Insignificant Prostate Cancer and Active Surveillance: From Definition to Clinical Implications

Patrick J. Bastian, Ballentine H. Carter, Anders Bjartell, Michael Seitz, Peter Stanislaus, Francesco Montorsi, Christian G. Stief, Fritz Schröder

Urologische Klinik und Poliklinik, Universitätsklinikum der Universität München – Großhadern, Ludwig-Maximilians-Universität, Munich, Germany
Erasmus MC, University Medical Centre, Rotterdam, the Netherlands
Division of Urological Cancers, Urology, Department of Clinical Sciences, Lund University, Malmo, Sweden
James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA
Università Vita-Salute San Raffaele, Via Olgettina 60, 20132 Milan, Italy

Abstract

Context: Due to early detection strategies, prostate cancer is diagnosed early in its natural history. It remains unclear whether all patients diagnosed with prostate cancer warrant radical treatment or may benefit from delayed intervention following active surveillance.

Objective: A systematic review of active surveillance protocols to investigate the inclusion criteria for active surveillance and the outcome of treatment.

Evidence acquisition: Medline was searched using the following terms: prostate cancer, active surveillance and expectant management for dates up to October 2008. Further studies were chosen on the basis of manual searches of reference lists and review papers.

Evidence synthesis: Numerous studies on active surveillance were identified. The recent inclusion criteria of the studies are rather similar. Keeping the short follow-up of all studies in mind, the majority of men stay on active surveillance, and the percentage of patients receiving active treatment is as high as 35% of all patients. Once a patient requires active treatment, most patients still present with curable prostate cancer. Furthermore, only few deaths due to prostate cancer have occurred.

Conclusions: Active surveillance is an alternative option to immediate treatment of men with presumed insignificant prostate cancer. It seems that criteria used to identify men with low-risk prostate cancer are rather similar, and immediate treatment of men meeting these criteria may result in an unnecessary number of treatments in these highly selected patients. Data from randomised trials comparing active surveillance and active treatment will provide additional insight into outcome and follow-up strategies.

© 2009 Published by Elsevier B.V. on behalf of European Association of Urology.
1. Introduction

Prostate cancer (PCa) is the most frequently diagnosed solid malignant tumour among men in the United States and Western Europe. A significant increase in the diagnoses of men with nonpalpable PCa has occurred since the beginning of the prostate-specific antigen (PSA) testing era in the late 1980s. The lifetime risk of developing PCa in the United States is 1 in 6, and the lifetime risk of death due to metastatic PCa is 1 in 30 [1]. The estimated age-standardised mortality rates for PCa per 100,000 men is 23.2 in Europe in 2006 [2]. However, the natural history of screen-detected PCa remains poorly understood. Autopsy studies have revealed that 50% of men in the age group of 40–49 yr harbour PCa [3]. Eighty percent of these cancers are of low volume (<0.5 cm³), and low grade and can be classified as insignificant according to the so-called Epstein criteria [4,5].

The advent of PSA testing and modified prostatic biopsy schemes have led to the establishment of overdiagnosis, which is an epidemiologic term and is defined as the diagnosis of cancers which will not be diagnosed clinically during life [6].

Even the introduction of more refined PSA testing (ie, complex PSA, free PSA, ratio of free PSA to total PSA) and PSA kinetics (ie, PSA doubling time [PSA DT] or PSA velocity) have not been able to solve this clinical dilemma [7–10].

At present, the rate of overdetection of PCa is suggested to be as high as 56% [6,11]. This has also led to the well-recognised phenomenon called “stage migration,” meaning that today more PCa is detected at earlier stages, potentially reducing cancer-specific mortality [12].

At present, active treatment of newly diagnosed PCa remains the gold standard, even considering earlier detection of PCa [7]. However, no matter what treatment option for localised PCa is chosen, there is always a chance of decreased quality of life once sexual function and urinary function are altered [13]. Using modern risk stratification, certain centres have gained experience to better identify patients with a low risk of PCa progression and have started to use active surveillance with delayed, selective, or curative therapy [14]. Interestingly, only limited numbers of patients under active surveillance require additional treatment. Thus, with short follow-up, it appears that delayed treatment in these highly selected cases does not alter outcome.

