%).

Prevalence

Four studies reported prevalence data for depression [14, 21, 25, 29]. Generally, the prevalence of depression was low; two studies reported mild depression ranging from 4-11% [14, 21], with moderate-severe depression reported in less than 5% of both AS and RP patients [21]. One study reported clinically significant depression in 12.5% of their sample [29]. There was disagreement regarding the severity of depression in comparison to non-cancer men. One study reported that although mild, depression was higher than literature reporting depression scores for men without a PCa diagnosis [14]. Conversely, depression levels were reportedly similar to normative data of clinical populations [25]. However, the latter study utilised a prospective, longitudinal design, with low attrition rates therefore reducing the impact of individual differences and increasing credibility of the findings. When compared to curative treatment, AS patients had the most favourable depression score [15, 26]. Although the difference between AS and RP patients immediately post-

diagnosis/early treatment was statistically significant, clinical significance was not reported [15].

One low quality study [29] reported a higher number of participants scoring within clinical levels; although the mean score of depression was low, 12.5% of patients' scores suggested presence of clinical depression.

Factors associated with depression

Five studies attempted to identify factors predicting depression (Table 3). Neurotic patients who experienced a major life event additional to their diagnosis demonstrated increased depression [24]. Extraversion, continued sexual activity, and higher QoL were associated with decreased depression [24]. Similarly, patients with higher QoL and low neuroticism reported lower depression at diagnosis [25]. It was concluded that patient-bound factors, e.g. personality, were the most important determinants of depressive symptoms [13, 15, 24]. Lack of a partner and impaired mental health (MH) were both predictive of poorer wellbeing [13]. Patients enrolled in AS protocols soon after diagnosis were more likely to adopt poor coping strategies and demonstrate maladaptive adjustment to cancer; these patients had less time to seek information to support their choice of AS and therefore understand that their PCa was manageable [13].

Change in depression over time

Six studies assessed depression longitudinally [15, 21, 23, 25-27]. Depression was reported to decrease with time in five studies [15, 21, 23, 26-27] for both mild [15, 21] and clinically significant depression [15, 29]. Conversely, in another high quality study with one of the lowest attrition of all included studies, depression remained stable up to 18-months post-diagnosis [25]. A high quality cross-sectional study [14] reported a correlation between increased time since diagnosis and increased depression; a finding that must be treated with caution given the limitations of cross-sectional designs.

Anxiety

Eighteen quantitative studies measured anxiety in 1639 AS patients [12-15, 18-30], using eight different scales (Table 2). Six studies included comparison groups of AT men [14, 15, 18, 21, 23, 26].

Quality appraisal

Eleven of the 18 studies assessing anxiety met 75% or 100% of the methodological quality criteria set out in the MMAT. Four met 50% of the criteria [12, 15, 18, 22], issues included a failure to report reasons for the low response rate [12, 18, 22], potential selection bias and failure to report the demographic information divided by treatment group [15], and no standardised tool for assessment of anxiety [18]. Three studies met 25% of the methodological quality criteria [16, 28, 29], issues with these studies included low sample size, potential selection bias, insufficient response rate or failure to report the response rate, reasons for non-participation not explained, failure to include a control group, and inappropriately timed baseline measurements.

Prevalence

The prevalence of anxiety ranged from 13-45% [12, 14, 21-22, 24-25, 27, 29-30]. One study reported up to 5% of patients with moderate-severe anxiety levels [21], and one with almost 25% of participants with clinical levels of anxiety [29]. The majority of studies reported anxiety comparable or lower than data from non-clinical populations [12, 14, 22, 24]. One study [21] reported that the majority of participants had anxiety higher than that of non-cancer men; however, the study cited to support these claims included no non-cancer data [35].

AS men appeared to have low anxiety when compared to patients opting for AT [15]. Only one study directly contradicted these findings [26]; however this can be attributed to potential

selection bias in the increased psychological dysfunction reported by those completing follow-up.

Change in anxiety over time

Six studies examined the temporal variability in anxiety [19-20, 21, 25-27]. With the exception of one study [25], statistically significant declines were observed over time. However, the one contradictory study [25] was of high methodological quality and maintained a high response rate during study follow-up. One study reported that although 20% of patients suffered from clinically significant anxiety levels at baseline (within 6 months of diagnosis), only 5% of the total sample chose to leave the AS protocol due to the psychological burden [27]. A significant decrease was observed in general anxiety and fear of disease progression over the course of the 18 month follow-up [27]. A number of other studies support these findings, also concluding that anxiety remained either stable or reduced over time [15, 20, 23-24, 26].

