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When and How Should Active Surveillance for Prostate Cancer End?

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Abstract

Despite widespread adoption of active surveillance (AS) for low-risk prostate cancer, less is known about how or when monitoring should be deintensified. We performed a narrative review of the available evidence and guidelines addressing transitions from active to passive monitoring, including watchful waiting. Increasing age and comorbidity limit quality-adjusted life years gained from curative intervention, although no universal thresholds exist to denote a transition from active monitoring. Despite observational studies indicating that AS intensity decreases over time, the risk of distant progression also increases with age, suggesting an opportunity to improve decision support that incorporates multiple factors when navigating these decisions.

Patient summary:

We reviewed the available evidence surrounding transitioning from active monitoring to observation. Clinical practice guidelines and research studies support decreasing intensity based on an appreciation of age, other medical problems, and patient preferences.

Keywords

Active surveillance; Watchful waiting; Transition; Prostate cancer; Monitoring

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Author contributions:

Michael S. Leapman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rajwa, Leapman.

Acquisition of data: Rajwa, Leapman.

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1. Introduction

Active surveillance (AS) has become the standard of care for most patients diagnosed with low-risk prostate cancer (PCa) [1,2]. Recent estimates indicate that approximately 50% of eligible patients with low-risk PCa are initially managed with AS in the USA, Australia, and Europe. For patients whose cancer-related risks recede due to advanced age or comorbidity, there is an emerging need to improve transitions away from intense forms of monitoring toward expectant management strategies such as “watchful waiting” (WW) [3]. Despite current clinical guidelines providing a high level of detail for initiating AS (Table 1), there is comparatively less guidance regarding *when* and *how* strategies of active monitoring can be de-escalated [1,2]. To anticipate the needs of an expanding population of men managed with AS, we performed a narrative review of the current evidence supporting de-escalation of AS for untreated PCa.

2. Life expectancy as the principal guidance

The feasibility of AS reflects an acceptably low probability of distant cancer progression during a patient’s observation period. In addition to accurate appraisal of the cancer’s capacity for distant spread, estimates of life expectancy, dictated by age and comorbidity, are critical factors for determining the appropriateness and intensity of monitoring. As a result, numerous AS protocols recommend AS until 75–80 yr, although several recent studies advocate transitions based on more comprehensive estimates of life expectancy (Table 2).

Virtually, all guidelines indicate that the transition from AS to WW should prominently incorporate age. Markov model analyses suggested that AS adds more life years than WW irrespective of the age at diagnosis; however, improvements were greatest in patients aged <75 yr (up to 1.03 yr) compared with those aged 75 yr and older (0.06–0.07 yr) [4]. Among patients aged ≥65 yr, no AS protocol added more quality-adjusted life years (QALYs) than WW; AS reduced QALYs by 0.10–0.34 [4]. A microsimulation analysis from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and Surveillance, Epidemiology and End Results (SEER) program indicated that benefit of AS depends primarily on life expectancy [5]. Moreover, increasing intensity of monitoring for patients unlikely to benefit from curative intervention has diminishing value. Even a single biopsy reduced QALYs among low-risk men aged ≥65 yr, and the ratio of overtreatment to life years gained from four biopsies increased with age nearly 14-fold (from 120:723 in patients aged 55–59 yr to 224:98 in those aged 70–74 yr) [5].

Increasing medical comorbidity, regardless of age, reduces the utility of intensive monitoring. In a study of 19 639 PCa patients in the SEER-Medicare database, the vast majority of those with Charlson Comorbidity Index (CCI) ≥2 died of non-PCa causes [6]. Among patients aged 66–74 yr with CCI ≥2 and diagnosed with cT2 PCa of Gleason score 5–7, 10-yr all-cause mortality was 74.6% (95% confidence interval [CI], 64.2–85.1%), in contrast to 1.0% (95% CI, 0.0–3.7%) for PCa-specific mortality [6]. Furthermore, age and comorbidity remained key predictors of 5- and 10-yr all-cause mortality among patients with high-grade disease (Gleason sum 8–10), with a small absolute risk of PCa-related death [6].