The aim of this review is to define insignificant PCa and, subsequently, potential candidates for active surveillance. A critical analysis of the results seen in PCa patients undergoing active surveillance as an alternative treatment option is also performed.

2. Evidence acquisition

Medline was searched using the following terms: prostate cancer, active surveillance and expectant management for dates up to October 2008. Further studies were chosen on the basis of manual searches of reference lists and review papers and from meetings of the European Association of Urology (EAU) and the American Urological Association (AUA). This approach was chosen because previous work has shown that manual search improves the database search. Since there are only limited reported data on active surveillance in PCa patients, we tried to include all major reported studies in this review. Thus, the information provided was not divided into different categories.

3. Evidence synthesis

3.1. Insignificant prostate cancer

A critical factor for successful active surveillance is the best possible patient selection. Obviously, patients with an identifiable low risk of progression are most likely to be safely observed and treated only when necessary. Epstein et al introduced prostate biopsy criteria to predict insignificant PCa (Table 1) [5]. These criteria include the following: clinical stage T1c, PSA density <0.15 ng/ml, no Gleason pattern 4 or 5, fewer than three positive cores, <50% cancer per core [5]. In addition to the original Epstein criteria, multiple selection criteria for insignificant PCa based on preference or on experience have been reported (Table 1) [15]. Using tables or current nomograms, one may better predict the individual risk of a patient [16].

Multiple studies have examined the outcome of insignificant and insignificant cancer. In the pioneering work of Epstein et al, their criteria correctly predicted the presence of pathologically insignificant PCa (tumour volume <0.2 cm³, pathologic Gleason score ≤6, and organ-confined disease) in 73% of all cases (41 of 157 cases) [5]. In a validation study of this model, Epstein et al demonstrated 94% accuracy to detect 17 pathologically insignificant PCas out of 163 radical prostatectomy (RP) cases [17]. A contemporary update by Bastian et al included a cohort of 237 nonpalpable (clinical stage T1c) PCa patients treated with RP at Johns Hopkins Hospital [18]. Within that cohort, 91.6% of cases fulfilled the
Epstein criteria that correctly predicted the presence of organ-confined disease [18]. Interestingly, 8.4% of cases that fulfilled the Epstein criteria were not organ confined at RP [18]. One drawback of this study was that there was no information on tumour volume available, so the biopsy criteria were used to predict organ-confined disease with negative margins and negative lymph node status. The reason that tumour volume was not used in this study was the negative association of tumour volume and clinical outcome in patients undergoing RP at Johns Hopkins Hospital [19]. Jeldres et al performed a European validation of the Epstein criteria in a cohort of 366 patients using the same methodology as Bastian et al [20]. In their series, 20% of patients who fulfilled the Epstein criteria had unfavourable findings at RP, which consisted of either pathologic Gleason 7 disease (n = 88, 24%) or non–organ-confined pathologic stage (n = 30, 8.3%). Taken together, these data indicate that pathologically confirmed insignificant PCa (tumour volume <0.5 cm³, pathologic Gleason score ≤6, and organ-confined disease) may be expected to be correctly predicted in only 73% of patients, according to data from 157 consecutive RP cases [5]. Consequently, 27% of patients with PCa characteristics that are more aggressive may be incorrectly classified as insignificant PCa. Since the natural history of these cases is unknown, the upper, arbitrary cut-off of the Epstein criteria remains uncertain. Furthermore, between 20% and 8.4% of patients who fulfil the Epstein criteria prior to definitive therapy may be expected to demonstrate non–organ-confined disease that may not be curable [16]. However, it needs to be pointed out that insignificant prostate cancer is a term that describes pathologic criteria of surgical specimen, and no data on the Epstein criteria concerning the natural history of PCa exist.

