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Active Surveillance for Prostate Cancer

Javier Romero Otero¹, Borja García Gómez¹, José Manuel Duarte Ojeda¹, Alfredo Rodríguez Antolín¹, Antoni Vilaseca Cabo², Sigrid Carlsson^{2,3}, and Karim Touijer²

¹ Urology Department, 12 de Octubre University Hospital, Madrid, Spain.

² Urology Department, Memorial Sloan Kettering Cancer Center, New York, USA.

³ Department of Surgery and Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, USA and Institute of Clinical Sciences, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

Abstract

INTRODUCTION—It is worth distinguishing between the two strategies of expectant management for PCa. WW entails administering non-curative androgen deprivation therapy to patients upon development of symptomatic progression, whereas AS entails delivering curative treatment upon signs of disease progression. The objectives of the two management strategies and the patients enrolled in either are different.

AIM—To review the role of AS as a management strategy for patients with low-risk PCa and review the benefits and pitfalls of AS.

METHODS—We performed a systematic review of AS for PCa in the literature using the National Center for Biotechnology Information's electronic database PubMed. We conducted a search in English using the terms: active surveillance, prostate cancer, watchful waiting, and conservative management. Selected studies were required to have a comprehensive description of the demographic and disease characteristics of the patients at the time of diagnosis, inclusion criteria for surveillance, and a protocol for the patients' follow-up. Review articles were included but not multiple papers from the same datasets.

CONCLUSIONS—AS appears to reduce overtreatment in patients with low-risk PCa without compromising cancer-specific survival at 10 years. Therefore AS is an option for select patients who want to avoid the side effects inherent to the different types of immediate treatment. However, inclusion criteria for AS and the most appropriate method of monitoring patients on AS have not yet been standardized.

Keywords

Active surveillance; biopsy; biological markers; magnetic resonance imaging; prostatic neoplasms

Corresponding author: Borja García Gómez, 12 de Octubre University Hospital, Córdoba Avenue, 28041, Madrid, Spain, Phone: +34658716520, Fax: +34913908121.

CONFLICT OF INTERESTS
None declared.

INTRODUCTION

PCa is of considerable public health importance. The introduction of tests for early detection, improved biopsy techniques, and an increasingly aging population have led to a significant increase in PCa incidence. It is currently the second most common malignancy in men and the sixth leading cause of cancer-specific death in the world.(1) This difference between incidence and mortality is due to a long latent preclinical stage that enables early detection. Furthermore, the growth rate of many PCa tumors is slow and relatively constant over time in contrast to the majority of other cancers. Autopsy studies have shown a high prevalence of occult PCa, with a rate of 0.9%–30.4% among men ages 30–39, and 21.2%–50.5% among men ages 70–79, depending on race.(2) PCa incidence in the US peaked in the early 1990s in all ages and races, while prostate-cancer mortality simultaneously decreased over the same decade.(3) Those changes were in part due to the large-scale introduction of PSA screening for PCa, which increased the number of tumors detected in early stages.

In the Prostate Cancer Intervention Versus Observation Trial (PIVOT) (4), 731 patients diagnosed with localized PCa were randomized to RP or observation. After a median follow-up of 10 years, there was no statistically significant difference in all-cause mortality between trial arms, (HR 0.88, 95% CI 0.71–1.08); 47% of patients assigned to the treatment group had died compared with 49% of those assigned to observation. However, cancer-specific mortality (or mortality related to treatment for cancer) was lower in the RP group than in the observation group, 5.8% vs 8.4%, respectively, albeit not reaching statistical significance, (HR 0.63, 95% CI 0.36–1.09). Men who underwent RP had a 60% lower risk of bone metastases compared with those who underwent observation, (HR 0.40, 95% CI 0.22–0.70, $P<0.001$). In a subgroup analysis of PSA levels, both cancer-specific mortality (5.6% vs. 12.8%, $P=0.02$) and all-cause mortality were reduced by 13.2% in patients who underwent RP with PSA >10 ng/ml (HR 0.67, 95% CI 0.48–0.94); however, there was no statistically significant difference in all-cause mortality between trial arms among men with PSA <10 ng/mL. Similarly, PCa mortality was lower among men with high-risk disease (Gleason score >7 or PSA >20, or T2c) in the RP group compared with those in the observation group (9.1% vs 17.5%, $P=0.04$), whereas there was no statistically significant difference in PCa mortality seen among men with low or intermediate risk tumors. The most important conclusion of this study was that patients with low-risk tumors defined as Gleason score ≤ 6 , PSA ≤ 10 ng/mL, and stage T1–2a, would not benefit from RP, which would justify undergoing AS. However, this conclusion should be taken cautiously as the design of the study included 2,000 patients and at least 1,200 were needed to keep statistical power. Also, while one entry criterion was having a life expectancy of >10 years, almost half of the patients had died at 10-year follow-up, 7.1% of them from PCa or treatment for PCa.