3. Transitions from active surveillance in clinical settings

Empirically, the intensity of AS decreases over time, leading to WW. Among patients with low-grade PCa in SEER-Medicare, ≤11.1% adhered to recommended protocols during 5 yr of AS [7]. Older age (≥70 yr) and greater comorbidity (CCI ≥1) were associated with lower odds of surveillance biopsies [7]. In a Swedish study of national healthcare registers, very-low risk PCa patients aged 68–72 yr spent a median of 4.6 yr (interquartile range 2.1–7.7) on AS, before 62.3% transitioned to WW [3]. Another Swedish study found that among 3116 patients with PCa, CCI ≥2 was associated with lower incidence of repeat biopsy, and that over 10 yr of AS, the frequencies of repeat biopsy and prostate-specific antigen testing decreased from 42% to 4% and from 90% to 55%, respectively [8]. It should be noted, however, that these studies evaluated adherence to older surveillance protocols that were more rigorous.

There are numerous practical challenges with de-escalating AS. First, interest in reducing the burden from biopsy is balanced by potential increases in PCa aggressiveness that occur with age. Reduced intensity of monitoring may increase patient anxiety about missed disease progression, with unexplored psychological impact. Recent improvements in risk stratification may facilitate assessment of disease trajectory, allowing the intensity of monitoring to be reduced in the setting of stable or profiles. Moreover, the contribution of other factors such as race or family history remains unclear in guiding the intensity of observation. A growing body of evidence supports the clinical utility of multiparametric magnetic resonance imaging (mpMRI) and genomic testing during AS, including the identification of lower-risk profiles such as stable mpMRI findings [1,2]. Currently, however, the optimal application of these tools during surveillance remains to be defined.

Lastly, expansion of AS to patients with intermediate risk factors adds complexity to deintensifying surveillance [1,2,4,7,8]. In a Dutch study of patients who were ineligible for Prostate Cancer Research International Active Surveillance (PRIAS), nonadherence to the PRIAS protocol was associated with a higher risk of metastasis [9]. Moreover, data from ERSPC and SEER suggest that intermediate-risk patients, aged <70 yr, may benefit from as many as 10 surveillance biopsies, implying a need for closer monitoring in this group [5]. Given the heterogeneity of the expanding surveillance population, adjunctive tools such as MRI and genomic testing may add value in clarifying individual risk trajectories.

4. Conclusions

The widespread adoption of AS for PCa highlights a need to clarify the optimal manner in which monitoring can be de-escalated. Prior observational and modeling studies indicate that increasing age and comorbidity are associated with diminishing utility of intensive monitoring; however, there is no universally accepted age or comorbidity cutoff to denote an appropriate transition from AS to WW. Given the complexity of these decisions, there is an ongoing need to improve the ways in which multiple dimensions—including risks contributed by PCa or other causes, and personal preference—are integrated to reduce the burden of monitoring for patients less likely to derive benefit.

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Table 1–

Summary of NCCN and EAU guidelines on active surveillance and observation (watchful waiting)

Organization	Risk group	Active surveillance		Watchful waiting	
		Estimated survival	Recommendation for AS	Estimated survival	Recommendation for WW
NCCN	Very low risk	≥10–20yr >20yr (preferred)[a]	Yes	<10yr	Yes
	Low risk	≥10yr (preferred)[a]	Yes	<10yr	
	Favorable intermediate risk	≥10yr[b]	Yes	<10yr (preferred)[c]	
	Unfavorable intermediate risk	NA	No	<10yr (preferred)[d]	
	High and very high risk	NA	No	≤5yr[e]	
EAU	Low risk	≥10yr	Yes (strong evidence)	<10yr	Yes
	Intermediate risk[f]	Not provided	Yes (weak evidence)		
	High risk	NA	No		

ADT = androgen deprivation therapy; AS = active surveillance; EAU = European Association of Urology; EBRT = external beam radiation therapy; NA = not applicable; NCCN = National Comprehensive Cancer Network; RP = radical prostatectomy; WW = watchful waiting.

[a] AS (preferred), EBRT or brachytherapy, and RP should be discussed.

[b] AS, EBRT or brachytherapy, and RP should be considered.

[c] WW (preferred), EBRT, or brachytherapy should be considered.

