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Is There a Role for Active Surveillance in Low-Risk Prostate Cancer?

Key Words

Active surveillance · Prostate cancer

Abstract

Background: Active surveillance (AS) represents an expectant treatment strategy for clinically localized prostate cancer (PCa) with low-risk features. **Objective:** The actual management as well as the pros and cons of AS were evaluated. **Methods:** A systematic review of the recent literature was performed using the Medline databases. **Conclusions:** Since a substantial number of men die with rather than from PCa, there is a considerable role for AS in carefully selected men. AS may also represent a strategy to reduce the burden of overtreatment rooted in intensified PSA testing. Facing the imprecision of risk stratification based on transrectal ultrasound-guided biopsy, accurate clinical staging represents a major medical challenge. Counseling and care require empathy as well as a profound understanding of the biology and the natural history of PCa.

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Introduction

Prostate cancer (PCa) represents the most common malignancy and the second leading cause of cancer-specific deaths in men [1]. Among all malignancies PCa alone accounts for 28% [1]. Typically the incidence and mortality rates of PCa increase with age [1, 2]. At autopsy

approximately one third of men >50 years of age will harbor PCa, reaching nearly 60% in men aged >80 years [2, 3]. In contrast, men's lifetime probability of being diagnosed with PCa and to die from it is estimated to be 15.3 and 2.7%, respectively [4, 5]. The discrepancy between the prevalence of latent cancers, clinically diagnosed tumors and mortality due to PCa indicates that a substantial proportion of tumors are not destined to pose a serious threat to life and consequently do not necessarily require therapy. In this case, expectant management might be a reasonable treatment option.

In detail, active surveillance (AS) represents an observational strategy for the management of clinically localized PCa which could also undergo local therapies such as surgery or radiotherapy with the intention to switch to intervention in the event of disease progression. The latter differs from watchful waiting (WW), which is another observational strategy intended for patients with a limited life expectancy not eligible for curative intervention.

The concept of AS clashes clearly with one major oncological paradigm that early diagnosis offers better outcome due to early treatment. So, the 11-year follow-up mortality rate of the European Randomized Study of Screening for Prostate Cancer (ERSPC) revealed a risk reduction for PCa-specific death in the screening cohort of 21% [6]. Thus, 1,055 men have to be screened to diagnose 37 PCa cases and consequently prevent one PCa-related death [6]. However, the reduction in cancer-specific mortality by PSA screening has to be weighed against overdiagnosis, which might be as high as 66% [7]. More-

over, overdiagnosis by population-based screening is closely related to lead time, meaning a chronologically advanced diagnosis that would not have been established in the absence of screening, which may range between 5.4 and 7.9 years in different statistical models [7]. In addition, overdiagnosis may also be affected by length time bias [8]. Length time bias of PCa screening arises because of the preferential diagnosis of more slowly-growing cancers while aggressive, fast-proliferating tumors are more likely to be missed by screening and are more probable to be detected from symptoms. Using a stochastic model correcting lead time, length time and overdetection biases, no precise survival benefit between screening-detected PCa and the control group could be calculated, whereas uncorrected estimates of survival may overstate the benefit of screening [8]. In screening trials, overdiagnosis appears to be strongly associated with age and PSA level. Thus, potential benefits of screening might be increased by the restriction of screening to men <70 years and to those >60 years with a PSA level >1 ng/ml [9]. Due to the complex scenarios mentioned before, the results of screening must be interpreted with caution, even more so as in the 11-year follow-up update of the ERSPC trial screening had no effect on overall mortality [6].

Beyond that, overdetection and subsequent overtreatment using a highly sophisticated armamentarium will inevitably raise healthcare expenditure. By reducing the number of costly therapies, AS may probably help to reduce the economic burden as well [10].

Clinical Challenge

From a clinical point of view there is a lot of controversy associated with AS. First of all, many a time PCa is a slowly-growing tumor. Nevertheless, PCa exhibits considerable biological variability and tumor heterogeneity. Subsequently, the challenge is to distinguish accurately potentially dangerous PCa from rather indolent lesions. Second, in view of AS age is another key issue to be considered, especially as life expectancy of both genders in the Western world is increasing persistently [11]. Third, local therapies are continuously evolving and the complication rate of treatments is still decreasing [12]. Finally, the knowledge to live with a potentially life-threatening disease may provoke anxiety and psychological distress [13].

