Active surveillance of men with low risk prostate cancer: evidence from the Prostate Cancer Outcomes Registry–Victoria

Melanie A Evans[1], Jeremy L Millar[1,2], Arul Earnest[1], Mark Frydenberg[3,4], Ian D Davis[3,4], Declan G Murphy[5,6], Paul Aidan Kearns[7,8], Sue M Evans[1]

The known Active surveillance is increasingly employed to manage men with low risk prostate cancer, both to avoid unnecessary treatment and to monitor them in a manner that allows detection of progression that would justify deferred radical treatment.

The new Active surveillance was not implemented according to published protocols in 73.5% of men diagnosed with low risk prostate cancer in this Victorian cohort study.

The implications The reasons for poor adherence to active surveillance require further investigation. It may reflect patient-, clinician-, and health service-related factors. Lack of surveillance increases the risk that men miss the opportunity to be treated with curative intent.

Abstract

Objective: To characterise the practice of active surveillance (AS) for men with low risk prostate cancer by examining the characteristics of those who commence AS, the rate of adherence to accepted AS follow-up protocols over 2 years, and factors associated with good adherence.

Design, setting: Retrospective cohort study; analysis of data collected from 38 sites participating in the Prostate Cancer Outcomes Registry–Victoria.

Participants: Men diagnosed with prostate cancer between August 2008 and December 2014 aged 75 years or less at diagnosis, managed by AS for at least 2 years, and with an ISUP grade group of 3 or less (Gleason score no worse than 4 + 3 = 7).

Main outcome measures: Adherence to an AS schedule consisting of at least three PSA measurements and at least one biopsy in the 2 years following diagnosis.

Results: Of 1635 men eligible for inclusion in the analysis, 433 (26.5%) adhered to the AS protocol. The significant predictor of adherence in the multivariate model was being diagnosed in a private hospital (*v* public hospital: adjusted odds ratio [aOR], 1.83; 95% CI, 1.42–2.37; $P < 0.001$). Significant predictors of non-adherence included being diagnosed by transurethral resection of the prostate (*v* transrectal ultrasound biopsy [TRUS]: OR, 0.54; 95% CI, 0.39–0.77; $P < 0.001$) or transperineal biopsy (*v* TRUS: OR, 0.32; 95% CI, 0.19–0.52; $P < 0.001$), and being 66 years of age or more at diagnosis (*v* < 55 years: OR, 0.65; 95% CI, 0.45–0.92; $P = 0.015$).

Conclusion: Almost three-quarters of men who had prostate cancer with low risk of disease progression did not have follow-up investigations consistent with standard AS protocols. The clinical consequences of this shortcoming are unknown.

Low risk prostate cancer is increasingly being managed with active surveillance (AS). The objectives of AS are to avoid unnecessary treatment, but to monitor men with low risk cancer according to a protocol that facilitates recognition of progression which justifies deferred radical treatment with curative intent.[1]

While AS has become an accepted management tool, evidence for the optimal frequency of monitoring and the most appropriate triggers for intervention is scarce.[2] Several AS protocols and guidelines with differing inclusion and follow-up criteria have been published (Box 1). The recommended frequency for measuring prostate-specific antigen (PSA) levels ranges from every 3[2,3,5] to every 6 months,[7,8] and the European Association of Urology guidelines acknowledge that the available evidence is inadequate for defining optimal timing.[6] It is generally accepted, however, that the first follow-up biopsy should be undertaken within 12 months of diagnosis;[2-5,7] the recommended timing of subsequent biopsies ranges from annually[5] to once every 5 years.[7]

The main shortcoming of all AS protocols and guidelines is that they have not been validated in randomised controlled trials.[2] While immediate and delayed treatment of prostate cancer have been compared in cohort studies,[9-11] the investigations did not directly compare different AS protocols or assess adherence.