In a cohort study conducted in Sweden in the pre-PSA era (5), 223 patients diagnosed with localized PCa underwent watchful waiting (WW) which involved being observed and treated with androgen deprivation therapy when they showed symptomatic progression. After 32 years of follow-up, 64% of the men did not receive hormone treatment and did not develop distant metastases or die of cancer, indicating that many patients with localized cancer, particularly older men, will not develop symptomatic progression during their lifetime.

Disease-specific mortality was observed to stabilize after 20 years of follow-up and men with low-grade PCa have minimal risk of dying from PCa during 20 years of follow-up.(6)

In the Scandinavian Prostate Cancer Group-4 (SPCG-4) study, where patients were randomized to either RP or WW, cancer-specific mortality in the RP group was 17.7% versus 28.7% in the WW group after a mean follow-up of 18 years.(7) The authors concluded that the benefit of surgery with respect to death from PCa was largest in men <65 years of age (RR, 0.45) and in those with intermediate-risk PCa (RR, 0.38). However, as mentioned by the authors, this data should be treated with caution, because the low-risk group was not typical of patients usually included in an AS program. Prostate cancer in men on AS is likely to be detected by screening programs and of a clinical stage T1c.

It is worth distinguishing between the two strategies of expectant management for PCa. WW entails administering non-curative androgen deprivation therapy to patients upon development of symptomatic progression, whereas AS entails delivering curative treatment upon signs of disease progression. The objectives of the two management strategies and the patients enrolled in either are different. Men under WW are probably elderly and unfit for treatment and at higher risk of competing mortality, whereas men under AS are fit for surgery or radiation, but definitive treatment is postponed until there is evidence of disease progression to avoid experiencing side-effects such as urinary incontinence and erectile dysfunction resulting from curative treatment. As patients under AS age, they may need to transition to a WW program

In this review, we will examine the role of AS as a management strategy for patients with low-risk PCa and review the benefits and pitfalls of AS.

Following the PRISMA statement guidelines (<http://www.prisma-statement.org/>), we performed a systematic review of AS for PCa in the literature using the National Center for Biotechnology Information's electronic database PubMed (www.pubmed.gov). We conducted a search in English using the terms: active surveillance, prostate cancer, watchful waiting, and conservative management. Selected studies were required to have a comprehensive description of the demographic and disease characteristics of the patients at the time of diagnosis, inclusion criteria for surveillance, and a protocol for the patients' follow-up. Review articles were included but not multiple papers from the same datasets.

DETECTION OF LOW-RISK PROSTATE CANCER

As many cases of PCa detected with PSA will not be especially aggressive, the question of whether it is necessary to immediately treat them arises. The clinical significance of PCa depends on both the tumor's intrinsic biology (small volume, localized, low grade) and a patient's clinical situation. Clinically insignificant PCa may show both low aggressiveness and limited clinical significance due to the patient's age or comorbidity profile. Likewise, indolent PCa can be low risk, independent of clinical status.(8) Most definitions of indolent PCa shown in the literature follow Epstein's definition from 1994,(9) organ-confined disease with a Gleason score ≤ 6, no Gleason pattern 4/5, and a tumor volume of <0.5 cc. New

definitions have been proposed, most of them challenging the independent prognostic value of tumor size.(10)

1. Gleason Grading System

Most definitions of indolent PCa include a Gleason score of ≤ 6 . Since 2005, cases of Gleason ≤ 6 are less aggressive due to the International Society of Urogenital Pathology (ISUP) recommending against the use of patterns 1 and 2 in biopsies because of their weak correlation with findings from the subsequent prostatectomy; thus all positive biopsies are at least $3 + 3$.(11)

2. Stage and Volume

Indolent PCa should be organ-confined. Studies have shown that whichever measure of the carcinoma is used in biopsy (laterality, number of cores, and percentage of those affected) will correlate with the extraprostatic extension observed in the prostatectomy specimens,(12) even when the various definitions only take into account the number of cores and the percentage of carcinoma found (overall, or in each core). For that reason, almost all diagnostic schemes only accept two positive cores, with cancer affecting a maximum of 50% of each core;(13) or PSAD ≤ 0.1 ng/ ng/mL/mg.