In a 30-month follow-up study [19], anxiety reduced significantly at 18- and 30-months post-diagnosis. Interestingly, 12- and 24-month follow-up data were not significant; typically this is when patients receive a biopsy to reassess their cancer and resulting course of treatment. Although, it must be noted that the trend of declining anxiety remained consistent across these time points.

Longitudinal studies documenting a general decline in anxiety during AS are supported by two of the three cross-sectional studies that asked men to report number of months spent on AS [14, 21, 24]. Although not significant, increased time undergoing AS was associated with stable or decreased anxiety [22, 24]. One cross-sectional study however found a significant increase in anxiety with reported increased time since diagnosis [14].

Individual differences are an important factor and cross-sectional studies must be interpreted with caution despite apparent high methodological quality, this study design may simply not

be appropriate to capture these men's experiences. Based on the results of the previously reported, high quality study [19](Table 1), anxiety appeared to fluctuate, therefore, the time point at which the cross-sectional studies assess men would be a crucial in terms of the anxiety reported, and may explain some of the conflicting results discussed.

Factors associated with anxiety

The factors that appeared to be predictive of anxiety were: high neuroticism [24], younger age at diagnosis [14], low QoL and fear of cancer recurrence [12], impaired MH, lack of a partner and decreased number of cores taken at diagnostic biopsy [13], patients' relationship status i.e. single/divorced [13, 29], misunderstanding of AS and resulting deferral of decision making to physician [13, 25, 30] (Table 3). The finding in relation to decreased number of cores taken at diagnostic biopsy, the authors suggested that this may a result of the patients' perception, however inaccurate, that more of their cancer had been removed [13]. High neuroticism and high PSA were associated with increased PCa-specific anxiety [24]. Fear of disease progression, a component of PCa-specific anxiety, was identified as a trigger for discontinuation of AS in favour of AT [19]. The combination of high QoL and low neuroticism, was reported to be significant in minimising anxiety [25].

Uncertainty

Six studies assessed uncertainty in 266 AS men. Three studies were qualitative [32-34], and three quantitative [17, 19, 28]. The quantitative studies used MUIS (Table 2) to measure uncertainty. Four additional papers were included in the uncertainty theme due to their assessment of decisional conflict [16, 24, 25, 27], a state of uncertainty, using the DCS (Table 2). One study included a comparison group of Irish and North American AS patients [17].

Quality Appraisal

Of the ten studies assessing uncertainty in the AS population, only one met 100% of the methodological quality criteria in the MMAT [24]. Three studies met 75% of the criteria [19,

25, 27], the absence of a comparison group in two of these studies prevented them from meeting all the methodological quality criteria [25, 27]; whereas potential selection bias in the recruitment of participants was an issue in the third study [19]. One qualitative study [32] also met 75% of the methodological criteria, as a result of failing to acknowledge their influence on their data. The two remaining qualitative studies [33, 34] met 50% of the methodological quality criteria due to the lack of acknowledgement of the researchers influence and the impact the context within which the research took place had upon the participants and resulting data. Two quantitative studies also met just 25% of the methodological criteria [16, 28]; failure to discuss the justification for their specific sample size, reasons for potential participants' non-participation, response rate and issues with sampling were the reasons for this. Finally, one additional paper met only 25% of the methodological criteria [17], this was due to the small sample (n = 29 participants), failure to apply appropriate inferential statistics as a result, as well as a failure to report the response rate.

Prevalence

None of the included studies reported the prevalence of clinically significant uncertainty using the MUIS. However, approximately 25% of patients scored clinical levels in DCS [24-25, 27].

The perception of uncertainty

The three qualitative studies included in this review identified similar themes regarding the nature of uncertainty experienced during AS, which contrasted with the quantitative findings. Men described 'intolerable uncertainty', a 'Dangerous Wait', characterised by uncertainty and a perception of 'risking one's life' [33]. Although this study included only those who had converted to AT which may overstate the impact of uncertainty in AS. The other qualitative studies interviewed men who remained on AS [32, 34]. The theme 'To be Uncertain, Afraid,

Worried' emerged in one of these qualitative studies [32] in participants still undergoing AS with respondents describing constant threat, fear and worry.

