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Active surveillance for low-risk prostate cancer – in pursuit of a standardized protocol

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Introduction Active surveillance (AS) is a management option recommended by most guidelines for low risk clinically-localized prostate cancer (LR-CLPC). Data shows that AS is being increasingly adopted into clinical practice worldwide. Our aim was to review the up-to date guidelines and observational studies in regards to AS in LR-CLRPC to gain insight into principles of contemporary clinical practice.

Material and methods Several guidelines on the management of low-risk prostate cancer were reviewed for evidence-based recommendations regarding the protocol of AS. We reviewed the available literature for most recent studies on AS in LR-CLPC.

Results No uniform protocol of AS in LR-CLPC has been recommended up to date and available guidelines significantly differ in terms of protocol schedules and the role of particular tools in monitoring for disease progression. Nevertheless, recent studies on AS in LR-CLPC, in which various protocols were adopted, have demonstrated promising outcomes in regards to cancer-specific survival (99–100% at 5 years, 98.1–99.9% at 10 years, and 94.3–96% at 15 years), with high rates of men remaining within the protocols (23–39% at 10 years).

Conclusions This article is a call for focusing further research on development and recommending a precise and standardized, evidence-based protocol for AS in LR-CLPC.

Key Words: prostate cancer ‹› active surveillance ‹› protocol ‹› guidelines

Prostate cancer (PC) is the most common malignancy diagnosed among men, with over one million new cases reported worldwide annually [1]. Patients with clinically localized low-risk prostate cancer (CL-LRPC) are at low risk of cancer progression and account for approximately one third of newly diagnosed PC cases [2]. This patient population is eligible for active surveillance (AS), as recommended by most world guidelines [3–8]. which entails actively monitoring the disease with a plan to deliver curative intent-therapy upon PC progression. The goal of AS is to defer treatment for CL-LRPC in order to mitigate potential treatment-related side effects, in most cases indefinitely. However, despite widespread and increasing adoption of AS for LR-CLPC [9], there is substantial heterogeneity in AS protocols among clinical practice guidelines. Overall, this suggests a paucity in literature with regards to optimal evidence-based surveillance strategies.

There are several components of AS protocols, which includes: serum prostate specific antigen (PSA) moni-

Table 1. *Summary of guidelines on management of active surveillance in prostate cancer*

Authors	PSA	DRE	Prostate biopsy		mpMRI	Initiation of active treatment	Terminating AS
			Confirmatory	Repeat			
EAU [3]	every 6 months	every 12 months	timing not specified[e]	not routinely recommended[f]	before confirmatory biopsy	decision based on a change in the biopsy results or T-stage progression	N/A
NCCN [4]	every ≥6 months	every ≥12 months	within 6 months[c]	every ≥12 months	as an optional confirmatory tool at enrollment, repeated every ≥ 12 months	Gleason pattern 4 or 5 at biopsy or an increase in number of cores involved or in core length involvement	<10-year life expectancy (end serial biopsy)
CCO [5]	every 3–6 months	every 12 months	within 6-12 months	every 3–5 years	indicated when clinical findings discordant with the pathologic findings	Gleason score ≥7 (if Gleason pattern 4 >10% total cancer) or significant increases in the volume of cancer	turning 80-year-old (end serial biopsy)
ASCO [6]	every 3–6 months	every ≤12 months	within 6–12 months	every 2–5 years	indicated when clinical findings discordant with the pathologic findings	Gleason score ≥7 or significant increases in the volume of cancer	in men with limited life expectancy
AUA [7]	unspecified[d]	unspecified[d]	within 24 months	unspecified[d]	may be included into the protocol, should be performed on at minimum a 1.5 T magnet and reviewed by an experienced radiologist	clinical upstaging or upgrading at subsequent biopsy	N/A
NICE [8]	every 3-6 months[a]	every 12 months	not recommended[b]	not routinely recommended[f]	offer to mpMRI-naïve patients; perform at 12–18 months of active surveillance	evidence of disease progression – not specified	N/A