In detail, the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) trial comparing men randomized to either WW or radical prostatectomy (RP) revealed

a relative risk reduction of 0.56 in favor of men undergoing surgery after 18 years of follow-up [14]. Thereby, the number needed to treat to prevent one death was 8 and the largest benefit of RP was in men younger than 65 years and in those with intermediate-risk PCa [14]. However, the study must also be interpreted cautiously as the cohort does not reflect contemporary patients with generally more favorable cancer characteristics due to early PSA testing, whereas PCa in the SPCG-4 trial was primarily diagnosed clinically due to symptoms or by digital rectal examination. So, only 5% of SPCG-4 PCas were detected by PSA testing and the mean PSA level of 13 ng/ml was substantially higher than in contemporary series [15]. Nevertheless, based on the SPCG-4 trial data, Vickers et al. [16] used a modeling approach to calculate individualized estimates of benefit. In their analysis, patients with Gleason 8 or 7 stage T2 tumors benefited from surgical intervention, whereas in patients with Gleason 6 stage T1 disease or in patients much above 70 years of age the benefit of surgery was limited [16]. In contrast to the SPCG-4 trial, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) did not find a significant reduction of cancer-specific or overall mortality after 12 years of follow-up [17]. Looking at the characteristics of the participants, 75% of tumors were detected due to PSA testing and the median PSA value was 9 ng/ml [15]. Thus, the clinical features of SPCG-4 and PIVOT differ markedly and hinder any comparison. Ongoing trials like Prostate Testing for Cancer and Treatment (ProtecT) and Standard Treatment Against Restricted Treatment (START), which aim to compare early interventions with AS in contemporary patient cohorts, may provide essential information in the future [15].

Inclusion Criteria for AS

In 1994, Epstein et al. [18] delineated the concept of 'insignificant cancer'. This type of tumor should be unlikely to progress clinically within an individual's lifespan and might be followed without immediate treatment. Those cancers were characterized by tumor volumes <0.5 cm³ and low Gleason score (≤6) in RP specimens. Subsequently, a model was established to predict insignificant cancers with preoperative features. The best models predicting insignificant tumors were based on PSA density (<0.15 ng/ml), Gleason score (≤6), number of cores containing PCa (≤2) and tumor extent on needle biopsy core specimen (≤50%) [18, 19]. Using these criteria for a T1c cohort, Bastian et al. [19] correctly predicted

the presence of organ-confined disease in 91.6%, but on the other hand, 8.6% of men showed non-organ-confined cancer. In 1998 D'Amico [20] figured out a three-scale risk stratification model with low-, intermediate- and high-risk cancers based on the three most common pre-clinical tumor features (PSA, clinical stage and biopsy Gleason score).

Thus, the majority of ongoing concepts and the current German S3 guidelines have adopted both prediction models mentioned before and propose the following criteria: PSA ≤ 10 ng/ml, clinical stage $\leq T2a$, Gleason score ≤ 6 , cancer in ≤ 2 cores and a maximum tumor extent of $\leq 50\%$ per core [21, 22]. However, some institutions apply additional (PSA density) or less stringent criteria (PSA 15 or Gleason score 3+4) [23, 24].

Unfortunately, adverse pathological features defined as upgrading to Gleason ≥ 7 or upstaging to $\geq pT3$ at RP will be found in men who were potential candidates for AS in 33–45% of patients [25]. Analyzing five prospective studies of AS with varying inclusion criteria, Conti et al. [26] found Gleason score upgrade in 28%, extracapsular extension in 21% and seminal vesicle involvement in 11%. Similar findings with unfavorable tumor characteristics in up to 33.5% were reported in a retrospective study using 16 different definitions for AS or low-risk PCa [27].