Using current clinical definitions, indolent PCa is considered low-risk (Gleason ≤ 6 , cT1c-cT2a, PSA ≤ 10 ng/mL) or very low-risk disease (Gleason ≤ 6 , cT1c, PSAD ≤ 0.15 ng/mL/mg, and involvement of no more than 2 cores and $\leq 50\%$ of each core, including the non-neoplastic intermediate segments).(14) The inclusion criteria used by various AS protocols are summarized in Table 1.

Some AS protocols employ modifications of Epstein's criteria, including the Prostate Cancer Research International: Active Surveillance (PRIAS) trial (17) that began in 2006 and included men who had clinical stage T1c-T2 PCa, PSA <10 ng/mL, PSAD <0.2 ng/mL/g, more than 2 affected cores, and a Gleason score of ≤ 6 .

OVERDIAGNOSIS

The widespread use of PSA screening has led to the overdiagnosis and subsequent overtreatment of PCa. Overdiagnosis is defined as the detection of latent disease that would not have been diagnosed in the patient's lifetime in the absence of PSA screening,(22) and can lead to unnecessary costs and possible harm if treated (overtreatment).(23) This has led to numerous studies evaluating the effectiveness of PSA screening to reduce the risk of patients dying from PCa. One of the first studies published in 1999, which was criticized for its methodology, included 46,193 patients ages 45–80 years who were randomized to screening versus no screening. During the 7-year follow-up, the study showed lower mortality in the screened group.(24) Subsequently, the US Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial evaluated the efficacy of screening for prostate cancer in 76,693 men aged 55–74 years. During the 7-year follow-up, a $>22\%$ incidence of PCa was observed in the screening group compared with the control group, but there was no significant difference in cancer-specific mortality between the two arms at 13 years, (RR 1.09, 95% CI 0.87–1.36).(25) On the other hand, the prostate tumors in the screening group

were found to have more favorable clinical and histological features than those in the control group. Moreover, 46%–85% of men in the control group had a PSA test at some point during the study.(26)

The European Randomised Study of Screening for Prostate Cancer (ERSPC) included and randomized 182,160 men between ages 50 and 74 into screening versus control groups and evaluated the effect of screening on the core age group 55–69 years, as predefined in the study protocol. While there was a 71% higher incidence of PCa in the screening group at 13 years, there was a significant reduction in PCa mortality of 21% in favor of screening, (RR 0.79, 95% CI 0.69–0.91). The authors further estimated that 781 men would need to be screened or 27 diagnosed and treated to prevent one PCa death.(27)

The difference between the US and European trials was that the PLCO trial was conducted in the US, where PSA testing was already widespread; while the ERSPC was conducted in Europe, where the background rates of PSA testing were very low. In the first year of the PLCO trial, 40% of men in the control arm underwent PSA testing, with contamination reaching 52% by year 6. Contamination in the European trial was no more than 15%.(28) While disagreement persists on the value of population screening in reducing mortality from PCa, its role in increasing overdiagnosis and subsequent overtreatment is evident. Therefore strategies such as AS appear to be reasonable management option to offset the negative effect of screening.

PROSTATIC BIOPSY

1. Initial Biopsy

European urology guidelines for prostate biopsy recommend at least 8 cores for glandular volumes of 30–40 mL.(29) A review of 87 studies, with a total of 20,698 patients, found that prostate biopsies that took between 10 to 12 cores led to significantly increased cancer detection rates compared with sextant biopsies. However, obtaining more than 12 cores did not appear to significantly improve the detection rate (30). Some authors have suggested that increasing the number of biopsy samples could improve detection of PCa. As most of the tumors detected in the additional cores were clinically significant, increasing biopsy samples would not apply to insignificant PCa (31). While other studies have shown that the number of biopsy cores is an independent predictor of the presence of insignificant tumors in the RP specimen (32), Ploussard *et al.* reported that a 21-core protocol increased the rate of men that would be eligible for AS compared to a 12-core approach without significantly increasing the rate of detected insignificant tumors (33).

