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Active Surveillance for Prostate Cancer: A Systematic Review of the Literature

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Abstract

Context: Prostate cancer (PCa) remains an increasingly common malignancy world-wide. The optimal management of clinically localized, early-stage disease remains unknown, and profound quality of life issues surround PCa interventions.

Objective: To systematically summarize the current literature on the management of low-risk PCa with active surveillance (AS), with a focus on patient selection, outcomes, and future research needs.

Evidence acquisition: A comprehensive search of the PubMed and Embase databases from 1980 to 2011 was performed to identify studies pertaining to AS for PCa. The search terms used included *prostate cancer* and *active surveillance* or *conservative management* or *watchful waiting* or *expectant management*. Selected studies for outcomes analysis had to provide a comprehensive description of entry characteristics, criteria for surveillance, and indicators for further intervention.

Evidence synthesis: Data from seven large AS series were reviewed. Inclusion criteria for surveillance vary among studies, and eligibility therefore varies considerably (4–82%). PCa-specific mortality remains low (0–1%), with the longest published median follow-up being 6.8 yr. Up to one-third of patients receive secondary therapy after a median of about 2.5 yr of surveillance. Surveillance protocols and triggers for intervention vary among institutions. Most patients are treated for histologic reclassification (27–100%) or prostate-specific antigen doubling time <3 yr (13–48%), while 7–13% are treated with no evidence of progression. Repeat prostate biopsy with a minimum of 12 cores appears to be important for monitoring patients for changes in tumor histology over time.

Conclusions: AS for PCa offers an opportunity to limit intervention to patients who will likely benefit the most from radical treatment. This approach confers a low risk of disease-specific mortality in the short to intermediate term. An early, confirmatory biopsy is essential for limiting the risk of underestimating tumor grade and amount.

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1. Introduction

Prostate cancer (PCa) continues to pose significant health care challenges worldwide. Estimates show that it remains the number one cancer diagnosis in North American and European men, with age-adjusted incidence rates of 85.6 and 59.3 per 100 000, respectively [1]. PCa treatment effects, however, can be profound and prolonged. Although published single-institution series describe varying functional outcomes with PCa treatment, findings from larger, diverse data sets relate substantial rates of urinary and sexual dysfunction [2]. Many contemporary prostate tumors are estimated to have a protracted natural history and pose little threat to patients during their lifetime. Despite this evidence, the majority of men with newly diagnosed PCa undergo some form of aggressive treatment regardless of risk, and the changing landscape of PCa has led to concerns regarding overdiagnosis and overtreatment. Active surveillance (AS) and organ-sparing focal therapies have emerged as alternative treatment options for men with early-stage disease and continue to be intensely investigated.

The American Urological Association, European Association of Urology, and the National Comprehensive Care Network have all published guidelines for the treatment of localized PCa that include AS [3–5]. In addition, the US National Institutes of Health recently issued a consensus statement on AS for managing men with localized PCa [6]. Despite these guidelines, many uncertainties remain, including the long-term all-cause and disease-specific mortality, optimal patient selection, surveillance strategies, and triggers for intervention. The goal of this review is to summarize the current state of the literature while discussing ongoing and future needs with unanswered questions. Updates from major published series with longer follow-up periods are reviewed, with a focus on expanding eligibility, surveillance strategies, and triggers for intervention.