While patients understood the information about their diagnosis and prognosis intellectually, they had not integrated the message emotionally [32]. An overarching theme of uncertainty prevailed in each participant's account, either implicitly or explicitly [32]. This theme was characterised similarly to those previously reported: persistent uncertainty surrounding mortality and potential spreading, potential need for AT, and patients' ability to cope with treatment-induced morbidities. Participants described living in 'shadowland' while they 'waited for a disaster' [232]. These subthemes were related back to patients' masculine identities: pressure to maintain sexual function, and to continue to provide financial stability for their families [34]. Qualitatively, participants described uncertainty as featuring more significantly throughout the AS experience than the quantitative data suggested, a finding warranting further study.

Change in uncertainty over time

Three of the included uncertainty studies assessed uncertainty longitudinally [19, 25, 27]. Attrition was generally low at initial follow-up points, with response rates >70% [19, 25, 27], however after 18 month follow-up response rate dropped to 67% [27] and 44% after 2 year follow-up [19]. Uncertainty decreased from baseline to 18-months, however this decrease was neither statistically nor clinically significant [27]. Uncertainty at 6-months post-diagnosis predicted scores after 9-months of AS, suggesting uncertainty remains stable within the first year. A significant decrease was found from baseline up to 30-months post-diagnosis [19] however attrition may have been an issue. Conversely, qualitatively patients reported that uncertainty was time sensitive and peaked leading up to monitoring appointments, PSA and biopsy results [34].

Factors associated with uncertainty

A number of factors were reported to increase uncertainty, including high neuroticism and increased role of clinician in decision-making [24, 25]. Patients who experienced depression, and had a more negative outlook were less satisfied with their treatment decision [16] (Table 3). Uncertainty was reported to be a significant factor, and had a resulting impact on QoL and fear of disease progression [19, 28]. It was reported that it was the perception of danger associated with AS that increased uncertainty and had the resultant impact on QoL [28]. Anxiety was also associated with uncertainty [28].

Factors reported to decrease uncertainty and decisional conflict were also discussed in the literature: high extraversion and the management of PCa in a university/specialist hospital appeared to be associated with lower decisional conflict [24, 25]. Palpable disease and older age at diagnosis reportedly had an additional favourable effect on the perceived risk of progression, a form of uncertainty, at follow up [25]. The finding in relation to palpable disease appears to be counter-intuitive, the authors posited that older patients with palpable disease at diagnosis may experience higher uncertainty initially, yet following a period of time on surveillance show greater improvement upon realising the feasibility of surveillance [25]. Favourable MH, optimism and higher self-efficacy (SE) as well as perceived consistency in medical information was associated with reduced uncertainty [16]. Qualitative data suggested stable or decreased disease characteristics at follow-up reduced uncertainty surrounding impending follow-up appointments and delays between monitoring appointments and receipt of results [34]. Patients also discussed feeling more secure when they saw the same clinician at follow-up appointments [34].

The role of clinicians was ambiguous. They were both sources of uncertainty in that they were potentially bearers of bad news that the cancer had progressed further, and of security in that they provided patients with the reassurance of regular check-ups [32].

Patients appeared to cope with uncertainty and decisional conflict in various ways, as was described in two qualitative studies [32, 34]. With regard to decision making, patients appeared to assume either a passive or active role in the process; while some patients opted to defer decision-making power entirely to their clinician, others chose to actively seek out further information or request a second opinion to engage more with the decision-making process [32]. Similarly, in response to diagnosis, some patients reported they decided to 'screen off' their cancer by setting aside feelings of threat or completely denying the existence of their cancer, while others compensated for the perceived threat of their cancer via lifestyle change [32]. Patients also described control as central to their coping, this control was asserted by 'living a normal life' [34], similar to 'screening off' [32], or by 'doing something extra', a theme that also converges with lifestyle change discussed previously [32].