The Prostate Cancer Outcomes Registry–Victoria (PCOR-Vic), formerly the Victorian Prostate Cancer Clinical Registry, was established in 2009 to improve knowledge of patterns of care and outcomes for men diagnosed with prostate cancer in Victoria.[12] Men are eligible for inclusion if they have a diagnosis of prostate cancer, have presented for diagnosis or treatment at a recruiting hospital, and are being treated by a clinician who has provided consent for patients to be approached and enrolled by the registry. After ethics approval has been granted, a hospital authorises the Victorian Cancer Registry (VCR) to release all prostate cancer notifications from that hospital to PCOR-Vic. Ethics approval for the PCOR-Vic was initially granted in March 2009, with permission to retrospectively collect data for men diagnosed from August 2008. The PCOR-Vic is able to assess the population coverage of its data by comparing them with summary notification data from the VCR for men who have received a diagnosis of malignant neoplasm of the prostate (International Classification of Diseases [ICD] code C61) or for whom a prostate biopsy pathology result was reported. This matching process has established that PCOR-Vic captures data from both public and private hospitals for 75% of patients with prostate cancer in Victoria.

In Victoria, 60% of men diagnosed with low risk prostate cancer are managed with AS.[13] This is higher than the proportions reported in

[1]Monash University, Melbourne, VIC. [2]Alfred Health, Melbourne, VIC. [3]Monash Health, Melbourne, VIC. [4]Eastern Health Clinical School, Monash University, Melbourne, VIC. [5]The Peter MacCallum Cancer Centre, Melbourne, VIC. [6]University of Melbourne, Melbourne, VIC. [7]Barwon Health, Geelong, VIC. [8]Geelong Urology, Geelong, VIC.
sue.evans@monash.edu
doi: 10.5694/mja17.00559 ▪ See Editorial, p. 430 ▪ Published online 28/05/2018
Podcast with Sue Evans and Melanie Evans available at https://www.mja.com.au/podcasts

1 Published peer-reviewed active surveillance protocols for men with low risk prostate cancer

Protocol or guideline	PSA assessment frequency	Biopsy frequency
Dall'Era et al (2008)[3]	Every 3–4 months	12 months, then every 1–2 years as indicated by PSA result examination
National Institute for Clinical Effectiveness (NICE) (2014)[4]	Every 3–4 months during first year, then every 3–6 months	12 months after diagnosis
Prostate Cancer Research International Active Surveillance (PRIAS) (2014)[5]	Every 3 months for first 2 years, then every 6 months	12 months, 4, 7 years after diagnosis
Cancer Council Australia Wiki (2015)[2]	Offer monitoring with PSA testing every 3 months	Reclassification biopsy 6–12 months after starting active surveillance; then every 2–3 years
European Association of Urology (EAU) (2015)[6]	Timing not defined*	Annually*
National Comprehensive Cancer Network (NCCN) (v3.2016)[7]	Every 6 months	Within 6 months, then annually
UpToDate (2016)[8]	Every 3–6 months	12 months after diagnosis, then every 2–5 years

PSA = prostate-specific antigen. * Follow-up should be based on digital rectal examination, PSA levels, and repeat biopsies; optimal follow-up interval is still unclear. ◆

the United States by the Michigan Urological Surgery Improvement Collaborative (MUSIC) (49%)[14] and the CaPSURE registries (40%),[15] but lower than reported in Sweden (74%).[16] However, the frequency of PSA testing and repeat biopsy in Victoria has not been reported. The aim of our study was therefore to characterise the practice of AS for men diagnosed with low risk prostate cancer in Victoria by examining the characteristics of those who commence AS, the rate of adherence to accepted AS follow-up protocols (ie, adequate active surveillance) over a 2-year period, and the factors associated with good adherence.

Methods

Study population

We analysed data from the Prostate Cancer Outcomes Registry—Victoria (PCOR-Vic).[12] Men were eligible for inclusion in our study if they were diagnosed with prostate cancer between August 2008 and December 2014, ensuring that all participants had had at least 2 years' follow-up; had AS recorded by their treating specialist as the primary management plan for their disease; were no more than 75 years old at diagnosis; had an initial International Society of Urological Pathology (ISUP) grade group of 3 or less (Gleason score no worse than 4 + 3 = 7); and did not transition to active treatment or die during the 2 years following diagnosis.