In contrast to insignificant PCa, the term indolent prostate cancer has been introduced to describe prospectively detected PCa with tools such as nomograms [21,22]. Indolent PCa occurs, by definition, early in the natural history; when treated actively, there is an excellent chance of a positive outcome [22].

3.2. Risk assessment of insignificant prostate cancer

As numerous studies have reported, while the amount of localised PCa has been increasing, the amount of locally advanced cancer has been decreasing during the last decade [23]. Due to this stage migration and PCa screening, a considerable lead-time bias occurs because cancers are diagnosed well before they may become clinically evident. In this context, screening may detect many more cancers that may never become clinically evident. Draisena et al detected a lead-time bias based on the European Randomised Study of Screening for Prostate Cancer (ERSPC) of 9.9 yr up to 13.3 yr [24], which was also confirmed by other studies [11,25].

In the ideal case, only potentially curable patients with clinically significant PCa and a significant risk to succumb to PCa would undergo treatment. Correctly identifying these patients is a challenging task for urologists. The use of predictive models has been progressively gaining popularity to help physicians when counselling patients [26]. Variables such as pretreatment PSA level, biopsy Gleason sum, and clinical stage are only few of the parameters included in these models. Commonly used tools are the Partin tables [12], the D’Amico risk classification [27], the Kattan nomogram [22] (validated by Steyerberg et al for screen detected PCA [21]), or contemporary nomograms to predict indolent PCa by Nakanishi et al [28], Chun et al, or Roemeling et al [16,29]. To understand these studies, it is important to remember that flipping a coin translates into an accuracy of 50%. The accuracy of the initial nomograms for indolent PCa ranges from 73% to 79% versus 73% for the Epstein criteria. Taken together, the nomogram studies indicate that these statistical tools are similar to the original Epstein criteria for insignificant PCa in their ability to predict pathologically confirmed insignificant PCa, but they offer the advantage of quantifying risks according to variable input of clinical information [16].

The nomogram recently published by Chun et al used pretreatment PSA level, biopsy Gleason sum, cumulative cancer-tissue length, and percentage of positive cores, and it revealed a predictive accuracy of 90%, possibly improving on the older models [16]. The reasons for this significant increase in accuracy remain to be identified. One possible reason may be the use of cancer-tissue length in the model.

Interestingly, the authors state that even their sophisticated statistical tool is unable to convincingly predict insignificant PCa and that caution is warranted when evaluating patients for active surveillance [16]. This is underlined by the review of Schröder et al on nomogram use in PCa, stating that most models lack external validation [30].

There is no doubt that multi-institutional, prospective trials comparing these criteria are needed to clarify the best entry criteria for active surveillance [14]. Furthermore, profiles of candidates for novel active surveillance that incorporate molecular biomarkers must be identified.
3.3. Investigations needed during active surveillance and detection of prostate cancer progression

In line with different models to identify insignificant PCa, the proposed follow-up protocols of patients undergoing active surveillance vary. Different active surveillance follow-up strategies are listed in Table 2. According to institutional guidelines and study protocols, the characteristics of the follow-up period differ. However, it seems that the criteria are rather similar. For instance, patients with active surveillance will have to undergo a yearly repeat biopsy at Johns Hopkins Hospital, compared with a repeat-biopsy scheme in Toronto of 12 mo to 18 mo [31,32]. Besides a regular repeat biopsy, regular PSA-level testing, digital rectal examination (DRE) and optional transrectal ultrasound (TRUS) studies are warranted [32]. During the individual counselling and decision making for active surveillance for low-risk PCa, the urologist must point out that regular follow-up visits are absolutely mandatory and that not overseeing progression constitutes higher risk. This is in line with the newly updated EAU guidelines on PCa [7].