In the baseline biopsy, the transrectal approach with 10 to 12 cores is therefore the most commonly used. According to the National Comprehensive Cancer Network guidelines, AS is suitable for patients at very low risk of tumor progression who have undergone a minimum of a 10-core baseline biopsy with PSAD of ≤ 0.15 ng/mL/g (34). PSAD appears to be associated with adverse histological findings when the biopsy is repeated and also predicts the existence of insignificant PCa in the RP sample. For patients in an AS program, currently available data emphasize the importance of determining PSAD to predict the

results of a repeat biopsy. However, the ideal cut off has not been established and may be biased in different series by the effect of prostate volume (35).

2. Confirmatory Biopsy

Inadequate diagnoses from transrectal biopsies lead to higher rates of upgrading and upstaging at prostatectomy, especially for low-grade tumors. The use of PSA, PSAD, or the number of cores in the baseline biopsy does not appear to be determinating in estimating the likelihood of misclassification of a prostate tumor which was initially suitable for AS (36).

The risk of PCa must be accurately assessed before a patient can be considered for inclusion into an AS program. Most published protocols include a confirmation biopsy, especially when the baseline biopsy was not performed using extended techniques. The time between baseline and confirmation biopsies varies between 3 and 12 months. While some protocols postpone the confirmatory biopsy up to one year (Table 2), it should still be performed early, especially if there is a possibility of high-risk features and/or insufficient prior sampling. Repeat biopsies performed 3 to 6 months after the initial procedure more clearly identify patients who would be ineligible for AS due to disease staging or volume (36). The percentage of patients with tumors previously classified as low risk, but who are reclassified as being unsuitable for AS upon confirmation biopsy varies between 16% at 6 months as reported by Adamy et al. (37) and 27% at 3 months as observed by Berglund *et al.* (19). Motamedinia *et al.* (34) reported that the higher incidence of progression observed in repeat biopsies would likely be related to the higher number of cores taken in comparison with other studies that used 12 to 14 cores (38). As a result, the majority of AS protocols recommend that the number of samples taken in a repeat biopsy should be in proportion to prostate size (39).

3. Transperineal Biopsy

Some authors have noted that transrectal biopsies may miss both a relatively high percentage of significant tumors and up to 80% of tumors between 0.2–0.5 cc, giving low accuracy rates for the detection of anterior prostate tumors (40). Other studies have compared transperineal and transrectal biopsy strategies using both standard and extended numbers of biopsies, but have obtained mixed results (41)(42)(43)(44). There is a clear need for further prospective studies; however, transperineal biopsy can be considered a reasonable alternative for patients who had previous negative biopsies with persistent suspicion of PCa and may be indicated for patients who are eligible for AS. Taira *et al.* (45) showed that an extended strategy of transperineal biopsy was a more reliable method for detecting anterior tumors and recommend it as a safe staging system for patients being considered for AS.

4. Biopsy Morbidity

When a patient is included in an AS protocol, he will undergo a variable number of further biopsies in addition to the initial biopsy (with or without confirmatory biopsy). For that reason, the patient should be evaluated and informed of any possible complications associated with the biopsies before deciding on his inclusion in the protocol. A review by Loeb *et al.* (46) indicated that infection was the primary cause of hospital admission after a biopsy (0%–6.3%) and that infection rates increased over time, despite the use of antibiotic

prophylaxis. Recent studies have shown that fluoroquinolone resistant and extended spectrum beta-lactamase producing isolates represent the most commonly identified organisms (47). Some measures that could reduce the risk of bacteremia include enemas, augmented prophylaxis, targeted prophylaxis, and adding gentamicin or amikacin to ciprofloxacin. However, the risk of increasing antimicrobial resistances has limited the use of the latter ones. In terms of lower urinary tract symptoms, 25% of patients will experience a worsening in voiding quality, which is usually transient, and fewer than 2% will suffer acute urinary retention requiring catheterization, more commonly after perineal biopsy. Hematuria and hematospermia are constant but moderate and usually self-limited, and pain can be alleviated with local anesthesia and measures to reduce anxiety. Other complications, such as erectile dysfunction, have been studied, and in summary the impact of prostate biopsies on erectile dysfunction is minimal, with no differences between the effect of multiple biopsies from that of the natural aging process on erectile function (48). Finally, mortality associated with biopsy is extremely rare and usually associated with infectious complications (49).