[a]every 3–4 months in the first year, every 6 months thereafter
[b]according to the guideline all men diagnosed with prostate cancer should have had an mpMRI-guided biopsy performed prior to the diagnosis; if not, an mpMRI should be offered and an mpMRI-guided biopsy performed if the results are discordant with the initial biopsy findings
[c]not obligatory, should be performed if initial biopsy was <10 cores or assessment discordant (eg. contralateral tumor on DRE)
[d]although serial testing with this tool is recommended, no specific time interval is provided in the guideline
[e]weak recommendation: no need for confirmatory biopsy if the primary biopsy was a targeted mpMRI-guided biopsy
[f]should be performed in case if progression suspected (based on PSA, DRE, or mpMRI)
PSA – prostate-specific antigen, DRE – digital rectal examination, mpMRI – multiparametric magnetic resonance imaging, AS – active surveillance, EAU – European Associoation of Urology, NCCN – National Comprehensive Cancer Network, CCO – Cancer Care Ontario, ASCO – American Society of Clinical Oncology, AUA – American Urology Association, NICE – National Institute for Health and Care Excellence, N/A – not available

toring, periodic digital rectal examination (DRE), transrectal or transperineal prostate biopsy (TRUS-Bx), and multiparametric magnetic resonance imaging (mpMRI) of the prostate. Table 1 summarizes several AS protocols for patients with CL-LRPC published by various professional organizations. As of now, there is no universally accepted consensus with regards to recommended frequency of surveillance and the timing of repeat biopsy. For example, confirmatory biopsy is recognized as a standard protocol by several North American guidelines, but not routinely recommended by the UK National Institute for Health and Care Excellence (NICE) [8] or by recently updated European Association of Urology guidelines [3]. Overall, as compared to European guidelines, in Canada and United States most patients are followed with more stringent protocols which entail PSA screening every 6 months, DRE every 12 months, and repeat TRUS-Bx every 2-5 years [5, 7].

As shown in Table 2, in the recent years many centers from around the world have published their experience with AS for CL-LRPC, reporting promising outcomes with low rates of adverse events [10–18]. However, due to heterogeneity among clinical practice guidelines, clinicians considering AS as a treatment strategy may be uncertain as to which surveillance strategies to adopt. In our opinion, one of the primary goals for improving the quality of care for patients on AS is to develop and recommend a precise, uniform, and standardized evidence-based protocol. It is likely that the optimal approach will be risk stratified. In order to achieve this goal, we believe that future research should focus on: (1) systematic analysis of all available evidence regarding the outcomes of employing each protocol, (2) even more extensive research into the natural history of low-risk prostate cancer and the role of each element of the protocol in detecting progression of the disease, (3) developing new tools (eg. molecular testing, novel imaging) or expanding the role of existing ones (especially mpMRI), and (4) further prospective evaluation of specific protocols within clinical stud-

Table 2. *Summary of outcomes of recent, large observational studies on active surveillance for prostate cancer*

Studies	Year	Number of patients	Median Age (years)	Median PSA at baseline (ng/ml)	Median follow up (months)	Overall survival (%)	Cancer-specific survival (%)	Curative intervention rate	On active surveillance (%)	Death from prostate cancer – related cause
Thompson et al. [10]	2015	650	63	6.2	55	NR	100 at median follow up	6.2 y: 38%	43.5 (≤12 cores) 56.2 (>12 cores)	0
Welty et al. [11]	2015	556	62	5.3	60	98 (at 5 years)	100% (at 5 years)	5 y: 40% 10 y: 50%	40[a]	0
Tosoian et al. [12]	2015	1,298	66	4.8	60	93 (at 10 years) 69 (at 10 years)	99.9 (at 10 years) 99.9 (at 10 years)	10 y: 50% 15 y: 57%	50 (at median follow up)	2
Klotz et al. [13]	2015	993	67.8	<2.5 in 14% 2.5–5 in 30% 5–10 in 43% >10 in 11% Unknown in 2%	>72	80 (at 10 years) 62 (at 15 years)	98.1 (at 10 years) 94.3 (at 15 years)	10 y: 36% 15 y: 45%	75.7 (at 5 years)	15
Godtman et al. [14]	2016	474	66	NR	96	80 (at 10 years) 51 (at 105 years)	99.5% (at 10 years) 96% (at 15 years)	10 y: 53% 15 y: 66%	57	6
Bokhorst et al. [15]	2016	5,302	65.9	5.7	622 were followed on active surveillance > 5 years 107 were followed for >7.5 years	97 (at 5 years) 89 (at 10 years)	99% (at 5 years) 99% (at 10 years)	5 y: 52% 10 y: 73%	48 (at 5 years) 27 (at 10 years)	1
Bruinsma et al. [16]	2018	15,101	65	5.4	2.2	62.8 (overall remaining on AS)	NR	NR	58 (at 5 years) 39 (at 10 years) 23 (at 10 years)	37
Stavrinides et al. [17]	2020	672	LR: 62 FIR: 64	LR: 6 ROR: 6.9	58	85 (at 3 years)[b] 72 (at 5 years)[b]	NR	NR	85 (at 3 years) 72 (at 5 years)	0
Tosoian et al. [18]	2020	1,818	VLR: 66 LR: 67	VLR: 4.6 LR: 5.9	60	93.2 (at 10 years)	99.9% (at 10 years) 99.1% (at 10 years)	NR	NR	4