The PCOR-Vic recruitment strategy and data collection methods have been described previously.[12] Since August 2008, all men diagnosed with prostate cancer in recruiting hospitals and alive at the time of medical record review are sent a letter inviting participation in the registry and including instructions on how to decline participation; the opt-out rate is 2.6%.[12] Diagnosis and treatment details are collected from medical records of hospitals and private consulting rooms by trained data collectors 6–10 months after diagnosis, and men are telephoned 12 months after diagnosis to confirm treatment details and their most recent PSA value, and to administer a quality of life survey. Men are deemed to be on AS if it is explicitly recorded in their medical record as their management plan. Men who go on to watchful waiting or have no treatment are coded differently by PCOR-Vic.

To collect ongoing AS management details, data collectors are provided with annual lists of all men on AS, the hospitals where AS is being managed, and their managing specialists. The consulting rooms and hospital medical records of men who commenced AS are audited annually, and any additional test results identified are sent to the PCOR-Vic.

Statistical analysis

Because there is no consensus regarding the optimal frequency of PSA measurement and biopsy testing during AS, the PCOR-Vic Steering Committee (comprising urologists practising in public and private, regional and metropolitan settings; a consultant medical oncologist and a radiation oncologist; and members of the public and epidemiologists) were asked to discuss a minimum standard for AS follow-up based on the guidelines and evidence available when AS was initiated (Box 1). The consensus requirement for adequate AS follow-up was defined as at least one repeat biopsy and at least three PSA tests during the 2 years following diagnosis, matching the recommendations published in 2008,[3] as well as the contemporary recommendations of the National Comprehensive Cancer Network (NCCN) guidelines[6] and UpToDate;[7] no published guidelines for AS recommend less frequent assessment.

Data included in analyses were age, PSA level at diagnosis, tumour stage, Gleason score and NCCN risk category at diagnosis (the categories "very low" and "low risk disease" were combined, as men in these categories will be managed with the same guideline recommendations), method of diagnosis, percentage of positive cores, and location and type of diagnosing institution. In men diagnosed by transurethral resection of the prostate (TURP), PSA levels have often not been measured before diagnosis, and the tissue cores collected are specific to transrectal ultrasound-guided (TRUS) and transperineal (TP) biopsies. Almost all of the missing or unclassified values for the variables "PSA level at diagnosis" and "percentage positive cores" were for men who were diagnosed by TURP. As missing data were probably systematic (not random) and collinear with the method of diagnosis, we did not perform multiple imputation and used complete case analysis.

The proportion of patients managed with AS and who adhered to the AS follow-up protocol was calculated. A univariate logistic regression model ascertained the characteristics associated with adherence, which were then assessed in a forward stepwise multivariate logistic regression model, using a likelihood ratio test. Data were analysed in Stata 14.0 (StataCorp); $P < 0.05$ was deemed statistically significant.

Ethics approval

This project received ethics approval from the Monash University Human Research Ethics Committee (reference, CF09/0931-2009000436), Cancer Council Victoria (reference, 0908), and from each participating health service.

Results

From August 2008 to December 2014, 2134 men from 38 Victorian hospitals were managed with AS. Eleven men who died and 488 who transitioned to active treatment during the first 2 years after diagnosis were excluded from the analysis. The median age at diagnosis of the 1635 included men was 64 years (interquartile range [IQR], 58.6–68.0 years) and the median PSA level at diagnosis was 5.4 ng/mL (IQR, 3.8–7.4 ng/mL). Most men (74.7%) were diagnosed by TRUS biopsy, had clinical stage T1 disease (67.4%), a diagnostic ISUP grade group 1 (Gleason score ≤ 6) (84.0%), and received their diagnosis in metropolitan centres (73.3%) and private practices (65.3%). Twenty men recorded by their consultant as being on AS had Gleason scores of 3 ($4 + 3 = 7$) (Box 2).

Adherence to active surveillance

In all, 433 men (26.5%) adhered to the recommended AS protocol. Of the men who commenced AS, 877 (53.6%) had one or more repeat biopsies in the 2 years after diagnosis, 132 men (8.1%) had a repeat biopsy more than 2 years after diagnosis, and 626 (38.3%) had no repeat biopsies. Of the 20 men who had presented with ISUP grade group 3 (Gleason $4 + 3 = 7$) disease, nine had a repeat biopsy. The median time to first repeat biopsy for the 1109 men who had one was 366 days (IQR, 184–525 days).