The detection of PCa progression in a patient selected for active surveillance remains a continuing challenge. What will serve as the best parameter to correctly identify men that progress to more aggressive cancer in order not to miss the window of curability is still a matter of debate. It seems that the PSA level is still of major importance during the decision process. According to the landmark study by D’Amico et al, a rapid pretreatment PSA rise is associated with an increased risk of dying from PCa [8]. The report by Carter et al supports these findings: it shows that PSA velocity 15 yr before diagnosis was significantly higher in patients who

---

### Table 1 – Definitions of insignificant or low-risk prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein et al [5] and Bastian et al [18]</td>
<td>Clinical stage T1c</td>
</tr>
<tr>
<td>D’Amico et al [22]</td>
<td>PSA density &lt;0.15 ng/ml</td>
</tr>
<tr>
<td>Dall’Era et al [13]</td>
<td>No Gleason pattern 4 or 5</td>
</tr>
<tr>
<td>Dall’Era et al [14] (commonly used criteria)</td>
<td>Clinical stage T2a or lower</td>
</tr>
<tr>
<td>Soloway et al [47]</td>
<td>PSA level &lt;10 ng/ml</td>
</tr>
<tr>
<td>Patel et al [74]</td>
<td>No Gleason pattern 4 or 5</td>
</tr>
<tr>
<td>Van den Bergh et al [72] (PRIAS)</td>
<td>Clinical stage T1c–T2b</td>
</tr>
<tr>
<td>Van As et al [38]</td>
<td>No Gleason pattern 4 or 5</td>
</tr>
<tr>
<td>Dall’Era et al [14] (commonly used criteria)</td>
<td>PSA level &lt;0.20 ng/ml</td>
</tr>
<tr>
<td>PSA &gt;10 ng/ml</td>
<td>Fewer than three positive cores</td>
</tr>
<tr>
<td>PSA = prostate-specific antigen; PRIAS = Prostate Cancer Research International: Active Surveillance.</td>
<td></td>
</tr>
</tbody>
</table>

---

### Table 2 – Follow-up criteria during active surveillance

<table>
<thead>
<tr>
<th>Study</th>
<th>DRE</th>
<th>PSA</th>
<th>Rebiopsy</th>
<th>TRUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van As et al [38]</td>
<td>Every 3 mo for 2 yr, then every 6 mo</td>
<td>Year 1: monthly</td>
<td>At 18–24 mo, then biannually</td>
<td>No mention</td>
</tr>
<tr>
<td>Dall’Era et al [46]</td>
<td>Every 3 mo</td>
<td>Every 3 mo for 2 yr, then every 6 mo if PSA level is stable</td>
<td>Every 12–24 mo</td>
<td>6–12-mo interval</td>
</tr>
<tr>
<td>Carter et al [31,49]</td>
<td>Every 3 mo</td>
<td>Every 3 mo for 2 yr, then every 6 mo if PSA level is stable</td>
<td>Every 12–24 mo</td>
<td>Optional</td>
</tr>
<tr>
<td>Klotz et al [32]</td>
<td>Every 3 mo</td>
<td>Every 3 mo for 2 yr, then every 6 mo if PSA level is stable</td>
<td>Every 12–24 mo</td>
<td>No mention</td>
</tr>
<tr>
<td>Patel et al [74]</td>
<td>Every 3 mo</td>
<td>Every 3 mo for 1 yr, then every 6 mo</td>
<td>At 6 mo</td>
<td>At 6 mo</td>
</tr>
<tr>
<td>Soloway et al [47]</td>
<td>Every 3 mo</td>
<td>Every 3 mo for 1 yr, then every 6 mo</td>
<td>At 6 mo</td>
<td>No mention</td>
</tr>
<tr>
<td>Hardie et al [43]</td>
<td>Every 3–6 mo for 2 yr, then every 6 mo</td>
<td>Every 3–6 mo for 2 yr, then every 6 mo if PSA is stable</td>
<td>Not routine</td>
<td>Not routine</td>
</tr>
</tbody>
</table>