The accuracy of Gleason score determination requires plenty of experience. Thus, it has been shown that the correlation of Gleason scores between biopsy and RP specimens will be enhanced by central review pathology [28]. Moreover, the agreement of Gleason score 6 between biopsy and RP specimens might be increased by the consideration of nuclear grading and nucleolar features [29].

The quality of initial prostate biopsy may also vary. To increase the accuracy of cancer classification, some authors recommend a repeat confirmatory biopsy at the beginning of AS, as up to one third of patients are undergraded [30], but even this repeat biopsy may vary. So, transperineal template-guided prostate mapping reclassified PCa primarily eligible for AS in 41–85% depending on definition as clinically important cancers compared to 8–22% in case of conventional transrectal confirmatory biopsy (12-core scheme) [31].

Finally, bilaterally positive biopsies might be another biopsy feature of interest. In a retrospective analysis of 165 men, Umbehr et al. [32] found a significant higher rate of non-organ-confined tumors in men with bilaterally positive biopsy cores than in those with unilaterally positive cores. These investigators concluded that bilaterally positive biopsies might represent a potential exclusion criterion for AS.

Clinical Outcome and Implications

Analyzing 391 patients after a biopsy with a minimum of 10 cores and undergoing RP due to PCa characterized by biopsy Gleason scores ≤ 6 , 75% of patients met the inclusion criteria of at least one of seven different AS protocols, and 23% were suitable for AS by all published criteria [33]. In the UK, where PSA testing is less prevalent, 20% of patients with localized PCa met the criteria for low-risk disease according to the classification of D'Amico et al. [20, 34]. Hence, the rigor of inclusion criteria and the PSA testing rate distinctly affect the proportion of men eligible for AS.

The aim of AS is to preclude men with low-risk PCa from intervention and intervention-related side effects, or at least to postpone intervention until disease progression eventually occurs. Therefore, it is essential to define accurate triggers for active intervention as long as treatment is still curative.

Based on the evidence that the risk of dying from PCa is strongly related to Gleason score, the histology of repeat biopsies represents a mainstay for decision-making in most series and guidelines [35]. Especially, progression of Gleason score and the number and/or extent of positive biopsy cores turn the balance to active treatment [21–23, 36–38]. Unfortunately, no standardized intervals between follow-up biopsies exist and the intervals may vary considerably between different institutions. For example, investigators of the Prostate Cancer Research International Active Surveillance (PRIAS) cohort have scheduled the repeat biopsies after 1, 4 and 7 years, whereas patients at Johns Hopkins are followed with annual biopsies [21, 23]. However, it is not clear at all whether changes in histology over time represent tumor growth and loss of differentiation or initial inadequate tissue sampling.

Another frequently used threshold that may indicate progression is PSA doubling time, usually with a lower limit of 3 years [21, 38]. For that reason, PSA measurements are performed 3- or 6-monthly to determine PSA kinetics. However, this criterion has been questioned because PSA doubling time was not significantly associated with grade of progression on repeated biopsy ($p = 0.83$) [39]. Subsequently, the Johns Hopkins group has abandoned PSA doubling time as a trigger for active treatment [23].

Using current inclusion and trigger criteria, roughly one third of men will undergo active treatment after 3 years. In detail, the PRIAS group reported on an active treatment-free survival at 2 years of 77.3% [21]. The Johns Hopkins group found an active treatment-free survival at 2, 5 and 10 years of 81, 59 and 41%, respectively. The me-

dian intervention-free survival was 6.5 years [23]. Other pioneers of AS, Klotz et al. [38], observed an active treatment-free survival at 2, 5 and 10 years of 84, 72 and 62%, respectively. Overall survival was 78.6% and the 10-year PCa actuarial survival was 97.2%. Soloway et al. [36] reported on an active treatment-free survival of 86% for a mean follow-up of 44 months, whereas 14% were treated after a mean follow-up of 33 months. Interestingly, investigators from the University of San Francisco compared a typical low-risk AS cohort with men affected by intermediate-risk PCa [40]. After 4 years of AS, 30% of the low-risk group and 35% of the intermediate-risk group ($p = 0.22$) underwent active treatment [40]. With special emphasis on low-volume intermediate-risk PCa with Gleason score 3+4, Park et al. [41] analyzed 66 patients who underwent RP in a retrospective study. Underestimation characterized by upstaging and upgrading on RP specimens could be avoided in men with a PSA <4.73 ng/ml and a maximum cancer involvement on positive cores of <15%.