A total of 601 men (36.8%) had at least three PSA assessments performed, and 80 men (4.9%) had none; the median number was three (IQR, 2–4). Of the 20 men who had presented with ISUP grade group 3 disease, two had had no subsequent PSA assessment. The median time to the first PSA measurement was 219 days (IQR, 147–292 days) and to the second 378 days (IQR, 300–572 days).

In the multivariate analysis, men diagnosed at a private hospital were more likely to adhere to follow-up than those diagnosed in a public hospital (adjusted odds ratio [aOR], 1.83; 95% confidence interval [CI], 1.42–2.37; $P < 0.001$). Factors statistically associated with non-adherence to AS included being diagnosed by TURP (aOR, 0.54; 95% CI, 0.39–0.77; $P < 0.001$) or TP biopsy (aOR, 0.32; 95% CI, 0.19–0.52; $P < 0.001$) rather than TRUS biopsy, and being 66 years of age or more at diagnosis (*v* men under 55: aOR, 0.65; 95% CI, 0.45–0.92; $P = 0.015$). There were no significant interactions between factors in the multivariate model (Box 3).

Discussion

Only 26.5% of Victorian men managed with AS after being diagnosed with low risk prostate cancer during August 2008 – December 2014 adhered to an AS regimen that included one subsequent prostate biopsy and three PSA measurements during the 2 years following diagnosis. Men diagnosed in private hospitals were more likely than those diagnosed in public hospitals to adhere to follow-up; men diagnosed by TURP or TP biopsy were less likely to adhere than men diagnosed by TRUS biopsy, and men aged 66 years or more at diagnosis were less likely to adhere to AS than those under 55.

2 Demographic and clinical characteristics of 1635 men diagnosed with low risk prostate cancer and managed with active surveillance, by adherence to adequate monitoring

	Adherent	Non-adherent	All men
Number of patients	433 (26.5%)	1202 (73.5%)	1635
Age at diagnosis (years)			
≤ 55	67 (28%)	169 (72%)	236
56–65	238 (31.6%)	516 (68.4%)	754
66–75	128 (19.8%)	517 (80.2%)	645
PSA value at diagnosis (ng/mL)			
≤ 4.0	115 (25.7%)	333 (74.3%)	448
4.01–10.0	275 (28.3%)	697 (71.7%)	972
≥ 10.01	38 (22%)	131 (78%)	169
Unknown	5 (11%)	41 (89%)	46
Method of diagnosis			
TRUS	364 (29.8%)	858 (70.2%)	1222
TURP	49 (18%)	220 (82%)	269
Transperineal	20 (14%)	124 (86%)	144
Percentage positive cores			
< 13%	137 (31.6%)	296 (68.4%)	433
13–33%	201 (27.3%)	536 (72.7%)	737
> 33%	45 (26%)	130 (74%)	175
Unknown	50 (17%)	240 (83%)	290
Clinical stage (TNM)			
T1	288 (26.1%)	814 (73.9%)	1102
T2	46 (29%)	112 (71%)	158
T3	0	2 (100%)	2
Unknown	99 (26%)	274 (74%)	373
Gleason score at diagnosis			
≤ 6	375 (27.3%)	999 (72.7%)	1374
3 + 4	57 (24%)	184 (76%)	241
4 + 3	1 (5%)	19 (95%)	20
NCCN risk categories			
Low/very low	279 (28.3%)	705 (71.7%)	984
Intermediate	96 (24%)	310 (76%)	406
High	3 (12%)	23 (88%)	26
Not classified	55 (25%)	164 (75%)	219
Diagnosing institution: location			
Metropolitan	338 (28.2%)	860 (71.8%)	1198
Regional	84 (22%)	279 (78%)	381
Unknown	11 (20%)	45 (80%)	56
Diagnosing institution: type			
Public	104 (20.2%)	410 (79.8%)	514
Private	319 (29.9%)	749 (70.1%)	1068
Unknown	10 (19%)	43 (81%)	53

NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; TRUS = transrectal ultrasound sound; TURP = transurethral resection of the prostate. ◆