2. Evidence acquisition

A systematic review of the electronic databases PubMed and Embase from 1980 to 2011 was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis statement guidelines and limited to the English language (Fig. 1). The search terms used included *prostate cancer* and *active surveillance* or *conservative management* or *watchful waiting* or *expectant management*. Selected studies for outcomes analysis had to provide a comprehensive description of the demographic and disease characteristics of the men at the time of diagnosis, provide
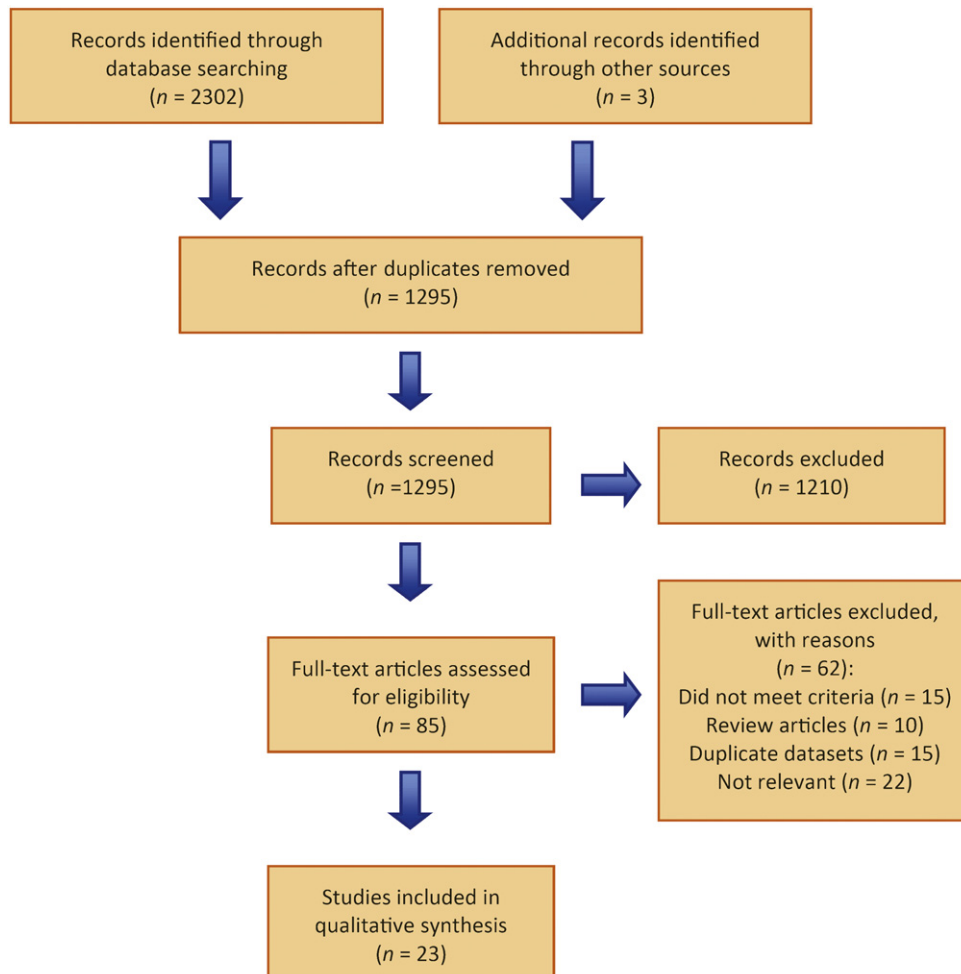

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart.

Table 1 – Inclusion criteria for active surveillance by institution[*]

Institution	Clinical stage	PSA	Gleason grade	Total positive cores	Single core positivity	Other
Johns Hopkins [7,8]	≤T2a	–	≤3 + 3	≤2	≤50%	PSA DT ≤0.15
University of Toronto [9]	NS	≤10	≤3 + 3[*]	NR	NR	–
UCSF [10]	≤T2a	≤10	≤3 + 3	≤33%	≤50%	–
ERSPC (PRIAS criteria) [11]	≤T2a	≤10	≤3 + 3	≤2	NR	PSA DT ≤0.2
Royal Marsden Hospital [12]	≤T2a	≤15	≤3 + 4	≤50%	NR	–
MSKCC [13]	≤T2a	≤10	≤3 + 3	≤3	≤50%	–
University of Miami [14,15]	≤T2a	≤10	≤3 + 3	≤2	≤20%	–

PSA = prostate-specific antigen; PSA DT = prostate-specific antigen doubling time; NS = not stated; NR = not recorded; UCSF = University of California, San Francisco; MSKCC = Memorial Sloan-Kettering Cancer Center.
[*] Prior to 2000, men >70 yr of age with a PSA ≤15 and Gleason score ≤3 + 4 were included.

inclusion criteria for surveillance, and include a protocol for following patients prospectively for signs of progression. Results were first screened for relevance to the topic and for inclusion criteria. Abstracts were reviewed for data analysis. Review articles and multiple papers from the same data sets were excluded. Raw data from tables were used whenever possible for results summary.

3. Evidence synthesis

3.1. Criteria for active surveillance

Criteria for AS set forth from published series are shown in Table 1 [7–15]. First described in 1994, and then updated in 2004, the Epstein criteria integrate biopsy criteria with clinical data to identify potentially low-risk tumors and are among the most commonly used methods to identify low-risk disease [16,17]. Characteristics of "insignificant" tumors include clinical stage T1; Gleason pattern ≤3 in the biopsy specimen (ie, no Gleason pattern 4); and either (1) prostate-specific antigen (PSA) density of ≤0.1 ng/ml per gram, two or fewer positive biopsy cores (minimum of six cores taken), and no cores with >50% involvement or (2) PSA density of ≤0.15 ng/ml per gram and cancer <3 mm on only one biopsy core (minimum of six cores taken). Most clinicians incorporate low Gleason grade (≤6), low clinical stage (≤T2a), and low PSA values (≤10) with estimates of tumor volume from the biopsy when selecting patients for contemporary AS. Use of more stringent criteria for entry will limit the number of men offered surveillance, and it remains unknown whether the most "conservative" selection criteria are optimal. Although some series describe results of surveying men with Gleason 7 (3 + 4) tumors, most limit this approach to men with Gleason 6 tumors [9,18–20]. Most centers do not have strict criteria with regard to patient age, and older men may opt for surveillance despite some higher-risk features, choosing to monitor their disease for early signs of progression when secondary local therapy can still be offered. When different criteria for AS are compared, there is a clear trade-off between sensitivity and specificity for predicting insignificant or organ-confined disease [21]. This trade-off equates with stricter criteria accurately selecting more men with lower-risk disease at the sake of excluding some potential candidates. Misclassification of insignificant disease based on entry criteria range from 22% to 33% of men [21]. Despite these differences, overall estimated 5-yr