Overall, patients who switched to active treatment showed a reasonable outcome. That way, after a median period of 1.3 years under AS, men treated by RP showed organ-confined disease in 80.8% and extracapsular extension in 19.2%. Gleason scores ≤ 6 , 3+4, 4+3 and 8 were found in 47.3, 38.3, 12.6 and 1.8% of specimens, respectively [42]. Comparing the pathological findings of men undergoing RP either immediately after diagnosis or after a delay of 18 months, Dall'Era et al. [43] found no difference for men with low-risk disease. This is in line with another study comparing men after immediate and delayed RP after a period of 2.6 years of AS. Both groups showed no differences in Gleason score >6, extracapsular extension and biochemical progression rates [44]. Unfortunately, available analyses provide an insight into short-term comparisons only. To overcome the lack of long-term outcomes, a statistical model was generated. This tool estimated that 2.8% of men on AS and 1.6% of men with immediate RP would die of their disease within 20 years [45]. Moreover, the average calculated increase in life expectancy due to immediate RP was 1.8 months, and on average men on AS would remain free of therapy for an additional 6.4 years compared to men treated immediately [45].

Psychological Aspects

Virtually all men diagnosed with PCa will have relatives or friends suffering from any kind of cancer, and nearly all of them will get some form of therapy. Some

men will worry over their raising or undulant PSA for years and PCa may be detected only after two or more series of biopsies. Also, during AS the fear to miss curative treatment only because of expectant management may be stressful to at least some patients. On the other hand, older age may probably give another view of one's own impairments [46]. In other words, it may be demanding for affected men to understand that despite its obvious limitations, AS could be a reasonable approach.

Analyzing 150 men from the PRIAS cohort with different questionnaires, patients on protocol-based AS mainly reported favorable levels of anxiety and distress, but a neurotic personality score was associated with unfavorable effects [47]. However, the invitation to complete the questionnaires was mailed to patients with PCa diagnosed within the last 6 months [47]. Another evaluation from the PRIAS cohort with 103 patients only and without a control group revealed that lack of a partner and impaired mental health were associated with low health-related quality of life (QoL) [48]. Based on the SPCG-4 trial data, Johansson et al. [49] compared QoL outcomes between men undergoing RP and WW. These authors found that on the basis of the numbers of physical symptoms, anxiety and depressed mood were less common, and sense of well-being and self-assessed QoL were better throughout the RP group than in the WW group. After a follow-up time of 6–8 years, a significant decrease in QoL was noted in the WW group [49]. However, in this study several patients of the WW group were treated with androgen deprivation therapy. It is important to note that AS will be converted to active treatment in case of progression and therefore focuses on another aim than the WW policy used in the SPCG-4 trial.

Basically, there is an urgent need for long-term data based on large cohorts to provide valid information about the impact of AS on QoL. In the meantime, statistical models may be helpful. Thus, Hayes et al. [13] calculated the quality-adjusted life years (QALYs) of AS and different forms of active treatment. QALYs represents a measure of the value of health outcomes, including both the aspect of QoL and the quantity of life lived. In this analysis, AS was associated with the highest QALYs (11.07), followed by brachytherapy (10.57), intensity-modulated radiation therapy (10.51) and RP (10.23), respectively [13].

QoL considerations are paramount for any decision-making process where individual preferences of both of the patient as well as the physician play a central role. Considering this, patients consulting a multidisciplinary clinic chose twice more often AS than those visiting an

individual practitioner [50]. Information material like the Fact Sheet, which describes comprehensively all aspects of PCa, was designed to support the decision-making process. Unfortunately, the comprehension of these tools appears currently still insufficient [51]. Thus, individual counseling remains a major challenge.

