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Prostate Cancer: New Insights into Minimal and Localised Disease: Active Surveillance

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1. Introduction

This paper summarises current views on active surveillance as presented during the session titled, "Prostate Cancer: New Insights to Minimal and Localised Disease," at the 2nd World Congress on Controversies in Urology (CURy) in Lisbon, Portugal.

Prostate-specific antigen (PSA) screening programmes have resulted in an increased and earlier detection of prostate cancer (PCa). An analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database in the United States showed that in 2000–2001, the proportion of low-risk tumours had almost doubled compared with 1990–1994, when screening was just introduced and exceptional (46.4% vs 27.5%) [1]. On average, clinical T stage, Gleason score, and percent of positive biopsies at diagnosis were lower in 2004–2007 than in 1990–1994 [1].

A significant proportion of patients diagnosed by PSA screening are much more likely to die *with* than to die *from* PCa, because they have indolent disease. Based on results of the Rotterdam section of the European Randomised Study of Screening for Prostate Cancer (ERSPC), the overdetection rate of PCa was estimated to be 48% for a screening programme with a 4-yr screening interval from age 55–67 [2]. The mean lead time (ie, time from detection at screening until the tumour would have been detected in the absence of screening) in this simulation was 11.2 yr. In a subgroup of patients with clinical stage T1c or T2a who were treated with radical prostatectomy (RP), 49% had indolent cancer, defined as pathologically organ-confined cancer ≤ 0.5 cm^3 without poorly differentiated elements [3]. Recent results of the ERSPC trial, which included 182,000 men, demonstrated that 48 men with screen-detected PCa would need to be treated in order to prevent one death from PCa [4].

Knowledge of the natural history of low-risk PCa has also improved. Parker et al estimated that the 15-yar PCa-specific mortality for conservative management of screen-detected PCa was 0–2% if the Gleason score were <7 [5]. Therefore, we can conclude that one of the results of screening for PCa is overdiagnosis, which leads potentially to significant overtreatment.

2. Who is a candidate for active surveillance?

Men with a high probability of indolent PCa can be considered for active surveillance. It is important to note that active surveillance does not equal "no treatment". A patient under active surveillance is under medical observation, and delayed treatment is started either upon request of the patient or when the disease progresses. Active surveillance is offered to men who are fit for radical therapy and includes serial PSA measurements and repeat biopsies.

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Table 1 – Epstein criteria for very low-risk prostate cancer according to Barocas et al [8]

Factor	Value
PSA	<10 ng/ml
Clinical stage	T1 or T2a
PSA density	<0.15
Positive biopsy cores	<1/3
Gleason score	≤6

PSA = prostate specific antigen.

To identify prostate tumours that are likely indolent, nomograms for risk assessment of PCa have been described [3,6], and criteria for low-risk disease have been established [7]. A recent observational study of the CaPSURE database revealed that 16% of men with localised PCa met the Epstein criteria for very low-risk disease (Table 1) and could be managed by active surveillance [8]. However, only 9% of the patients with very low-risk PCa chose this option. For a considerable number of men, initially on active surveillance, (radical) treatment is not avoided, only delayed—more often out of patient anxiety than because of disease progression.

Caution is needed when offering active surveillance as a treatment option, according to recent publications. Suardi et al reported the rate of misclassification of PCa risk associated with the use of five different selection criteria for active surveillance [9]. Out of 4885 patients who underwent RP, 14–27% of those who fulfilled criteria for active surveillance were misclassified (ie, non–organ-confined disease or Gleason score 8–10). In another study, patients with low-risk disease underwent repeat biopsy within 3 mo of the first positive biopsy; for 27% of these patients, the biopsy resulted in upgrading or upstaging of the tumour [10]. Therefore, a reconfirmation biopsy should be offered to all men opting for active surveillance, especially if the initial sampling had ≤10 cores.

Eligibility criteria for active surveillance were also defined in the Prostate Cancer Research International: Active Surveillance (PRIAS) study [11]. The subgroup of men in the screening arm of the ERSPC trial who had been diagnosed with PCa met the PRIAS criteria and initially chose active surveillance and had a calculated 10-yr PCa-specific survival of 100% (in contrast with an overall survival [OS] of 77%) [12]. Therefore, the authors concluded that active surveillance seems justified in selected men with screen-detected PCa. The prospective longitudinal surveillance programme at Johns Hopkins also shows that expectant management can be a valuable treatment option for carefully selected T1c PCa [13].

3. Do we have clinical tools that make active surveillance safe?

3.1. Repeat biopsies

Repeat prostate biopsies are recommended after 1 yr of active surveillance, then every 12–24 mo or in case of changes in PSA or digital rectal examination (DRE) [14]. It has been suggested that a saturation repeat biopsy (≥20 cores) would be of interest for patients on active surveillance because of the decreased chance of missing a small tumour. A study in which 27 high-risk patients with ≥3 previous negative biopsies underwent saturation biopsy (mean number of cores: 62) showed that only three patients had PCa; moreover, all three had minimal disease [15]. Therefore, it is probably not worthwhile to perform repeat saturation biopsies.

3.2. Magnetic resonance imaging

Another procedure that could improve safety is to perform a magnetic resonance imaging (MRI) scan to exclude a missed tumour before starting the active surveillance protocol. Although single-centre reports from the University of Toronto and the Memorial Sloan-Kettering Cancer Center, New York, show that MRI has significant added value, it remains questionable whether these results could be generalised and whether this procedure is cost-effective.