biochemical recurrence (BCR)–free survival is good, with no differences between groups.

3.2. How many men are candidates for this approach?

Data from the Unites States–based Cancer of the Prostate Strategic Urologic Research Endeavor registry suggest that 36% of men diagnosed with PCa are considered low risk by D'Amico criteria. Estimating the percentages of men eligible for surveillance is sensitive to the criteria used and the disease characteristics of contemporary men presenting with PCa. In PSA-screened American men undergoing radical prostatectomy (RP), rates range from 7% to 69.1% [21,22]. Within the British Association of Urological Surgeons Cancer Registry, based in a country with a relatively low rate of PSA screening, only 9% of newly diagnosed PCa cases between 2000 and 2006 met criteria for low-risk disease, defined as having Gleason 6 histology, PSA <10, and clinical stage T1c–T2a [23]. It is likely that increased use of PSA screening with concomitant lowering of PSA thresholds for biopsy lead to a higher proportion of men diagnosed with disease amenable to AS. Clearly, the most stringent or conservative criteria limit the number of eligible men and likely exclude some potential candidates.

3.3. Treatment-free survival, disease-specific mortality, and all-cause mortality

All reviewed series describe strict inclusion criteria for AS at their institution largely based on low clinical stage, low PSA, well-differentiated tumor histology, and estimates of small tumor volume from prostate biopsy (Table 1). It is important to note, however, that many patients described in these series were included retrospectively and did not meet the "strictest" criteria often used in contemporary AS protocols. Table 2 depicts the reported outcomes from the reviewed AS series [24–27]. Not unexpectedly—and despite varying entry criteria—the disease-specific and all-cause survival over the short term is high. Up to 1/3 of patients receive further treatment after a median of about 2.5 yr of surveillance. The cohort from Toronto, Canada, reported the longest median follow-up—of 6.8 yr [9]. The median age of men in this series is generally older (70 yr of age) than the other series, which likely contributes to the higher all-cause mortality noted. This cohort contains both low-risk and intermediate-risk men (30% of patients), with men older

Table 2 – Summarized key findings from the largest published series within the past 2 yr

Institution	Yr	Age, median	*n*	Follow-up, yr, median	No. treated (%)	Time to treatment, median	Primary trigger for treatment	Treated at 2 yr, %	PCSM, %	ACM, %
Johns Hopkins [8]*	2011	66	769	2.7	255 (33)	2.2	Histology	19	0	2
University of Toronto* [9]	2010	70.3	450	6.8	135 (30)	NR	PSA	16	1	21.4
UCSF* [24]	2011	61.9	649	3.9	113 (30)**	3.5	Histology	–	0	3
ERSPC* [25]	2009	66	988	3.9	197 (32)	2.6	NR	22	0.2	11.2
Royal Marsden Hospital* [12]	2008	67	326	1.8	65 (20)	1.3	PSA	NR	0	2
MSKCC [13,26]	2011	62	238	1.8***	25 (11)	NR	Histology	NR	NR	NR
University of Miami [15,27]	2011	64	272	2.9	67 (25)	2.6	Histology	NR	0	2

PCSM = prostate cancer–specific mortality; ACM = all-cause mortality; NR = not recorded; PSA = prostate-specific antigen; UCSF = University of California, San Francisco; ERSPC = European Randomized Study of Screening for Prostate Cancer; MSKCC = Memorial Sloan-Kettering Cancer Center.
* Studies with some men having Gleason >3 + 3 disease.
** Percentage treated is of 337 men meeting strict inclusion criteria.
*** Median follow-up for patients without progression.

than 70 yr of age included with PSA values up to 15 ng/ml and Gleason scores up to 3 + 4. The 5- and 10-yr cancer-specific survival rates were 99.7% and 97.2%, respectively, and the authors report five PCA-specific deaths that are discussed in detail in a separate manuscript [28]. Of note, all patients who died from PCa (*n* = 5) had a rapid PSA doubling time (DT) of <1.6 yr, with only three men undergoing radical therapy. All patients had a PSA value <10 at diagnosis but were found to have Gleason 7 disease on repeat biopsy.