DRE = digital rectal examination; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.
die of PCa [33]. Furthermore, Freedland et al showed that in men with biochemical failure following RP, the postoperative PSA DT is a strong predictor of PCa-specific mortality [34]. Khatami et al also showed that a PSA DT of <2 yr in men undergoing surgical treatment following active surveillance was the strongest predictor of biochemical failure [35]. All these studies underline the importance of PSA testing and PSA kinetics to predict PCa behaviour and to identify the correct timing for more aggressive treatment. However, the pitfalls of PSA testing in terms of sensitivity, specificity, and reproducibility are well understood [7]. As we have learned over the years, PSA level seems to be a valid marker for PCa and its progression, but novels marker are acutely needed and may improve active-surveillance monitoring. A comprehensive review on PSA kinetics in clinical decision-making during active surveillance for early PCa was published recently by van den Bergh in this journal [36].

Multiple active surveillance intervention strategies are listed in Table 3. The study by van As et al uses PSA kinetics profiles, progression of Gleason grade, and increased percentage of cancer per core as indicators to stop active surveillance in men with low-risk PCa [37,38]. Interestingly, in the cohort of Klotz et al, only 4% of patients were treated because of progression of Gleason grade alone [39]. The greatest trigger for intervention in the Toronto cohort remains the PSA DT, with 21% of the cohort having a PSA DT <3 yr [40,41]. Interestingly, Stephenson et al found that men with stage progression detected by DRE on active surveillance were more likely to have a PSA DT <2 yr [42]. Again, this underlines the importance of PSA kinetics in the progression of presumed clinically insignificant PCa.

Current serial imaging techniques, such as ultrasound or magnetic resonance, may also have a potential role, but are unproven. It will be interesting to see whether contrast-enhanced ultrasound can improve the detection of progression.

### 3.4. Outcomes of active surveillance

Multiple studies have reported their experience with active surveillance, but most studies are compromised by a relatively short follow-up time (Table 3). In a recent study from the Royal Marsden Hospital in the United Kingdom, van As et al reported on 326

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment criteria</th>
<th>Median age, yr (range)</th>
<th>Percentage of patients with active treatment, % (total no. of patients)</th>
<th>Mortality (related to prostate cancer)</th>
<th>Median follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van As et al [38]</td>
<td>PSAV &gt;1 ng/ml per year, Gleason score ≥4 + 3 or &gt;50% cancer per core</td>
<td>67 (50–79)</td>
<td>20 (326)</td>
<td>None</td>
<td>22</td>
</tr>
<tr>
<td>Dall’Era et al [46]</td>
<td>Gleason score ≥7 on rebiopsy, rising PSA, increase in volume by biopsy parameters</td>
<td>63.4 (40–86)</td>
<td>21 (321)</td>
<td>None</td>
<td>24</td>
</tr>
<tr>
<td>Carter et al [31,49]</td>
<td>Gleason score ≥7 on rebiopsy, any pattern 4, 5 &gt;2 cores involved, &gt;50% any single core involved</td>
<td>65.7 (45.8–81.5)</td>
<td>31 (320)</td>
<td>None</td>
<td>23</td>
</tr>
<tr>
<td>Klotz et al [32]</td>
<td>PSA DT &lt;2 yr, Gleason score ≥8</td>
<td>NA</td>
<td>34 (299)</td>
<td>None</td>
<td>64</td>
</tr>
<tr>
<td>Patel et al [74]</td>
<td>Gleason score increase, PSAV &gt;0.75/yr, increase DRE/TRUS detected lesion, increase biopsy volume</td>
<td>Mean: 65.3 (44–79)</td>
<td>35 (88)</td>
<td>None</td>
<td>44</td>
</tr>
<tr>
<td>Hardie et al [43]</td>
<td>Rising PSA, clinical judgment</td>
<td>70.5 (59–81)</td>
<td>14 (80)</td>
<td>None</td>
<td>42</td>
</tr>
<tr>
<td>Roemeling et al [29]</td>
<td>PSA DT</td>
<td>69.5 (25–75)</td>
<td>29 (278)</td>
<td>None</td>
<td>40</td>
</tr>
<tr>
<td>Ercole et al [75]</td>
<td>Increase in tumour volume, Gleason score progression, urinary symptoms, change of DRE, patient preference</td>
<td>68 (52–75)</td>
<td>7.8 (40)</td>
<td>None</td>
<td>48</td>
</tr>
<tr>
<td>Soloway et al [47]</td>
<td>Gleason score increase, PSA and PSA DT increase, stage progression, increase biopsy volume, patient preference</td>
<td>67 (mean: 66.02)</td>
<td>&lt;1 (99)</td>
<td>None</td>
<td>45.3 (mean)</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; PSA DT = PSA doubling time; PSAV = PSA velocity; DRE = digital rectal examination; TRUS = transrectal ultrasound; NA = not available.
patients who underwent active surveillance (criteria are listed in Table 2). They found that 20% of men received delayed radical treatment after a median follow-up of 22 mo. Within this time frame no patient developed metastatic disease or died of PCa [38]. Hardie et al reported similar findings at a median follow-up of 42 mo [43]. Approximately 91% of the patients had a Gleason score <6 and 73% a PSA level <10 ng/ml. All patients revealed organ-confined disease in the pathologic specimen, with 58% of patients presenting with pT1-stage disease. Note that the median PSA DT in that study was 12 yr.