3.3. Prostate-specific antigen kinetics

Less controversial is monitoring PSA kinetics, because a rapid increase is associated with adverse outcomes. In a Canadian study in patients with favourable-risk PCa, a PSA doubling time (PSA-DT) <67 mo was associated with an increased risk of disease progression on biopsy [16].

The largest prospective study on active surveillance is the Toronto experience [17]. The study included 299 patients on active surveillance, and after a median follow-up of 64 mo, 66% of them were still on active surveillance. At 8 yr, the PCa-specific survival was 99.3%. Only two patients died of PCa; both had a PSA-DT <2 yr.

To improve evidence on active surveillance as a treatment option, a phase 3 randomised, controlled trial is currently recruiting patients. The Standard Treatment Against Restricted Treatment (START) trial has been initiated to compare the disease-specific survival (DSS) of patients with favourable-risk PCa treated with radical therapy at the time of initial diagnosis versus active surveillance and selective intervention based on pre-specified criteria.

3.4. Future tools

In the future, gene markers could help to identify patients who have a poor outcome. Genes involved in tumour progression will be identified, and predictive biomarkers will be developed [18]. Ultimately, this might enable better patient management based on improved risk stratification.

The benefit of 5α-reductase inhibitors (5-ARI) for patients on active surveillance is currently not clear. An analysis of the Prostate Cancer Prevention Trial (PCPT) suggests that 5-ARI (finasteride) increased the sensitivity of PSA testing for detecting PCa [19]. The Reduction with Dutasteride of clinical progression Events in Expectant Management of prostate cancer (REDEEM) trial will evaluate whether 5-ARIs could delay PCa progression in 302 patients on active surveillance [20]. Results are expected in 2010.

Table 2 – Follow-up schedule for patients under active surveillance

Diagnosis	3 mo	6 mo	9 mo	12 mo	q 6 mo	q 24 mo
PSA	X	X	X	X	X	
DRE	X	X	X	X	X	
MRI						?
(Re)biopsy						X
QoL	X	X	X	X	X	X

mo = months; q = quaque (every); PSA = prostate-specific antigen; DRE = digital rectal examination; MRI = magnetic resonance imaging; QoL = quality of life.

4. What should be the follow-up of patients on active surveillance?

A literature review on active surveillance was performed in 2008 [14]. The authors emphasised that thorough patient follow-up is critical for the success of active surveillance. The responsibility for this lies with both patient and physician. A schedule for follow-up is presented in Table 2.

It is remarkable that currently, many men stop active surveillance and are treated despite the absence of evidence of PCa progression. This is partly the result of anxiety and illness uncertainty.

5. Conclusions

Active surveillance includes close monitoring of PSA kinetics, repeat biopsies, and treatment initiation when necessary. In men with indolent PCa detected by PSA screening, active surveillance could be a safe treatment option. However, further studies are necessary to evaluate selection criteria and define predictive factors that can be included in selection criteria and follow-up. A better definition of these aspects could also contribute to the psychological support of men choosing active surveillance.

Conflicts of interest

Laurent Boccon-Gibbod is member of the advisory board of Ferring and organiser of the post-graduate teaching sessions supported by Takeda France. Ziya Kirkali has no conflicts of interest related to this manuscript. Neil Fleshner is a scientific advisor involved in a trial of GlaxoSmithKline.

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References

[1] Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. J Urol 2007;178(pt2):S14–9.

[2] Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003;95:868–78.

[3] Steyerberg EW, Roobol MJ, Kattan MW, van der Kwast TH, de Koning HJ, Schroder FH. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. J Urol 2007;177:107–12.

[4] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.

[5] Parker C, Muston D, Melia J, Moss S, Dearnaley D. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. Br J Cancer 2006;94:1361–8.

[6] Roemeling S, Roobol MJ, Kattan MW, van der Kwast TH, Steyerberg EW, Schröder FH. Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations. Cancer 2007;110:2218–21.

[7] 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.

[8] Barocas DA, Cowan JE, Smith Jr JA, Carroll PR. CaPSURE investigators. What percentage of patients with newly diagnosed carcinoma of the prostate are candidates for surveillance? An analysis of the CaPSURE database. J Urol 2008;180:1330–4.

[9] Suardi N, Capitanio U, Chun FK, et al. Currently used criteria for active surveillance in men with low-risk prostate cancer: an analysis of pathologic features. Cancer 2008;113:2068–72.

[10] 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.

[11] van den Bergh RCN, 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.

[12] van den Bergh RCN, 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.

[13] 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.

[14] Dall'era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer 2008;112:1650–9.

[15] Stav K, Leibovici D, Sandbank J, Lindner A, Zisman A. Saturation prostate biopsy in high risk patients after multiple previous negative biopsies. Urology 2008;71:399–403.

[16] Al Otaibi M, Ross P, Fahmy N, et al. Role of repeated biopsy of the prostate in predicting disease progression in patients with prostate cancer on active surveillance. Cancer 2008;113:286–92.

[17] Klotz L. Active surveillance with selective delayed intervention for favorable risk prostate cancer. Urol Oncol 2006;24:46–50.

[18] Paris PL, Andaya A, Fridlyand J, et al. Whole genome scanning identifies genotypes associated with recurrence and metastasis in prostate tumors. Hum Mol Genet 2004;13:1303–13.

[19] Thompson IM, Chi C, Ankerst DP, et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. J Natl Cancer Inst 2006;98:1128–33.

[20] Fleshner N, Gomella LG, Cookson MS, et al. Delay in the progression of low-risk prostate cancer: rationale and design of the reduction by dutasteride of clinical progression events in expectant management (REDEEM) trial. Contemp Clin Trials 2007;6:763–9.