Using more expanded selection criteria, investigators from Johns Hopkins University have prospectively followed men expectantly with suspected low-risk PCa since 1995. Epstein et al. previously demonstrated that low PSA density predicts for small, organ-confined prostate tumors based on pathologic findings at the time of RP [16]. Based on this work, the group from Johns Hopkins University defines *low-risk disease* as Gleason score ≤6, clinical stage ≤T1c, PSA density ≤0.15, two or more positive biopsy cores, and ≤50% single-core involvement. This study reports a median follow-up of 2.7 yr, with no deaths attributable to PCa and no cases of metastatic disease [8].

One of the larger series consists of 988 men, with a median follow-up of 3.91 yr, from the European Randomized Study of Screening for Prostate Cancer (ERSPC) [25]. The authors report an estimated 10-yr PCa-specific survival of 100%, with one patient dying from PCa 11 yr after diagnosis. Again, it is important to note that many men were included retrospectively, and only 62% of this cohort

met the strictest criteria for low-risk disease as defined by Prostate Cancer Research International: Active Surveillance (PRIAS) [29]. Eligible men for PRIAS met fairly stringent entry criteria: clinically localized disease (cT1–T2), PSA level <10, Gleason score ≤6, PSA density ≤0.2, and no more than two prostate biopsy cores involved with cancer. The initial publication from this series after a median follow-up of 1.02 yr showed a treatment-free survival of 73% after 2 yr, with no deaths from PCa to date.

3.4. Outcomes from repeat biopsy

Repeat prostate biopsies over time have been incorporated into most surveillance strategies. As Gleason grade remains one of the greatest predictors of prognosis for men with PCa, it is important to identify higher-grade disease that may not be best managed expectantly. It has been recognized for some time that many men undergoing immediate RP after cancer diagnosis are found to have higher-grade disease than known preoperatively, and this risk of clinical undergrading with a 12-core biopsy is estimated to be 20–30% [22,30,31]. Biopsy technique can affect both overall and clinically significant prostate tumor detection. Extended biopsy schemes with laterally directed biopsies have proven superior to sextant biopsies for PCa detection [32].

It is unknown whether changes in histology over time represent tumor de-differentiation and growth or simply tissue undersampling; however, it is likely a combination of the two [33]. Serial prostate biopsy serves to identify both

Table 3 – Outcomes from confirmatory or first surveillance prostate biopsy

Study	No. or cores at diagnosis, median	Time to first biopsy	No cancer, %	No change, %	Increased grade, %	Increased cores or percentage of positivity*, %
Johns Hopkins [8]	NR	1.3 yr (mean)	NR	NR	13.8	16.8
UCSF [34]	6–12	12–16 mo	24	53	21	NR
MSKCC [13]	10	<3 mo	26	57	16	22
PRIAS [35]	8	1.03 yr (median)	36.6	41.9	8.9	17.2
Royal Marsden Hospital [36]	NR	1.5–2.0 yr	21	61	28	9
University of Miami [15]	10 (min)	NR	50	46	2.5	1.5

NR = not recorded; UCSF = University of California, San Francisco; MSKCC = Memorial Sloan-Kettering Cancer Center; PRIAS = Prostate Cancer Research International: Active Surveillance.
* Beyond inclusion criteria for institution.

situations, with the early "confirmatory" biopsy aimed at minimizing the risk of undersampling. Table 3 displays the pathologic outcomes after the first repeat biopsy from the series identified [34–36]. Investigators from Memorial Sloan-Kettering Cancer Center used a strategy of early (within 3 mo) confirmatory biopsy in a cohort of men on AS [13]. Twenty-seven percent of men were identified with adverse pathologic features on 12-core confirmatory biopsy, rendering them ineligible for surveillance per their protocol, while 26% of men demonstrated negative histology. A follow-up analysis with a larger sample size suggests that up to 35% of men may no longer be candidates after immediate rebiopsy [26].

Within the PRIAS cohort, 78.5% of men had either no cancer detected or cancer still meeting all criteria for surveillance after a confirmatory biopsy [35]. Nine percent of men had higher Gleason grade disease found, while 17% had higher-volume disease. Overall, 21.5% had adverse pathologic features after the first surveillance biopsy, rendering them ineligible for surveillance. Multivariate analysis showed that higher PSA density and more positive cores at diagnosis (2 vs 1) were associated with higher grade or higher cancer volume at repeat biopsy.