Another supporting study was published by Carter et al from Johns Hopkins Hospital, where a prospective programme of active surveillance was initiated in 1995 [31]. In the 2002 update the authors described evidence of PCa progression in 31% of 81 patients (median follow-up: 23 mo) [44]. Of these, 25 patients experienced progression, 13 patients underwent RP, and 12 of 13 patients (92%) had curable PCa [44]. PSA density was significantly higher and the percentage of free PSA was significantly lower in men with progression compared with men without evidence of progression. In the 2007 study report, Carter et al updated their experience on active surveillance, of 407 men [31]. With a median follow-up of 3.4 yr, 59% (239 men) remained on active surveillance and 25% (103 men) underwent curative intervention at a median of 2.2 yr after diagnosis (range: 0.96–7.39 yr) [31]. In this analysis, only older age at diagnosis and earlier date of diagnosis were significantly associated with the decision to treat. Surprisingly, PSA level, PSA density, PSA slope, number of positive cores, or percentage of cancer per core were not predictors of progression in the Cox model [31]. Of the 103 men undergoing a potentially curative procedure, 53 (51%) underwent RP. Incurable disease was defined as pT2 stage if Gleason sum was ≥7 (4 + 3) and/or surgical margin positive with any grade, stage pT3aN0 if Gleason sum was ≥7 and/or surgical margin was positive, any stage higher than pT3a regardless of grade or margin, or any N+ stage [44]. Some 20% of patients had incurable disease [31].

In one of the largest studies by Klotz et al (299 patients), the overall survival rate was 85%, and the disease-specific survival rate was 99.3% at 8 yr [40]. Again, the median PSA DT was 7 yr, while 42% had a PSA DT >10 yr. In consistency with the Johns Hopkins Hospital study, the Gleason grade remained the same in 92% of the cohort [32]. Of 24 patients undergoing RP for a PSA DT <2 yr, 14 patients (58%) were pT3a to pT3c, and 2 patients (8%) were N+. Considering this a low-risk PCa cohort, these numbers seem rather high [32]. However, at the beginning patients with cT2b disease, PSA values of up to 15 ng/ml, and a Gleason score of 7 were included, meaning that these patients were very likely to have more advanced disease. Interestingly, in a recent study the PSA DT was increased to 3 yr, hoping to improve the outcome of these patients [45].

In the University of California at San Francisco (UCSF) study of 500 patients, 24% received secondary treatment a median of 3 yr (range: 1–17 yr) following the initiation of active surveillance. In this cohort, 38% had a Gleason grade progression in their repeat biopsy, and this was the greatest driver of secondary treatment [46].