Differing rates of adherence to AS protocols have been reported. The Prostate Cancer Research International: Active Surveillance (PRIAS) study found very high levels of adherence with respect to PSA testing (94% at one year) and repeat biopsies (81%).[1] This high

3 Multivariate analysis of adherence to follow-up by 1635 men diagnosed with low risk prostate cancer and managed with active surveillance

	Univariate model		Multivariate model	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at diagnosis (years)				
≤ 55	1		1	
56–65	1.16 (0.84–1.61)	0.36	1.22 (0.88–1.70)	0.23
66–75	0.62 (0.44–0.88)	0.007	0.65 (0.45–0.92)	0.015
PSA value at diagnosis (ng/mL)				
≤ 4.0	1			
4.01–10.0	1.14 (0.89–1.47)	0.30		
≥ 10.01	0.84 (0.55–1.28)	0.41		
Method of diagnosis				
TRUS	1		1	
TURP	0.53 (0.38–0.73)	< 0.001	0.54 (0.39–0.77)	< 0.001
Transperineal	0.38 (0.23–0.62)	< 0.001	0.32 (0.19–0.52)	< 0.001
Percentage positive cores				
< 13%	1			
13–33%	0.81 (0.63–1.05)	0.11		
> 33%	0.75 (0.50–1.11)	0.15		
Clinical stage (TNM)				
T1	1			
T2	1.16 (0.80–1.68)	0.43		
T3	Omitted*			
Unknown	1.02 (0.78–1.33)	0.88		
Gleason score at diagnosis				
≤ 6	1			
3 + 4	0.83 (0.60–1.14)	0.24		
4 + 3	0.14 (0.02–1.05)	0.06		
NCCN risk categories				
Low/very low	1			
Intermediate	0.78 (0.60–1.02)	0.07		
High	0.33 (0.10–1.11)	0.07		
Not classified	0.85 (0.61–1.19)	0.33		
Diagnosing institution: location				
Metropolitan	1			
Regional	0.72 (0.55–0.95)	0.018		
Unknown	0.62 (0.32–1.22)	0.16		
Diagnosing institution: type				
Public	1		1	
Private	1.68 (1.31–2.16)	< 0.001	1.83 (1.42–2.37)	< 0.001
Unknown	0.92 (0.45–1.89)	0.81	0.86 (0.42–1.78)	0.69

CI = confidence interval; NCCN = National Comprehensive Cancer Network; OR = odds ratio; PSA = prostate-specific antigen; TRUS = transrectal ultrasound sound; TURP = transurethral resection of the prostate. * Number of patients insufficient for analysis. ◆

rate of adherence might reflect a selection bias, as only the most enthusiastic proponents of AS enrolled in the project. Our study findings are consistent with those reported by a study in Michigan, where only 30% of men had at least three PSA assessments and one repeat biopsy during the 2 years following diagnosis.[17] Similarly, a European study found that fewer than 30% of men underwent a repeat biopsy within 12 months of diagnosis.[18] Another large American study reported low rates of compliance with AS protocols, with fewer than 13% of patients undergoing repeat biopsy beyond 2 years.[19]

The authors of a recent systematic review characterised barriers to AS adherence according to cancer characteristics, patient, family, and social support, provider, health care organisation and practice, and health policy factors.[20] The review recommended that internationally ratified AS guidelines be developed and argued that international databases, such as those established by the GAP3 Movember project, will assist develop consensus AS definitions.[20]

There may be several explanations for our finding that the method of diagnosis influenced adherence to AS. A decision to actively treat men should be based on their health status and level of fitness, not just their age and risk group;[21] expert guidelines recommend curative treatment for patients whose life expectancy is at least 10 years.[6] PCOR-Vic does not capture data on major comorbidities. Men diagnosed with symptomatic disease by TURP may have had more comorbidities than those diagnosed by TRUS, and the treating specialists consequently chose watchful waiting — a strategy in which treatment is avoided until symptoms or signs of progressive disease are evident[2] — as conservative management, even when AS was recorded in case documentation.