The time interval for surveillance prostate biopsy also varies among the series reviewed. PRIAS recommends prostate biopsy at 1, 4, and 7 yr, while men from the Johns Hopkins group are followed with yearly biopsies. With a median follow-up of 54 mo after diagnostic biopsy, University of California, San Francisco (UCSF) investigators described the results of multiple surveillance biopsies over time [34]. The risk of grade progression with subsequent surveillance biopsies ranged from 22% to 30% with each biopsy round, with the majority of upgrades being to Gleason 3 + 4 disease.

3.5. The role of prostate-specific antigen in active surveillance

The value of PSA kinetics over time for predicting disease progression on AS remains unknown. Monitoring PSA over time for men on AS is based on the correlation between high PSA velocity in the year before diagnosis and PCa mortality after treatment [37,38]. PSA DT—the period of time it takes for the PSA to double in value—can be calculated using several methods, and the Toronto group uses a general linear mixed model considering at least eight PSA values to assess risk and account for PSA fluctuations between measurements [39,40]. Although arbitrarily selected, most series describe PSA testing every 3 mo.

Klotz et al. originally used a PSA DT cut-off <2 yr to recommend treatment; however, they increased this value to <3 yr, which applied to approximately 20% of this cohort [9]. Among men on AS from the ERSPC, 44% had a prolonged PSA DT (negative or >10 yr) [41]. Overall, 7.3% of men experienced PSA DTs <2 yr. Within a subgroup of patients remaining on AS from the Toronto series, after a median follow-up of 6.1 yr, 38% had at least one PSA value >10, 37% had a PSA DT <2 yr at least once, and 42% had a PSA velocity (PSAV) >2 ng/ml per year at some point during surveillance [39]. None of these men died from PCa, and none showed evidence of metastatic disease over the period of study. Although men from this cohort already selected for treatment were not included in this analysis, it does suggest that PSA kinetics are not static, and single PSA trigger points should be interpreted carefully. Further questioning the role of PSA changes over time for men on AS, the Johns Hopkins group showed no correlation between PSA DT and adverse pathology at surveillance biopsy or RP for those who eventually underwent surgical management [42]. Similarly, within the UCSF cohort, little concordance was found between PSAV and biopsy progression [43]. Although 23% of men eventually progressed histologically, only a single patient had a PSA DT <3 yr. Conversely, within the PRIAS cohort, 181 men had PSA DT <3 yr, which was associated with disease reclassification after repeat biopsy [35]. Data from the Royal Marsden cohort suggest that PSAV may be more predictive than PSA DT, showing that a PSAV >2.0 ng/ml per year was significantly associated with Gleason grade change from 3 + 3 to ≥3 + 4, more than half of the cores positive for cancer, or primary Gleason grade ≥4 [20].

When interpreting these data, it is important to consider the indications for repeat biopsy in the differing studies, as ascertainment bias can lead to stronger associations if men with rising PSA values were more likely to undergo frequent biopsy. In practice, PSA changes are unlikely to justify treatment in isolation but may prompt an earlier surveillance biopsy. A lack of histology progression with rising PSA, however, may prompt intervention.

3.6. The role of imaging

The lack of adequate imaging modalities for early-stage PCa has been a critical issue for AS. Most men with low-risk PCa have normal ultrasound findings, and serial transrectal ultrasound thus far has not proved beneficial for tumor characterization or monitoring for disease progression [10]. Multiple investigators have evaluated magnetic resonance imaging (MRI) for PCa, as this modality offers advantages over other imaging modalities, including enhanced delineation of pelvic anatomy as well as the opportunity for functional assessment.

As a potential screening tool for AS candidates, findings for extracapsular disease may predict a higher rate of biopsy progression than men with normal MRI findings [13]. MRI with spectroscopic imaging was performed at the time of cancer diagnosis on 114 men from the UCSF cohort [44]. Seventy-five percent of men had either concerning lesions or metabolic activity suggestive of cancer. When comparing visible anatomic lesions to spectroscopically functional lesions only, the anatomic MRI was associated with biopsy progression and receipt of treatment. Recently, diffusion-weighted MRI techniques have been applied to prostate imaging and may improve tumor imaging over standard MRI [45].

Other investigators studied the ability of MRI findings to predict high-risk disease features at the time of RP for men with presumed low-risk disease (based on 21-core diagnostic biopsy) and found no independent predictive value; therefore, the role of MRI for AS remains unclear [46].

As technology continues to improve, however, prostate imaging will likely become important and remains an important avenue of investigation for selecting and monitoring men with PCa for surveillance.