5. Role of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the prostate is increasingly used because of its potential as a noninvasive technique. As a diagnostic tool, 3 Tesla multiparametric MRI (3T MP-MRI) can identify abnormal lesions in the prostate that may be missed by transrectal ultrasound, especially in the anterior lobe (50). Also, a positive preoperative MRI can predict higher upgrading rate compared to negative MRI (43% vs 27%). However, upstaging will remain even (10% vs 8%) (51). Emerging techniques combining MRI and ultrasound to generate higher reclassification percentages than those obtained with standard biopsy confirmation (22%–27%) are also becoming more common (52). A negative MRI will have a reclassification rate of 17% compared to a positive MRI with 39% (51). To date, although MRI can be used to detect clinically significant disease in men undergoing AS, there is no evidence to support the replacement of repeated biopsies to detect progression. However, MRI-TRUS fusion biopsies may be important to AS protocols, as they target high-grade tumors and avoid detecting low-grade tumors. MRI-TRUS biopsies have proven to have twice the detection rate of random TRUS biopsies and are able to detect 67% more Gleason 4+3 tumors while missing 36% of Gleason 3+4 tumors, thus reducing the detection of low-risk tumors (52).

6. Proteomic and Genomic Biomarkers

To improve the detection of potentially aggressive tumors, several biomarkers are being studied. Recently, two laboratory-developed tests have been described to analyze prostate biopsy samples. Oncotype DX, from Genomic Health Inc., measures the expression of 12 cancer-related genes representing four different biological pathways (androgen pathway, cellular organization, proliferation pathway, and stromal response) and five reference genes (53). They are combined to calculate a Genomic Prostate Score that is used to improve NCCN risk criteria discrimination of PCa into very low-, low- and modified intermediate-risk. Prolaris from Myriad genetics Inc., is a molecular test that measures cell growth characteristics to stratify disease progression by testing 46 different gene expressions. High

expression of these genes is associated with higher risk of disease progression, thus closer monitoring or active treatment should be required for those patients (54).

FOLLOW-UP FOR PATIENTS UNDER ACTIVE SURVEILLANCE

Patients who elect AS as a management strategy for their PCa need to be properly informed of the difference between AS and WW and the benefits and pitfalls of AS. Additionally, patients need to understand the importance of compliance to a rigorous follow-up schedule. Follow-up in most AS protocols is based on clinical data, including digital rectal examination, PSA results, and repeat biopsies. Table 2 lists some of the most commonly used follow-up schedules.

1. Prostate-Specific Antigen

Although not very specific, PSA is a valid marker for both the diagnosis and monitoring of patients with PCa, including patients in AS. It was found, for example, that patients with PSADT <3 years tended to have more aggressive Gleason scores at repeat biopsy and generally had higher mean PSA levels (17). However, post-diagnostic PSA kinetics do not reliably predict adverse pathology and should not be used to replace annual surveillance biopsy for monitoring men on AS (56) (Table 3). PSAD proved to be a more specific marker for the diagnosis of PCa in patients with PSA <10, as well as a good predictor of adverse pathologic features and biochemical recurrence after RP. Its usefulness as a marker depends on finding a cut-off point that can be used to determine when to take action, but its sensitivity and specificity are too low to allow its use as a single marker (57). Data from several AS protocols suggest that a PSAD <0.15 ng/mL/g indicates smaller and less aggressive tumors (Table 3).

2. Repeat Biopsies

Repeat biopsies form the basis of follow-up for patients in an AS program. However, there is no consensus on whether a repeat biopsy is necessary or when it should be performed. Similarly, there is little uniformity in the intervals between repeat biopsies, though protocols using more restrictive criteria tend to suggest that they should be performed annually while others use wider intervals of up to 3 years (Table 2).

3. Other Follow-up Methods

In 2012, the European Society for Urogenital Radiology (ESUR) published a guide for MRI for PCa (58). Some groups already include MRI in their protocols, either as standard procedure or when dealing with specific situations (Table 2).

The literature shows mixed results regarding the utility of PCA3 in AS protocols (59)(60), although the majority of publications suggest that it can be useful in predicting tumor size and/or aggressiveness. For example, a recent study indicated that PCA3 <20 could identify indolent tumors that would be good candidates for AS (61). Other recent paper, showed that baseline %p2PSA and phi were the only independent predictive factors of the likelihood of pathological reclassification 1 year after the inclusion in the AS protocol (62).