[d] WW (preferred), and EBRT ± brachytherapy ± ADT should be considered.

[e] In asymptomatic men WW or EBRT (or ADT), when metastasis and/or complications are expected.

[f] <10% pattern 4.

Table 2–

Summary of studies addressing de-escalation of active monitoring for prostate cancer

Study	Country	*N*	Modality	Outcomes	Key findings
Van Hemelrijck et al (2017) [3]	England/ Sweden	7278	Transition from AS to WW	Transition from AS to WW	• Among men at very low risk, older age al AS initiation was associated with transitioning to WW, whereas younger age was associated with transilioning to radical treatment. • Men at very low risk remained on AS for a median of 5 yr, and 48% transitioned to WW over a lifetime. • The prevalence simulation of men initiating AS revealed a slow increase of transition to WW during the first years, rapid rise during the next 10–20 yr, and stabilizing after 30 yr.
Loeb et al (2017) [4]	USA	NA	AS vs WW	LYG, QALY	• Regardless of age al diagnosis, AS added more LYG, although fewer at more advanced age (0.64–1.03 for age ≥40 yr vs 0.06–0.07 for age ≥75 yr). • For patients aged ≥65 years at diagnosis, AS was associated with QALY lost (−0.10–0.34).
de Carvalho et al (2017) [5]	The Netherlands	10k	AS vs CM	LYG, QALY, overtreatment, cost effectiveness	• Performing four biopsy rounds in the age groups of 55–59 and 70–74 yr resulted in 723 LYG at a cost of 120 overtrcated men and in only 98 LYG with 224 overtreated men per 1000 patients, respectively. • Compared with CM, even one biopsy round resulted in lost QALY for men aged >65 yr, and 7 annual biopsy rounds are cost effective for men aged <65 yr at low risk and for men <75 yr at intermediate risk.
Albertsen et al (2011) [6]	USA	19 639	AS/CM	All-cause and PCa-specific mortality	• Higher comorbidity burden strongly increased the overall to PCa-specific mortality ratio. • For example, cTl, GS 5–7 patients with CCI = 0 vs those with CCI ≥2 had 10-yr overall and PCa-specific mortality of 28.8% vs 83.1% and 4.8% vs 5.3%, respectively.
Loeb etal (2016) [7]	USA	5192	AS	Compliance with AS protocols, intensity of surveillance biopsy	• During 5 yr of AS, only 11.1% and 5.0% met the testing standards of the Sunnybrook/ PRIAS and Johns Hopkins programs, respectively. • Surveillance biopsy was less likely in patients of an older age (OR [95% CI] for those aged ≥80 vs <70 yr: 0.86 [0.82–0.90]) and with more comorbiditics (for those with CCI ≥1 vs CCI = 0: 0.93 [0.90–0.97]). • Surveillance biopsy was more likely in patients with above median income (OR [95% CI]: 1.01 [1.00–1.02]) and with a more recent year of diagnosis (OR [95% CI]: 1.13 [1.11–1.141).
Olssonetal(2019) [8]	Sweden	3116	AS	PSA and rebiopsy rates	• PSA and rebiopsy rates were higher in patients in later years of diagnosis or with higher PSA at diagnosis. • Rebiopsy rates decreased with older age and more comorbidities.
Soeterik et al (2019) [9]	The Netherlands	958	AS	Compliance with AS protocols, oncological outcomes	• PSA and repeat biopsy rounds were in compliance with PRIAS guidelines in 43% men.

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Study	Country	*N*	Modality	Outcomes	Key findings
					• Among PRIAS-ineligible patients, PRIAS-discordant PSA monitoring was associated with a higher risk of developing PCa metastases during AS compared with patients with recommended follow-ups (HR [95% CI]: 5.25 [1.02–27.1]). • Among PRIAS-eligible patients, no such difference was observed.

AS = active surveillance; CCI = Charlson Comorbidity Index; CI = confidence interval; CM = conservative management; GS = Gleason score; HR = hazard ratio; LYG = life years gained; NA = not applicable; OR = odds ratio; PCa = prostate cancer; PRIAS = Prostate Cancer Research International Active Surveillance; PSA = prostate-specific antigen; QALY = quality-adjusted life years; WW = watchful waiting.