Discussion

Main Findings

From a quantitative perspective it would appear that men undergoing AS show favourable psychological wellbeing, with only a small number reporting maladjustment. These findings are consistent with those of previous systematic reviews [5, 6] in spite of differing inclusion criteria particularly in relation to inclusion of papers referring to AS as WW in the present review. While this convergence strengthens confidence in the results, a number of methodological issues remain outstanding. Specifically, a lack of appropriate comparison/control groups, and unavailability of baseline data leads to an inability to determine if men who choose AS are fundamentally less anxious than those who opt for immediate AT. Although potential predictors of adverse psychological adjustment were identified, these methodological limitations reduce confidence that they fully captured the experience of these men; therefore resulting implications for practice must also be treated cautiously. This lack of confidence is reinforced by conflicting results emanating from

different research designs. Particularly pertinent were differences in results relating to anxiety and depression between cross-sectional and longitudinal studies. It must be noted that although levels of anxiety and depression appeared to resolve over time when they were followed up longitudinally, attrition and response rate must be considered when evaluating the strength of the evidence. This is reflected in one study [25] that contradicted other longitudinal studies that reported decreasing anxiety and depression at later follow-up points, the same study had one of the lowest rates of attrition with an 84% response rate. This highlights the importance of reporting reasons for non-response and analysis of potential socio-demographic differences between complete and incomplete responders.

As well as different findings resulting from longitudinal and cross-sectional evidence, further differences were observed in relation to qualitative and quantitative uncertainty data. In terms of prevalence, quantitative studies indicated that uncertainty appears to be low in this population. However when the nature of uncertainty was explored in qualitative studies, it appears to have a more significant impact on men than is reflected in the quantitative data. This idea is comparable to how quality of life is conceptualised in the severity of symptoms versus the 'bother'/impact that is experienced by the patient as a result i.e. the impact of uncertainty on the individual cannot be ignored. Because no qualitative studies reported on anxiety or depression, potential differences in these areas remain moot, requiring further investigation.

Limitations of the included studies

Some questions need to be raised in relation to the comparators chosen in the reviewed studies. This is a significant issue because it is only through comparison that the extent of difficulties, or perhaps lack thereof, can be fully understood. Several studies included patients opting for AT as comparators, while others compared their results to reference values. Arguably, a more appropriate comparison is age-matched men with no PCa diagnosis in

addition to patients opting for AT. Due to the high incidence of undiagnosed lower-risk PCa in men over 60 years [36], it can be extrapolated that the psychological differences between patients and age-matched volunteers would be attributable to PCa, and the AS experience.

A further criticism of the studies was that, because the patients sampled had already selected AS as a treatment course, it is possible that patients who were naturally less anxious, depressed, or uncertain, chose AS due to increased ability to cope. One study attempted to assess selection bias [21], observed that participants who completed follow-up reported greater psychological dysfunction than those lost to follow-up, illustrating an additional potential bias in terms of the type of patient that remains involved in psychological studies.

None of the studies utilised a mixed-methods (MM) design and only a limited number were qualitative, and these only reported results for uncertainty. This is limiting in that men on AS are not being afforded the opportunity to express their interpretation of their experiences. MM research would be of particular benefit in this area, maintaining generalisability while still providing an opportunity to gain a deeper understanding of patients' experiences of AS and PCa generally [7]. The value of this approach is illustrated in men's description of uncertainty. In qualitative studies, participants described overwhelming uncertainty that continued throughout AS [32-34], whereas in quantitative studies, uncertainty reportedly decreased over time. This discrepancy warrants further exploration. This review returned no qualitative papers relating to anxiety or depression; a qualitative study examining these outcomes may have presented different findings, as was the case with uncertainty.

Limitations of the review

Due to the absence of universal measures for each psychological dimension studied, and indeed consistency in the definitions of each psychological dimension e.g. interchangeable use of the terms distress and depression, it was not possible to combine the data of multiple

quantitative studies in a meta-analysis. Because of the small number of qualitative studies included, a meta-synthesis was also not feasible.

Although attempts were made to minimise the impact of the use of varying terminology for the process of AS, by using multiple terms in the search strategy (Fig. 1), it remains a possibility that studies using different terminology for AS/studies failing to provide sufficient definitions for the management programme assessed, were not retrieved.

The papers included in this review were also checked against those studies included in previous systematic reviews [5, 6]; neither review uncovered additional papers, aside from those discussed as limitations previously, i.e. inclusion of WW papers.

Recommendations for future research

Future research should include appropriate comparison groups, timelier baseline measures, and steps to minimise selection bias. Ideally, baseline assessment should occur prior to treatment decision-making with the aim of assessing patients over time to determine potential temporal variability, thereby controlling for individual differences. The value of longitudinal data has been highlighted, evident in the non-linear declines in anxiety. Although overall anxiety declined up to 30-months, demonstrating increasing resilience over time, anxiety peaked at certain time-points. This fluctuation was particularly pertinent at follow-up appointments or while awaiting results [19]. Cross-sectional data would not have detected this variability.