The majority of patients who move on to treatment with curative intent from AS do so after restaging, which occurs during the first 3 years. This is probably not due to those patients having progressive disease, but rather due to understaging at initial biopsy (63). In several protocols, the percentage of patients who abandoned AS because of personal preference varied between 1% and 8.7%, indicating high acceptance rates for AS as a valid therapeutic option. Table 3 shows the criteria used to define progression in several trials.

OUTCOMES OF ACTIVE SURVEILLANCE

The results of an AS program should be assessed based on its ability to avoid overtreatment while ensuring the same oncological outcomes as immediate treatment. Determining the extent to which avoidance of overtreatment is met means measuring the percentage of patients who remain treatment-free, while the evaluation of oncological outcomes involves the measurement of overall and cancer-specific survival rates, metastasis-free survival, and understaging. Secondary objectives should involve evaluation of the impact on patient quality-of-life and the costs related to AS and compared other management approaches.

Klotz *et al.* reported long-term outcomes of AS based on series of 993 patients. (16), with over 200 patients followed for 10 years, and 50 for more than 15 years. After a median follow-up of 6.4 years, 726 (73%) remained on AS and treatment-free (75.7% at 5 years, 63.5% at 10 years, and 55% at 15 years). Cancer-specific survival was 98.5% and development of metastasis was seen in 2.8% of the cohort with a median time from diagnosis of 7.3 years. In addition to treatment-free survival, one of the key objectives of an AS program is to ensure that oncological outcomes are at least equivalent to those achieved with immediate curative treatment. Assessment of these outcomes involves consideration of overall mortality, cancer-specific mortality, and metastasis-free mortality. The variety of inclusion criteria and follow-up periods used in the different series published to date, as well as the indications used for active treatment, make comparison difficult. However, despite the limited follow-up time in most of those studies, the outcomes to date have been similar to those achieved in patients receiving immediate curative treatment (Table 4).

When initiating a new AS protocol, given the well-accepted clinicopathological differences in prostate cancer between the population in Western countries and other regions, it is important to remark that the well-defined existing protocols may not be applicable for these other populations (64).

COST EFFECTIVENESS OF ACTIVE SURVEILLANCE

In 2007, Wilson *et al.* were among the first groups to carry out a study of initial and accumulated costs (65). They stratified patients and treatments by risk groups and included patients assigned to AS in the WW group. They concluded that WW had the lowest accumulated costs after 5 years, followed by brachytherapy, RP, cryotherapy, radiotherapy, and hormonal therapy. However, they also noted that a more objective assessment would need to include the costs of adverse effects and relapses. In 2012, Keegan *et al.* (66) compared the costs of an AS program with RP, radiotherapy, brachytherapy, or hormonal therapy given as monotherapy. They designed a model which included 2 theoretical cohorts

of 120,000 men assigned to either AS or one of the active treatments and were followed for 10 years. The costs of the AS cohort were calculated using cost data from an equivalent protocol at the University of California, to which they added the costs generated by 7% of patients who would initiate active treatment annually. The costs in the active treatment arm included biopsy, type of treatment, and subsequent 3–6 month follow-up. Taking into account the model's weaknesses (costs associated with complications were not included), 5 years of AS led to savings of \$16,042 per patient, though after 10 years this amount was reduced by 38% to \$9,944 per patient. It was observed that the frequency of biopsy was decisive in the final costs of AS and that patients who started AS but then switched to active treatment generated disproportionately high costs. The only cost-effectiveness analysis performed to date was published by Hayes *et al.* in 2013 (67). They compared active treatment and observation (AS and WW) in patients with low-risk PCa between 65 and 75 years of age. Health benefits were evaluated by comparing quality adjusted life expectancy for each treatment option and the authors concluded that if the proportion of patients with low-risk PCa who are treated conservatively increased from the current 10% to 50%, the American health care system would achieve a savings of \$500 million.

Since the first publication of an AS protocol in 2002 (69), several studies have confirmed the usefulness of AS in the management of patients with low- and intermediate-risk PCa, with an estimated cancer-specific survival of 96%–100% at 10 years(16)(63)(70). However, we must not lose sight of the long natural history of PCa nor the fact that localized PCa, which is not detected by PSA has an indolent course, with a cancer-specific survival rate of over 90% in the first 10–15 years when managed conservatively (71).