It is unclear why men diagnosed by TP biopsy were less likely to adhere to AS than those diagnosed by TRUS biopsy. TP biopsy is more accurate when selecting patients for AS,[22] and clinicians perhaps trust TP findings of low risk cancer more than those of TRUS biopsy, and therefore delay offering a further biopsy. There is also growing interest in magnetic resonance imaging (MRI) for both initial diagnosis and for assessing change over time.[23] International clinical guidelines recommend that multi-parametric MRI be used in conjunction with biopsy for men on AS at 12 months,[9] but clinicians may choose to monitor men on AS with MRI rather than with a repeat biopsy. PCOR-Vic, however, does not currently record MRI findings for men on AS, so that further investigation of this question is required.

There are several potential reasons for men diagnosed in public hospitals being less likely to adhere to AS follow-up than those diagnosed in private hospitals. Men managed with AS in the public sector may have had their PSA level monitored by their general practitioner but not provided the result to the hospital managing their AS. However, the patient should return to the diagnosing hospital for the surveillance biopsy, as the GP

cannot undertake it, and a PSA history would usually be collected before the biopsy. Hospital information systems and administrative staff may have fewer resources for sending reminders to patients and to pursue those who miss appointments. This problem is compounded by the fact that patients are likely to see different medical staff at different appointments, resulting in diffused responsibility for their management. Further, patient-related factors may influence their ability and motivation to attend for follow-up. The patient may be reluctant to have a repeat biopsy; a qualitative study of 50 men found that one-quarter found the biopsy painful, and the others found it uncomfortable or embarrassing.[24] Another reason for patients not re-presenting for biopsy might be the risk of infection, although infection rates are less than 2.0%.[25]

A major strength of our study is that the PCOR-Vic is a comprehensive clinical quality registry that collects consistent clinical and patient-reported outcomes for about 75% of patients with prostate cancer in Victoria. PCOR-Vic receives 80% of notifications registered by the VCR for public hospitals and 63% of notifications received from private hospitals ($P < 0.001$).

However, we acknowledge a number of limitations. The narrow dataset collected by PCOR-Vic does not capture all potential predictors of non-adherence to an AS protocol, such as comorbidities, surgical bias, attempts to contact patients, and the use of MRI as an alternative to biopsy. Another limitation is that data collectors are restricted to documenting what is recorded in the medical record; it may be that specialists occasionally record AS as management when they are actually performing watchful waiting. Men were excluded from the analysis if they had transitioned to active treatment within 2 years of diagnosis; they may have adhered to an AS protocol that prompted transition to treatment, leading to our underestimating the level of adherence. However, we were primarily interested in conservatively gauging longer term adherence rates, both to enable a direct comparison with community practice in the US[17] and to identify patients likely to be lost to follow-up.

Despite these limitations, our findings have important implications for patients, health services, and, given the numbers of men affected, health policy. If they are not being followed appropriately according to AS protocols, men may miss the opportunity to be treated with curative intent. Further exploration of patient-, clinician- and health system-related factors associated with adherence to AS is required. To improve adherence, a multifaceted approach may be required, including an education campaign that highlights the need for men to undergo regular PSA assessment and prostate biopsy. PCOR-Vic might serve as a surveillance system that provides reminder prompts to men diagnosed with prostate cancer and commenced on AS, and to monitor the longer term outcomes of compliance with AS and its impact on disease progression and mortality.

Acknowledgements: Funding for this project has been provided by the Movember Foundation. Ian Davis is supported by a National Health and Medical Research Council Practitioner Fellowship (APP1102604). Sue Evans is supported by a Monash Partners Academic Health Science Centre Fellowship.

Competing interests: No relevant disclosures.

Received 8 June 2017, accepted 31 Oct 2017. ■

1 Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol* 2013; 63: 597-603.

2 Prostate Cancer Foundation of Australia; Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel. PSA testing and early management of test-detected prostate cancer: active surveillance (Clinical practice guidelines). Jan 2016. http://wiki.cancer.org.au/australiawiki/index.php?oldid=122836 (viewed March 2017).

3 Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. *Cancer* 2008; 112: 1650-1659.

4 National Institute for Health and Clinical Excellence. Prostate cancer: diagnosis and management (CG175). Jan 2014. http://www.nice.org.uk/guidance/cg175/resources/prostate-cancer-diagnosis-andmanagement-35109753913285 (viewed Feb 2017).