None of the included studies utilised a MM design. The use of this design would facilitate a more comprehensive understanding of the impact of AS on men, allowing researchers to better understand the holistic needs of patients without compromising generalisability.

Finally, researchers should cooperate to standardise the psychological measures used in AS research therefore facilitating comparison and aiding transferability of international AS expertise.

Recommendations for practice

Clinicians reading previous reviews and managing the care of men undergoing AS, could easily assume the favourable wellbeing of men receiving AS. Results of the present review discuss the various reasons why this may not necessarily be accurate. Evidence should be interpreted with consideration for the limitations discussed. Patients with favourable-risk PCa deciding on treatment options may require additional reassurance and support when considering AS and continuing this monitoring strategy.

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Table 1. Study characteristics

Study	Design	Assessment period	Setting, country; total sample/response rate	Participants (N; age, years; time on AS at assessment)	Comparison	MMAT
[12]	Cross-sectional	NR	UH. Australia. 260/33%	86; 65.7; 43 mths on AS	None	**
[13]	Cross-sectional	2007-2012	CC. Italy. 154/67%	103; 67; 10 months post-biopsy	None	****
[14]	Cross-sectional	NR	CC. Britain. 493/67%	329, 100 AS; 67.12; 28.61 months	Currently undergoing AT and Previously underwent AT	***
[15]	Longitudinal	2001-2005	CC. Australia. 211/91.4% (not split by treatment group)	T1: 193 – 61 WW; T2: 172 – 55 WW; Demographics not split by treatment group – 66.15 years; Diagnosis/early treatment; 12months later	RP, HT	**
[16]	Cross-sectional	2007-2008	Support group database. USA. NR.	34; 63.1; 14.1 months	None	*
[17]	Cross-sectional	NR	Cancer registry, physician referral/advertisement. USA and Ireland. Irish sample 92/10.8%, USA sample NR.	Ireland 10; 76.5; mean 27.6months USA 19; 76; mean 48.5months	AS men in south of Ireland and USA	*
[18]	Longitudinal	1997-2002	Community/University clinic. USA. NR.	105; 75.5; >6 months	Those who ceased AS for AT	**
[19]	Longitudinal	2006-2012	CC. USA.180/71%	180; 67.2; <6 months	None	***
[20]	Longitudinal	NR	Database. USA. 195/100%	195; 66.5; commencement	None	***
[21]	Longitudinal	2007-2010	Urology dept., USA. 864/77% (Response rate not divided by treatment group)	122; 60.5; >6 months	RP	****
[22]	Cross-sectional	2010	CC. Switzerland. 283/44.9%	133 couples; patients 69.3 years; Range 17-136 months	None	**
[23]	Longitudinal	NR	CC. Germany, France, Spain, Italy, Sweden. 672/48.5% (not divided by treatment group)	12 WW/AS; Demographics not split by treatment type – 65 years; <2 months of diagnosis, 3 months, 12 months	RP, External beam RT, brachytherapy, combined HT and RT, HT, RP followed by salvage RT	***
[24]*	Cross-sectional	2007-2008	UH. The Netherlands. Sample 150/86%.	129; 64.9; 2.2 months	None	****
[25]*	Longitudinal	2007-2008	UH. The Netherlands. 150/86%	129; 64.3 years; 0-6months	None	***
[26]*	Cross-sectional	NR	UH. The Netherlands. (AS sample only) 150/86%	129 AS; 64.9; 6 and 18 months post-diagnosis	AT	***
[27]*	Longitudinal	2007-2008	UH. The Netherlands. Sample: 150/86%	129; 64.6; <6months since diagnosis/commencing AS	None	***
[28]	Cross-sectional	NR	Physician referral/advertisement. USA. NR.	19; 76; 4.5 years	None	*
[29]	Cross-sectional	2012	CC. England.426/73.47%	313; 70.49; >2 months, mean NR.	None	*
[30]	Cross-sectional	2013	Database. Australia. 67/77%	47; 62; NR	None	***