Soloway et al reported from Miami on 99 patients undergoing active surveillance with a mean follow-up of 45 mo, mean age of 66 yr, and a mean PSA level of 5.77 ng/ml [47]. On the initial repeat biopsy, about 63% of patients did not have PCa, whereas 34% had PCa with a Gleason sum ≤6 [47]. Of these patients, eight underwent treatment (three patients underwent androgen deprivation therapy, and five were treated with curative intent). Of the five patients treated with curative intent, two underwent RP and three chose radiotherapy. These patients are free of biochemical recurrence with follow-up time of up to 83 mo. Kaplan-Meier analyses revealed a 5-yr probability of treatment-free survival on active surveillance of 85% [47]. No patient in this cohort died of PCa. Cox regression analysis identified PSA DT and clinical stage as significant predictors to predict progression to treatment [47].

Taken together, about 2–6% of patients died of other causes [31,38,43]. For instance, in one study with a median follow-up of 64 mo, only 2 of 299 patients (<1%) died of PCa [32]. Both patients had PSA DTs <2 yr, and both deaths occurred within 5 yr of the initial diagnosis, implying that both may have had micrometastatic disease at the time of diagnosis, and earlier intervention (both developed metastatic disease within 6 mo after the beginning of active surveillance) may not have altered the outcome [32].

3.5. Psychosocial aspects of active surveillance and delayed treatment

As we all know from clinical practice, the diagnosis of cancer dramatically changes the lives of every patient and his family. Additionally, due to the vast amount of secondary literature, the decision-making process of choosing therapy has become complicated. Fortunately, Freedland et al observed no adverse pathologic features or biochemical recurrences in men with low-risk PCa who delayed...
RP up to 6 mo [48]. Similar findings by Warlick et al from Johns Hopkins Hospital showed no difference between patients undergoing immediate or delayed (median time to intervention: 26.5 mo) RP for low-risk PCAs, confirming these findings [49]. However, it must be recognised that prognostic risk assessment is far from perfect, but there is plenty of time to provide counsel and to discuss all available treatment options.

Since the initial report of Litwin et al some 15 yr ago, only a few reports on psychosocial ramifications of watchful waiting have appeared [50]. Studies on watchful waiting describe various forms of anxiety, illness uncertainty, and reduced quality of life [51–54]. It remains unclear whether these changes may also apply to men who underwent active surveillance or immediate treatment [14]. A randomised trial from Sweden in patients undergoing radical treatment or watchful waiting demonstrated no difference in quality of life after 5 yr. Worry, anxiety, and depression were equally distributed in each arm of the study [55]. It seems that all patients, no matter what treatment is chosen, are worried about cancer recurrence or progression. However, anxiety can be a greater confounder than biochemical progression or other clinical parameters in active surveillance of patients heading into active treatment [56]. There is no doubt that thorough patient education about the low-risk nature of the cancer is the best instrument to circumvent psychological problems, even though cultural, social and intellectual differences cannot be neglected [57]. The need for improved patient counselling and education is underlined by the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) report by Barocas et al showing that only a small subset of patients eligible for active surveillance did actually choose this form of treatment [58].

Unfortunately, data on this important topic are scarce in active surveillance cohorts. Since a well-recognised difference between watchful waiting and active surveillance exists, it remains unclear whether all of these psychological aspects may also apply to patients undergoing active surveillance for PCa.