CONCLUSIONS

AS appears to reduce overtreatment in patients with low-risk PCa without compromising cancer-specific survival at 10 years. Therefore AS is an option for select patients who want to avoid the side effects inherent to the different types of immediate treatment. However, inclusion criteria for AS and the most appropriate method of monitoring patients on AS have not yet been standardized. The heterogeneity in criteria of selection, deselection, and follow-up protocols stems from the evolving knowledge about PCa and the change in risk assessment tools.

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ABBREVIATIONS

AS	active surveillance
MRI	magnetic resonance imaging
MRI-TRUS	magnetic resonance imaging-transrectal ultrasonography
PCa	prostate cancer

PSA	prostate-specific antigen
PSAD	prostate-specific antigen density
PSADT	prostate-specific antigen doubling time
RP	radical prostatectomy
US	United States
WW	watchful waiting

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Table 1

Inclusion criteria of different AS protocols

AS protocol	Clinical Stage	PSA	Gleason	Positive Cores	Core Positivity (%)
Tosoian <i>et al.</i> (15)	<T2a	—	3+3	2	50%
Klotz <i>et al.</i> (16)		10 [*]	3+3 [*]	—	—
Bul <i>et al.</i> (17)	T2	10	3+3	2	
Dall'Era <i>et al.</i> (18)	T2a	10	3+3	33%	50%
Berglund <i>et al.</i> (19)	T2a	10	3+3	3	50%
Van As <i>et al.</i> (20)	T2a	15	3+3	50%	—
Soloway <i>et al.</i> (21)	T2a	10	3+3	2	20%

* Until 1999, PSA 15 and Gleason 3+4 was used

Table 2

Follow-up of different AS protocols

Protocol	DRE	PSA	Biopsy	Imaging Techniques
Tosoian <i>et al.</i> (15)	6 months	6 months	Annual	
Klotz <i>et al.</i> (16)	3 months (2 years) 6 months if PSA stable	3 months (2 years) 6 months if stable	Confirmation: 6–12 months Repetition: 2 years (to age 80 years)	MRI optional
Bul <i>et al.</i> (17)	3 months (2 years) 6 months (after)		1, 4, and 7 years If PSADT=3–10, repeat biopsy	
Dall'Era <i>et al.</i> (18)	3 months	3 months	1–2 years (since 2003)	TRUS 6–12 months
Berglund <i>et al.</i> (19)			Confirmation: 3 months Repetition: annual	MRI prior to confirmation biopsy
Soloway <i>et al.</i> (21)	3 months (2 years) 6 months if PSA stable	3 months (2 years) 6 months if stable	Confirmation: 9–12 months Repetition: annual	
Carter <i>et al.</i> (55)	6 months	6 months	Annual	

Abbreviations: DRE = digital rectal exam, PSA = prostate-specific antigen, PSADT = prostate-specific antigen doubling time, TRUS = transrectal ultrasonography, MRI = magnetic resonance imaging

Table 3

Criteria for progression used in AS protocol

Protocol	Gleason	Positive Cores	Percentage of Core Affected	PSADT
Tosoian <i>et al.</i> (15)	>6	>2	>50	—
Klotz <i>et al.</i> (16)	>4+3	—	—	<3
Dall'Era <i>et al.</i> (18)	Increase	—	—	—
Soloway <i>et al.</i> (21)	>3+3	>2	—	—
Thomsen <i>et al.</i> (63)	4+3	>3	—	<3/5

Abbreviation: PSADT = prostate-specific antigen doubling time

Table 4

Oncological outcomes associated with various active surveillance protocols

Protocol	Patients	Mean Follow-up (years)	Treatment-Free survival	Cancer-Specific Mortality
Tosoian <i>et al.</i> (Johns Hopkins)(15)	769	2.7	59% at 5 years	0
Klotz <i>et al.</i> (University of Toronto)(16)	450	6.8	70% at 5 years	0.3% at 10 years
Bul <i>et al.</i> (PRIAS)(17)	2494	1.6	77% at 2 years	0
Soloway <i>et al.</i> (Miami)(21)	230	2.6	85.7% at 5 years	0
Dall'Era <i>et al.</i> (18)	321	3.6	67% at 5 years	0
Selvadurai <i>et al.</i> (Royal Marsden)(68)	471	5.7	70% at 5 years	2% at 8 years