[31]	Cross-sectional	2007-2011	UC. USA. 452/16%	71; 65.4; 16.52 months	None	**
[32]	Qualitative, cross-sectional	NR	Database. Sweden. 8/87.5%	7; 62-6; 16-35 months	None	***
[33]	Qualitative, cross-sectional	NR	UC. USA. 6/100%	6; 70; >6 months AS	None	**
[34]	Qualitative, cross-sectional	NR	CC. Canada. 45/55.5%	25; 68; <2 years	None	**

***The same cohort of 129 participants were studied in multiple papers [25-28]*
For further breakdown of the MMAT scores please contact the first author.
Abbreviations: not reported (NR); cancer clinic (CC); urology clinic (UC); University Hospital (UH); patients/participants (pts); active surveillance (AS); watchful waiting (WW); radical prostatectomy (RP); radiotherapy (RT); active treatment (AT); hormone therapy (HT).

Table 2. Scales used

	STUDY																						
SCALES	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**
HADS-A: Hospital and Anxiety Depression Scale-Anxiety subscale	X																						
STAI-T: State-Trait Anxiety Inventory-trait subscale	X																						
MAX-PC: Memorial Anxiety Scale for Prostate Cancer	X				X		*	**	X		X		X	X		X	X		X				
Symptom checklist		X																					
Mini-MAC: Mini-mental adjustment to cancer		X																					
HADS: Hospital and Anxiety Depression Scale			X								X	X						X					
BSI-53: Brief Symptom Inventory				X																			
MUIS: Mishel's Uncertainty in Illness Scale					X			X															
CMS: Fife Constructed Meaning Scale					X																		
MHI-5: Mental health index-5					X																		
SE: Lepore's self-efficacy for prostate symptom management scale					X																		
MUIS-C: Mishel Uncertainty in Illness Scale− Community form						X											X						
Folkman and Lazarus Appraisal Scale						X											X						
STAI-S: State-Trait Anxiety Inventory-state subscale								X															
EPIC: Expanded Prostate Cancer Index Composite								X															
SF-12: Short form Health Survey								X															
EPIC-26: Expanded Prostate Cancer Index Composite short form									X														
AUA-SI: American Urological Association – Symptom Index									X														
PHQ-9: Patient health questionnaire										X													
GAD-7: General Anxiety Disorder Scale										X													
DT: Distress thermometer										X													
WPAI: Work Productivity Assessment Index												X											
DCS: Decisional Conflict Scale													X	X		X							
CES-D: Centre for Epidemiologic Studies Depression													X	X	X	X							
STAI-6: State-Trait Anxiety Inventory short form													X	X	X	X							
EPQ: Eysenck Personality Questionnaire													X	X									
Charlson Comorbidities Index																				X			
MOCS: Measure of Current Status Scale A																				X			
PCPC: The profile of Concerns about PCa																				X			
IES-R: Impact of Event Scale-Revised.																				X			
Qualitative interviews																					X	X	X

*3 items only ** Fear of Recurrence subscale only

Table 3. Variables associated with each psychological outcome.		
Psychological outcome		
↑ Anxiety	↑ Depression	↑ Uncertainty
↓Number of cores at biopsy [12] ↓Age [13, 24] ↑Time since diagnosis [13] Receipt of curative treatment [17] ↓QoL [18] ↑Fear of progression [18] ↓Time on AS [12, 18, 19, 24] ↑Role of the physician [12, 23, 29] ↓QoL [23] MH impairment [12] ↑Neuroticism [23] ↑PSA [23] ↑Uncertainty [27] Divorce, lack of partner [12, 28] ↓PCa knowledge [29] ↓Coping [30] ↑PCa concerns [30] ↓Optimism [30]	↑Time since diagnosis [13] ↓QoL [13] ↑Neuroticism [24]	↓Time since diagnosis [18] ↓QoL [18] ↑Fear of progression [18] ↑Role of the physician↑ [24] ↑Neuroticism [24] ↑Anxiety [27] ↑Perception of danger [27] Perceptions of being 'alone' [31] Compromised masculinity [31, 33] Conflicting relationship with physician [31, 32] Fear/worry, 'risking one's life' [31, 32] Fear of treatment failure/disease recurrence/spread [32, 33] ↑Side effects [32, 33] Temporal variability of uncertainty [33] ↓age and increased biopsy pain – patients compared biopsy with rape [33]

Figure 1. PRISMA Flow Diagram (study selection and search terms