5 Prostate Cancer Research International: Active Surveillance (PRIAS). Guideline and study for the expectant management of localized prostate cancer with curative intent: study protocol. Nov 2014. https://www.prias-project.org/uploads/pdfs/2014-11-27%20Protocol%20versie%205.0%20(FINAL).pdf (viewed March 2017).

6 Mottet N, Bellmunt J, Briers E, et al. EAU/ESTRO/SIOG guidelines on prostate cancer. European Association of Urology, 2016. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2016.pdf (viewed Feb 2017).

7 National Comprehensive Cancer Network. Prostate cancer (NCCN clinical practice guidelines in oncology). Version 3.2016. May 2016. https://www.tri-kobe.org/nccn/guideline/urological/english/prostate.pdf (viewed Feb 2017).

8 Klotz L. Active surveillance for men with low-risk, clinically localized prostate cancer. UpToDate; Aug 2016. http://www.uptodate.com/contents/active-surveillance-for-men-with-low-risk-clinically-localized-prostate-cancer#H12016 (viewed Feb 2017).

9 Cheng JY. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) in perspective. *J Clin Med Res* 2013; 5: 266-268.

10 Hamdy FC, Donovan JL, Neal DE. 10-Year outcomes in localized prostate cancer. *N Engl J Med* 2017; 376: 180.

11 Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; 367: 203-213.

12 Evans SM, Millar JL, Wood JM, et al. The Prostate Cancer Registry: monitoring patterns and quality of care for men diagnosed with prostate cancer. *BJU Int* 2013; 111: E158-E166.

13 Sampurno F, Earnest A, Kumari PB, et al. Quality of care achievements of the Prostate Cancer Outcomes Registry—Victoria. *Med J Aust* 2016; 204: 319. https://www.mja.com.au/journal/2016/204/8/quality-care-achievements-prostate-cancer-outcomes-registry-victoria

14 Womble PR, Montie JE, Ye ZJ, et al. Contemporary use of initial active surveillance among men in Michigan with low-risk prostate cancer. *Eur Urol* 2015; 67: 44-50.

15 Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990—2013. *JAMA* 2015; 314: 80-82.

16 Loeb S, Folkvaljon Y, Curnyn C, et al. Uptake of active surveillance for very-low-risk prostate cancer in Sweden. *JAMA Oncol* 2016; Oct 20: 1393-1398.

17 Luckenbaugh AN, Auffenberg GB, Hawken SR, et al. Variation in guideline concordant active surveillance followup in diverse urology practices. *J Urol* 2017; 197: 621-626.

18 Bokhorst LP, Alberts AR, Rannikko A, et al. Compliance rates with the Prostate Cancer Research International Active Surveillance (PRIAS) protocol and disease reclassification in noncompliers. *Eur Urol* 2015; 68: 814-821.

19 Loeb S, Walter D, Curnyn C, et al. How active is active surveillance? Intensity of followup during active surveillance for prostate cancer in the United States. *J Urol* 2016; 196: 721-726.

20 Kinsella N, Stattin P, Cahill D, et al. Factors influencing men's choice of and adherence to active surveillance for low-risk prostate cancer: a mixed-method systematic review. *Eur Urol* 2018; doi:10.1016/j.eururo.2018.02.026 [Epub ahead of print].

21 Droz JP, Aapro M, Balducci L, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. *Lancet Oncol* 2014; 15: e404-e414.

22 Vyas L, Acher P, Kinsella J, et al. Indications, results and safety profile of transperineal sector biopsies (TPSB) of the prostate: a single centre experience of 634 cases. *BJU Int* 2014; 114: 32-37.

23 Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol* 2015; 67: 627-636.

24 Chapple AB, Ziebland S, Brewster S, McPherson A. Patients' perceptions of transrectal prostate biopsy: a qualitative study. *Eur J Cancer Care (Engl)* 2007; 16: 215-221.

25 Roth H, Millar JL, Cheng AC, et al. The state of TRUS biopsy sepsis: readmissions to Victorian hospitals with TRUS biopsy-related infection over 5 year. *BJU Int* 2015; 116: 49-53. ■