Future Prospects

A mainstay of AS is precise tumor characterization, and it is obvious that there is an urgent need for tools to classify tumor features more accurately. For that matter, new tumor markers have been intensely analyzed.

Lin et al. [52] analyzed urinary markers like PCA3 and TMPRSS2:ERG scores. Both of them were significantly associated with the presence of high-grade disease and higher-volume disease. Unfortunately, the findings in the literature are inconsistent. Thus, in an analysis of 294 men enrolled in the Johns Hopkins surveillance program, Tosoian et al. [53] found that PCA3 was not significantly associated with progression on biopsy. Moreover, a recent analysis could not establish a significant correlation between PCA3 and Gleason score or cancer volume either [54]. Different variants of [-2]proPSA (e.g. prostate health index) might also play a role in the future. Tosoian et al. [55] found that these markers were significantly associated with biopsy reclassification and showed a high predictive accuracy for high-grade cancer. Despite these promising results, research is still at the very beginning.

Over the last years magnetic resonance imaging (MRI) has evolved dramatically. Starting with 1.5 tesla (T) and

endorectal coil, 3T devices have become the standard, and 7T machines have already appeared on the horizon. Thereby, enhanced magnetic fields promise better resolution. In addition, the introduction of multiparametric evaluation, meaning special applications together with the classical T1- and T2-weighted images such as dynamic contrast-enhanced as well as diffusion-weighted imaging and spectroscopy, seem to distinctly enhance diagnostic accuracy. In a cohort of 133 patients, Turkbey et al. [56] evaluated multiparametric 3T MRI for the identification of men who might be candidates for AS. Multiparametric MRI showed a sensitivity of 93%, a positive predictive value of 57% and an overall accuracy of 92% in identifying men eligible for AS compared to the Epstein criteria with 64, 45 and 88%, respectively.

Conclusion

Since a substantial number of men die rather with than from PCa, there is a considerable role for AS in carefully selected men. Moreover, AS may also represent a strategy to reduce the burden of overtreatment due to intensified PSA testing. Facing the imprecision of risk stratification based on transrectal ultrasound-guided biopsy, accurate clinical staging represents a major medical challenge. Some new tumor markers as well as multiparametric MRI may increase staging accuracy. Men ultimately switching from AS to active treatment due to disease progression show results comparable to those treated initially. Counseling and care require empathy as well as a profound understanding of the biology and natural history of PCa.

References

- 1 Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. *CA Cancer J Clin* 2013;63: 11–30.
- 2 Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, Kido M, et al: Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. *J Natl Cancer Inst* 2013;105:1050–1058.
- 3 Franks LM: Latent carcinoma of the prostate. *J Pathol Bacteriol* 1954;68:603–616.
- 4 National Cancer Institute: Lifetime risk (percent) of being diagnosed with cancer by site and race/ethnicity: males, 18 SEER areas, 2008–2010. SEER Cancer Statistics Review 1975–2010, table 1.16, 2013. http://seer.cancer.gov/archive/csr/1975_2010/results_merged/topic_lifetime_risk_diagnosis.pdf.
- 5 National Cancer Institute: Lifetime risk (percent) of dying from cancer by site and race/ethnicity: males, total U.S., 2008–2010. SEER Cancer Statistics Review 1975–2010, table 1.19, 2013. http://seer.cancer.gov/archive/csr/1975_2010/results_merged/topic_lifetime_risk_death.pdf.
- 6 Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al: Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012;366:981–990.
- 7 Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al: Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009;101:374–383.
- 8 Wu GH, Auvinen A, Yen AM, Hakama M, Walter SD, Chen HH: A stochastic model for survival of early prostate cancer with adjustments for leadtime, length bias, and over-detection. *Biom J* 2012;54:20–44.
- 9 Vickers AJ, Sjoberg DD, Ulmert D, Vertosick E, Roobol MJ, Thompson I, et al: Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. *BMC Med* 2014;12:26.
- 10 Kim S 2nd, Dall’Era MA, Evans CP: Economic analysis of active surveillance for localized prostate cancer. *Curr Opin Urol* 2012;22:247–253.
- 11 World Health Organization: Life expectancy – data by country 2014. <http://apps.who.int/gho/data/node.main.688?lang=en>.