PSA – prostate specific antigen, NR – not reported, VLR – very low risk, LR – low risk, FIR – favorable intermediate risk (Gleason 3+4)
[a]the treatment rate was 60% in men who both did and did not meet strict AS clinical criteria
[b]remained on an magnetic resonance-led active surveillance program

ies. An AS strategy that encompasses these areas of research must be conscious of resource constraints and cost effectiveness.

Creating a global consensus on how to monitor the patients with LR-CLPC on AS is one of the major goals of the Global Action Plan Prostate Cancer Active Surveillance (GAP3) initiative [16]. We believe that with further joint efforts of both researchers and health or professional organizations, men diagnosed with LR-CLPC will benefit from reliable, evidence-based, and standardized protocols which would ensure the best safety outcomes and have the least negative impact on the quality of life.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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References

1. Rawla P. Epidemiology of prostate cancer. World J Oncol. 2019; 10: 63-89.
2. Carter HB. Management of low (favourable) – risk prostate cancer. BJU Int. 2011; 108: 1684-1695.
3. European Association of Urology. Guidelines. Prostate Cancer. [Online] [Accessed: 07 05 2020.] http://uroweb.org/guideline/prostate-cancer/#6.
4. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Prostate cancer. [Online] [Accessed: 07 05 2020.] http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf.
5. Cancer Care Ontario. Active Surveillance for the Management of Localized Prostate Cancer. [Online] [Accessed: 01 03 2020.] https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2286.
6. American Society of Clinical Oncology. Active Surveillance for the Management of Localized Prostate Cancer Endorsement. [Online] [Accessed: 01 03 2020.] https://ascopubs.org/doi/pdf/10.1200/JCO.2015.65.7759.
7. American Urological Association. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. [Online] 01 03 2020. https://www.auanet.org/guidelines/prostate-cancer-clinically-localized-(2017).
8. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management. [Online] [Zacytowano: 01 03 2020.] https://www.nice.org.uk/guidance/ng131.
9. Mahal BA, Butler S, Franco I, et al. Use of active surveillance or watchful waiting for low-risk prostate cancer and management trends across risk groups in the United States, 2010-2015. JAMA. 2019; 321: 704-706.
10. Thompson JE, Hayen A, Landau A, et al. Medium-term oncological outcomes for extended vs saturation biopsy and transrectal vs transperineal biopsy in active surveillance for prostate cancer. BJU Int. 2015; 115: 884-891.
11. Welty CJ, Cowan JE, Nguyen H, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. J Urol. 2015; 193: 807-811.
12. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol. 2015; 33: 3379-3385.
13. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015; 33: 272-277.
14. Godtman RA, Holmberg E, Khatami A, et al. Long-term results of active surveillance in the Göteborg randomized, population-based prostate cancer screening trial. Eur Urol. 201; 70: 760-766.
15. Bokhorst LP, Valdagni R, Rannikko A, et al. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. Eur Urol. 2016; 70: 954-960.
16. Bruinsma SM, Zhang L, Roobol MJ, et al. The Movember Foundation's GAP3 cohort: a profile of the largest global prostate cancer active surveillance database to date. BJU Int. 2018; 121: 737-744.
17. Stavrinides V, Giganti F, Trock B, et al. Five-year outcomes of magnetic resonance imaging-based active surveillance for prostate cancer: a large cohort study. Eur Urol. 2020, S0302-2838 (20) 30210-4.
18. Tosoian JJ, Mamawala M, Epstein JI, et al. Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort. Eur Urol. 2020, S0302-2838 (19) 30961-3. ■