3.7. Progression to treatment: outcomes from delayed intervention

Estimating the number of men who will progress on AS is highly sensitive to the definition of *progression* chosen and the criteria used to select AS candidates. Many clinicians define *progression* as changes in PSA over time, the detection of higher-volume or grade cancer on surveillance biopsy, or concerning changes on physical exam of the prostate, although palpable changes of early prostate tumors are likely rare. In truth, many cases of progression are likely better described as disease *reclassification*, especially during the early periods of AS, as more sampling of the prostate is performed with rebiopsy. As men progress or are reclassified beyond the initial inclusion criteria of their institution (ie, they no longer meet the entry criteria), treatment is often recommended. It is important to note, however, that not all men considered progressors undergo immediate treatment, just as a subset of men elect to have treatment with no change in their clinical condition.

Anxiety over the uncertainty of the future or fear of losing the opportunity for a cure is an important driver of treatment [47]. In the series from the University of Toronto, for example, PSA DT <3 yr is the primary outcome driving treatment, while other series are much more sensitive to pathologic changes over time [8–10]. A more objective end point in AS series is the number of men remaining on surveillance after a specified time interval, or *treatment-free survival.* Table 2 lists the number of men in each series who ultimately received active treatment, which ranges from 11% up to 32% with longer median follow-up.

Several papers have described the outcomes from delayed intervention after a period of AS [48–50]. In one of the earliest reports from Johns Hopkins, rates of "noncurable" PCa after delayed intervention were low (23%) and did not differ from men undergoing immediate surgery [50]. Of patients with sufficient data within the Toronto cohort (*n* = 117), 50.4% had BCR after secondary therapy. This number must be tempered by the fact that this cohort contains some men with intermediate-risk disease and that relatively few men have been treated. Also, although this may seem like a high percentage for a group of men who were AS candidates, when viewed as a whole, this represents 50% of the 28% who underwent treatment. In other words, 86% of men remained untreated or without secondary treatment failure.

Of 27 men undergoing RP after progression from the PRIAS study, 17% had evidence of pT3a disease on final pathology, and 38% had positive surgical margins. Duffield et al. reported on the outcomes after RP for 48 men previously on AS from the Johns Hopkins cohort. The mean time from first biopsy to prostatectomy was 29.5 mo. Only one patient had lymph node involvement at the time of surgery, and one patient had seminal vesicle invasion.

Sixty-five percent of men had organ-confined (pT2) disease, and 27% of men had indolent disease defined pathologically as organ-confined disease with a dominant nodule <0.5 cm^3 in size and no Gleason pattern 4 or 5. The authors also noted that tumors where the predominant nodule was >1 cm^3 were located in the anterior aspect of the prostate, leading them to suggest that all patients undergoing surveillance biopsies should have anterior zone sampling.

3.8. Expanding the criteria for active surveillance

As the most conservative inclusion criteria for AS limit the number of candidates for this approach, it becomes important to identify criteria to possibly expand the pool of patients who can be offered AS. Patient factors must be considered along with tumor characteristics, as clinicians may tolerate some higher-risk features in older men or men with significant comorbidities. Men with Gleason 7 cancer otherwise meeting the criteria for surveillance based on stage, PSA, and estimates of tumor volume have been managed with AS. With a median follow-up of 3.4 yr, actuarial PCa-specific and all-cause 6-yr survival of 21 men were 100% and 68%, respectively [11]. The UCSF group studied 90 men with intermediate-risk disease within their AS cohort, as defined by the validated UCSF Cancer of the Prostate Risk Assessment score 3–5 [18]. Thirty-two percent of this cohort had Gleason 7 disease with higher % biopsy cores positive, median PSA was 10.3 ng/ml, and 38% were clinical stage T2. Of 63 men having at least one surveillance biopsy, 30% were upgraded over time. Progression-free survival was 61% at 4 yr, and 35% of men from this cohort ultimately received secondary treatment—rates not dissimilar for primarily low-risk men on surveillance. Ideally, advances in PCa imaging and biomarker discovery will allow the inclusion criteria for surveillance to expand.

3.9. Active surveillance and clinical trials

Ideally, answers to questions regarding entry criteria and outcomes from conservative management of PCa would come from well-designed, randomized clinical trials. Along with ongoing data from the series presented in this article, single-armed AS trials will answer many questions with this approach as well as hopefully identify markers for appropriate patient selection and early evidence of progression [51]. Accruing trials such as the Prostate Active Surveillance Study [51] and PRIAS offer prospectively collected data for men on AS, while the British Prostate Testing for Cancer and Treatment trial aims to compare surveillance with RP and radiation therapy for localized PCa in a randomized fashion.