- 12 Schostak M, Baumunk D, Jagota A, Klopff C, Winter A, Schafers S, et al: Time trends in prostate cancer surgery: data from an Internet-based multicentre database. *BJU Int* 2012;109:355–359.
- 13 Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST, et al: Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA* 2010;304:2373–2380.
- 14 Bill-Axelsson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, et al: Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014;370:932–942.
- 15 Wilt TJ: SPCG-4: a needed START to PIVOTAL data to promote and protect evidence-based prostate cancer care. *J Natl Cancer Inst* 2008;100:1123–1125.
- 16 Vickers A, Bennett C, Steineck G, Adami HO, Johansson JE, Bill-Axelsson A, et al: Individualized estimation of the benefit of radical prostatectomy from the Scandinavian Prostate Cancer Group randomized trial. *Eur Urol* 2012;62:204–209.
- 17 Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al: Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203–213.
- 18 Epstein JI, Walsh PC, Carmichael M, Brendler CB: Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994;271:368–374.
- 19 Bastian PJ, Mangold LA, Epstein JI, Partin AW: Characteristics of insignificant clinical T1c prostate tumors. A contemporary analysis. *Cancer* 2004;101:2001–2005.
- 20 D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969–974.
- 21 Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, et al: Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol* 2013;63:597–603.
- 22 AWMF S3 – Leitlinie Prostatakarzinom 2014. http://leitlinienprogramm-onkologie.de/uploads/tx_sbdownloader/LL_Prostata_Langversion_3.1.pdf.
- 23 Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, Partin AW, et al: Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol* 2011;29:2185–2190.
- 24 van As NJ, Norman AR, Thomas K, Khoo VS, Thompson A, Huddart RA, et al: Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. *Eur Urol* 2008;54:1297–1305.
- 25 Vellekoop A, Loeb S, Folkvaljon Y, Stattin P: Population based study of predictors of adverse pathology among candidates for active surveillance with Gleason 6 prostate cancer. *J Urol* 2014;191:350–357.
- 26 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;181:1628–1633; discussion 1633–1634.
- 27 Palisaar JR, Noldus J, Loppenberg B, von Bodman C, Sommerer F, Eggert T: Comprehensive report on prostate cancer misclassification by 16 currently used low-risk and active surveillance criteria. *BJU Int* 2012;110(6 Pt B):E172–E181.
- 28 Kuroiwa K, Shiraishi T, Naito S: Gleason score correlation between biopsy and prostatectomy specimens and prediction of high-grade Gleason patterns: significance of central pathologic review. *Urology* 2011;77:407–411.
- 29 Helpap B, Kristiansen G, Kollermann J, Shaikhibrahim Z, Wernert N, Oehler U, et al: Significance of Gleason grading of low-grade carcinoma of the prostate with therapeutic option of active surveillance. *Urol Int* 2013;90:17–23.
- 30 Motamedinia P, Richard JL, McKiernan JM, DeCastro GJ, Benson MC: Role of immediate confirmatory prostate biopsy to ensure accurate eligibility for active surveillance. *Urology* 2012;80:1070–1074.
- 31 Barzell WE, Melamed MR, Cathcart P, Moore CM, Ahmed HU, Emberton M: Identifying candidates for active surveillance: an evaluation of the repeat biopsy strategy for men with favorable risk prostate cancer. *J Urol* 2012;188:762–767.
- 32 Umbehre MH, Largo RA, Gfeller S, Tremp M, Poyet C, Paul M, et al: Bilaterally positive biopsy cores are associated with non-organ-confined disease in prostate cancer patients eligible for active surveillance. *Urol Int* 2014;93:176–181.
- 33 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;62:462–468.
- 34 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;106:1161–1164.
- 35 Albertsen PC, Hanley JA, Gleason DF, Barry MJ: Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998;280:975–980.
- 36 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;58:831–835.
- 37 Adamy A, Yee DS, Matsushita K, Maschino A, Cronin A, Vickers A, 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;185:477–482.
- 38 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;28:126–131.
- 39 Ross AE, Loeb S, Landis P, Partin AW, Epstein JI, Kettermann A, 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;28:2810–2816.
- 40 Cooperberg MR, Cowan JE, Hilton JF, Reese AC, Zaid HB, Porten SP, et al: Outcomes of active surveillance for men with intermediate-risk prostate cancer. *J Clin Oncol* 2011;29:228–234.
- 41 Park HJ, Ha YS, Park SY, Kim YT, Lee TY, Kim JH, et al: Incidence of upgrading and upstaging in patients with low-volume Gleason score 3+4 prostate cancers at biopsy: finding a new group eligible for active surveillance. *Urol Int* 2013;90:301–305.
- 42 Bul M, Zhu X, Rannikko A, Staerman F, Valdagni R, Pickles T, et al: Radical prostatectomy for low-risk prostate cancer following initial active surveillance: results from a prospective observational study. *Eur Urol* 2012;62:195–200.
- 43 Dall'era MA, Cowan JE, Simko J, Shino-hara K, Davies B, Konety BR, et al: Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. *BJU Int* 2011;107:1232–1237.
- 44 van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T, 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;116:1281–1290.
- 45 Xia J, Trock BJ, Cooperberg MR, Gulati R, Zeliadt SB, Gore JL, et al: Prostate cancer mortality following active surveillance versus immediate radical prostatectomy. *Clin Cancer Res* 2012;18:5471–5478.
- 46 Palgi Y, Shmotkin D: The predicament of time near the end of life: time perspective trajectories of life satisfaction among the old-old. *Aging Ment Health* 2010;14:577–586.

- 47 van den Bergh RC, Essink-Bot ML, Roobol MJ, Wolters T, Schroder FH, Bangma CH, et al: Anxiety and distress during active surveillance for early prostate cancer. *Cancer* 2009;115:3868–3878.
- 48 Bellardita L, Rancati T, Alvisi MF, Villani D, Magnani T, Marengi C, et al: Predictors of health-related quality of life and adjustment to prostate cancer during active surveillance. *Eur Urol* 2013;64:30–36.
- 49 Johansson E, Bill-Axelsson A, Holmberg L, Onelov E, Johansson JE, Steineck G: Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. *Eur Urol* 2009;55:422–430.
- 50 Aizer AA, Paly JJ, Zietman AL, Nguyen PL, Beard CJ, Rao SK, et al: Multidisciplinary care and pursuit of active surveillance in low-risk prostate cancer. *J Clin Oncol* 2012;30:3071–3076.
- 51 Okihara K, Mikami K, Kamoi K, Kitamura K, Kawauchi A, Miki T: Assessment of screeners' knowledge on prostate cancer: results of a questionnaire using the Fact Sheet. *Urol Int* 2013;91:49–54.
- 52 Lin DW, Newcomb LF, Brown EC, Brooks JD, Carroll PR, Feng Z, et al: Urinary TMPRSS2:ERG and PCA3 in an active surveillance cohort: results from a baseline analysis in the Canary Prostate Active Surveillance Study. *Clin Cancer Res* 2013;19:2442–2450.
- 53 Tosoian JJ, Loeb S, Kettermann A, Landis P, Elliot DJ, Epstein JI, et al: Accuracy of PCA3 measurement in predicting short-term biopsy progression in an active surveillance program. *J Urol* 2010;183:534–538.
- 54 Augustin H, Mayrhofer K, Pummer K, Mannweiler S: Relationship between prostate cancer gene 3 (PCA3) and characteristics of tumor aggressiveness. *Prostate* 2013;73:203–210.
- 55 Tosoian JJ, Loeb S, Feng Z, Isharwal S, Landis P, Elliot DJ, et al: Association of [-2]pro-PSA with biopsy reclassification during active surveillance for prostate cancer. *J Urol* 2012;188:1131–1136.
- 56 Turkbey B, Mani H, Aras O, Ho J, Hoang A, Rastinehad AR, et al: Prostate cancer: can multiparametric MR imaging help identify patients who are candidates for active surveillance? *Radiology* 2013;268:144–152.