AS also offers a unique opportunity for therapeutic and intervention studies by allowing for repeat biospecimen collection over time. Many men on AS may also be motivated to pursue dietary and lifestyle changes that may alter the course of disease. Early data suggest that such modifications may help maintain and even improve quality of life as well as reduce the risk of men proceeding to secondary treatment, perhaps through relieving patient anxiety over doing "nothing" [52]. The Prostate Cancer

Lifestyle Trial, a randomized trial comparing intensive dietary and lifestyle modifications for men on AS compared to usual care, reported significantly lower rates of secondary PCa treatment for the intervention arm at 2 yr [53]. Specific to men on AS, an ongoing multicenter study sponsored by the Cancer and Leukemia Group B is testing whether a dietary intervention can delay time to "progression," defined by PSA >10 ng/ml [54].

4.   Conclusions

As AS series continue to mature, data show that disease-specific mortality remains low, with moderate rates of intervention over the first few years. Decisions regarding management of localized PCa, including AS, should be made with an individualized approach after careful risk assessment. Men should be counseled upfront on the need for ongoing surveillance as well as the definitions of *progression* that may lead to a recommendation for treatment. A confirmatory biopsy within the first year is critical to limiting the risk of undergrading.

References

[1] Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012; 61:1079–92.

[2] Huang GJ, Sadetsky N, Penson DF. Health related quality of life for men treated for localized prostate cancer with long-term followup. J Urol 2010;183:2206–12.

[3] Thompson I, Thrasher JB, Aus G, et al., AUA Prostate Cancer Clinical Guideline Update Panel. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol 2007;177:2106–31.

[4] Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011;59:61–71.

[5] Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw 2010; 8:162–200.

[6] Ganz PA, Barry JM, Burke W, et al. National Institutes of Health state-of-the-science conference: role of active surveillance in the management of men with localized prostate cancer. Ann Intern Med 2012;156:591–5.

[7] Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol 2007;178:2359–64, discussion 2364–5.

[8] Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011;29:2185–90.

[9] Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010;28: 126–31.

[10] Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. Cancer 2008;112:2664–70.

[11] van den Bergh RC, Vasarainen H, van der Poel HG, et al. Short-term outcomes of the prospective multicentre 'Prostate Cancer Research International: Active Surveillance' study. BJU Int 2010;105: 956–62.

[12] van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008;54:1297–305.

[13] Berglund RK, Masterson TA, Vora KC, Eggener SE, Eastham JA, Guillonneau BD. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for active surveillance. J Urol 2008;180:1964–7, discussion 1967–8.

[14] Soloway MS, Soloway CT, Williams S, Ayyathurai R, Kava B, Manoharan M. Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. BJU Int 2008;101:165–9.

[15] Soloway MS, Soloway CT, Eldefrawy A, Acosta K, Kava B, Manoharan M. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. Eur Urol 2010;58:831–5.

[16] Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368–74.

[17] Bastian PJ, Mangold LA, Epstein JI, Partin AW. Characteristics of insignificant clinical T1c prostate tumors. A contemporary analysis. Cancer 2004;101:2001–5.

[18] Cooperberg MR, Cowan JE, Hilton JF, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. J Clin Oncol 2011;29:228–34.

[19] van den Bergh RC, Roemeling S, Roobol MJ, et al. Gleason score 7 screen-detected prostate cancers initially managed expectantly: outcomes in 50 men. BJU Int 2009;103:1472–7.

[20] Ng MK, Van As N, Thomas K, et al. Prostate-specific antigen (PSA) kinetics in untreated, localized prostate cancer: PSA velocity vs PSA doubling time. BJU Int 2009;103:872–6.

[21] Iremashvili V, Pelaez L, Manoharan M, Jorda M, Rosenberg DL, Soloway MS. Pathologic prostate cancer characteristics in patients eligible for active surveillance: a head-to-head comparison of contemporary protocols. Eur Urol 2012;62:462–8.

[22] Suardi N, Briganti A, Gallina A, et al. Testing the most stringent criteria for selection of candidates for active surveillance in patients with low-risk prostate cancer. BJU Int 2010;105:1548–52.

[23] McVey GP, McPhail S, Fowler S, McIntosh G, Gillatt D, Parker CC. Initial management of low-risk localized prostate cancer in the UK: analysis of the British Association of Urological Surgeons Cancer Registry. BJU Int 2010;106:1161–4.

[24] Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. J Clin Oncol 2011;29:3669–76.

[25] van den Bergh RC, Roemeling S, Roobol MJ, et al. Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. Eur Urol 2009;55: 1–8.

[26] Adamy A, Yee DS, Matsushita K, et al. Role of prostate specific antigen and immediate confirmatory biopsy in predicting progression during active surveillance for low risk prostate cancer. J Urol 2011;185: 477–82.

[27] Soloway MS, Manoharan M, Rosenberg D, Kava B. Active surveillance for prostate cancer: an update of the Miami experience [abstract]. Presented at: 31st Congress of the Societe Internationale D'Urologie; October 16–20, 2011; Berlin, Germany.

[28] Krakowsky Y, Loblaw A, Klotz L. Prostate cancer death of men treated with initial active surveillance: clinical and biochemical characteristics. J Urol 2010;184:131–5.

[29] van den Bergh RC, Roemeling S, Roobol MJ, Roobol W, Schröder FH, Bangma CH. Prospective validation of active surveillance in prostate cancer: the PRIAS study. Eur Urol 2007;52:1560–3.

[30] Conti SL, Dall'era M, Fradet V, Cowan JE, Simko J, Carroll PR. Pathological outcomes of candidates for active surveillance of prostate cancer. J Urol 2009;181:1628–33, discussion 1633–4.

[31] Smaldone MC, Cowan JE, Carroll PR, Davies BJ. Eligibility for active surveillance and pathological outcomes for men undergoing radical prostatectomy in a large, community based cohort. J Urol 2010; 183:138–43.

[32] Presti Jr JC, O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol 2003;169:125–9.

[33] Epstein JI, Walsh PC, Carter HB. Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage T1c disease. J Urol 2001;166:1688–91.

[34] Porten SP, Whitson JM, Cowan JE, et al. Changes in prostate cancer grade on serial biopsy in men undergoing active surveillance. J Clin Oncol 2011;29:2795–800.

[35] Bul M, van den Bergh RC, Rannikko A, et al. Predictors of unfavourable repeat biopsy results in men participating in a prospective active surveillance program. Eur Urol 2012;61:370–7.

[36] Venkitaraman R, Norman A, Woode-Amissah R, et al. Predictors of histological disease progression in untreated, localized prostate cancer. J Urol 2007;178:833–7.

[37] D'Amico AV, Chen MH, Roehl KA, Catalona WJ, Preoperative PSA. velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 2004;351:125–35.

[38] D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. JAMA 2005;294:440–7.

[39] Loblaw A, Zhang L, Lam A, et al. Comparing prostate specific antigen triggers for intervention in men with stable prostate cancer on active surveillance. J Urol 2010;184:1942–6.

[40] Zhang L, Loblaw A, Klotz L. Modeling prostate specific antigen kinetics in patients on active surveillance. J Urol 2006;176:1392–7, discussion 1397–8.

[41] Roemeling S, Roobol MJ, de Vries SH, et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. Eur Urol 2007;51:1244–51, discussion 1251.

[42] Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol 2010;28:2810–6.

[43] Whitson JM, Porten SP, Hilton JF, et al. The relationship between prostate specific antigen change and biopsy progression in patients on active surveillance for prostate cancer. J Urol 2011;185:1656–60.

[44] Fradet V, Kurhanewicz J, Cowan JE, et al. Prostate cancer managed with active surveillance: role of anatomic MR imaging and MR spectroscopic imaging. Radiology 2010;256:176–83.

[45] Afaq A, Koh DM, Padhani A, van As N, Sohaib SA. Clinical utility of diffusion-weighted magnetic resonance imaging in prostate cancer. BJU Int 2011;108:1716–22.

[46] Ploussard G, Xylinas E, Durand X, et al. Magnetic resonance imaging does not improve the prediction of misclassification of prostate cancer patients eligible for active surveillance when the most stringent selection criteria are based on the saturation biopsy scheme. BJU Int 2011;108:513–7.

[47] Latini DM, Hart SL, Knight SJ, et al. The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. J Urol 2007;178:826–31, discussion 831–2.

[48] Dall'Era MA, Cowan JE, Simko J, et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. BJU Int 2011;107:1232–7.

[49] van den Bergh RC, Steyerberg EW, Khatami A, et al. Is delayed radical prostatectomy in men with low-risk screen-detected prostate cancer associated with a higher risk of unfavorable outcomes? Cancer 2010;116:1281–90.

[50] Warlick C, Trock BJ, Landis P, Epstein JI, Carter HB. Delayed versus immediate surgical intervention and prostate cancer outcome. J Natl Cancer Inst 2006;98:355–7.

[51] Newcomb LF, Brooks JD, Carroll PR, et al. Canary Prostate Active Surveillance Study: design of a multi-institutional active surveillance cohort and biorepository. Urology 2010;75:407–13.

[52] Daubenmier JJ, Weidner G, Marlin R, et al. Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. Urology 2006;67:125–30.

[53] Frattaroli J, Weidner G, Dnistrian AM, et al. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. Urology 2008;72:1319–23.

[54] Parsons JK, Newman V, Mohler JL, Pierce JP, Paskett E, Marshall J. The Men's Eating and Living (MEAL) Study: a Cancer and Leukemia Group B pilot trial of dietary intervention for the treatment of prostate cancer. Urology 2008;72:633–7.