3.6. The future of active surveillance: novel biomarkers

Due to the advances in understanding the molecular biology of prostate carcinogenesis and its progression, we continually improved our ability to categorise PCAs. Multiple susceptibility genes and many additional mechanisms involved in carcinogenesis and cancer progression have been discovered [59]. However, no single biomarker able to improve the common clinical parameters included in the currently used predicting models has yet been identified [60]. One promising study from Demichelis et al demonstrated an association of the TMPRSS2:ERG gene fusion with PCA-specific mortality [61]. They suggested that PCA containing the TMPRSS2:ERG fusion gene may have a more aggressive phenotype, possibly mediated through increased ERG gene expression [61]. Epigenetic events, mainly DNA hypermethylation at various gene loci is of major importance during prostate carcinogenesis and progression. It was introduced some 25 yr ago by the Vogelstein et al, while Nelson et al introduced GSTP1 hypermethylation as a central part of prostate carcinogenesis [62,63]. A study of PCa precursor lesions revealed that GSTP1 hypermethylation occurs in otherwise histologically benign prostate tissue called proliferative inflammatory atrophy [64]. One study comparing the GSTP1 hypermethylation status in serum samples of men undergoing RP showed that GSTP1 hypermethylation is the single most powerful predictor of biochemical recurrence in patients with presumed localised cancer [65]. The study by Haese et al investigated the use of PCA3 in a rebiopsy setting of patients with a negative prostate biopsy. In their work, the risk to detect PCA increased with increasing PCA3 scores [66]. These findings are also supported by Nakanishi et al from a North American study [67]. Contrary to this, Deras et al found that PCA3 testing is independent from tumour volume, thus the true value of the test in the setting of active surveillance remains unclear at this point [68].

Other studies on DNA alterations and gene expression added valuable information on the progression of PCa [69–71]. All of these biomarkers have the potential to advance into clinical routine once larger, multi-institutional studies have confirmed the promising results.

3.7. Current trials of active surveillance

Only few randomised trials for the treatment of PCa are ongoing, but we are awaiting with great interest the results of two trials that are investigating active surveillance as a treatment option.

The Standard Treatment Against Restricted Treatment (START) trial is a Canadian trial that will enrol 2130 men in Canada, the United States, and the United Kingdom with low-risk localised PCAs as defined by Klotz et al [32]. START will compare early active treatment in the form of RP, external-beam radiation, or brachytherapy to active surveillance with delayed intervention.
Another interesting trial is the Prostate Cancer Research International: Active Surveillance (PRIAS) study of the Rotterdam section of the ERSPC and the Department of Urology of the Erasmus Medical Centre in Rotterdam, Netherlands (www.prias-project.org) [72]. The trial is entirely Web based and will enrol patients from Europe and North America with PCa and clinical stage T1c or T2, Gleason sum ≤6, PSA level ≤10 ng/ml, and PSA density ≤0.2 ng/ml. Repeat biopsies are performed as late as 10 yr after the enrolment. Besides the evidence-based guideline for active surveillance, important information on PSA changes and PSA kinetics will be provided [72].

Another trial to study the effectiveness of active surveillance and active treatment (surgery or radiation) is the Prostate Testing for Cancer and Treatment (ProtecT) trial in the United Kingdom [73]. The recruitment phase lasted until 2008, and the trial will include a follow-up of 10–15 yr.

4. Conclusions

In summary, active surveillance is an alternative treatment option to immediate treatment of men with presumed low-risk PCa. It seems that criteria used to identify men with low risk PCa are rather similar, and immediate treatment of men meeting these criteria may result in an unnecessary number of treatments in these highly selected patients. However, today the criteria to predict low-risk, organ-confined PCa are not perfect, and certain number of patients that warrant immediate treatment may be missed. Furthermore, information from randomised trials comparing active surveillance and active treatment will provide additional insight into the outcome of active surveillance compared to active treatment and the required follow-up strategies.

Hopefully, by using the modernised progression criteria, no patients with progression will miss the window of curability. With the improvement of molecular biomarkers, the identification of PCA progression may become easier and more accurate.

Author contributions: Patrick Bastian 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: Bastian, Montorsi, Stief.
Acquisition of data: Bastian, Stanislaus, Seitz.
Analysis and interpretation of data: Bastian, Carter, Bjartell, Seitz, Stanislaus, Montorsi, Stief, Schröder.
Drafting of the manuscript: Bastian, Seitz, Stanislaus, Montorsi, Schröder, Stief.

Critical revision of the manuscript for important intellectual content: Bastian, Carter, Bjartell, Seitz, Stanislaus, Montorsi, Stief, Schröder.
Statistical analysis: none.
Obtaining funding: none.
Administrative, technical, or material support: none.
Supervision: Montorsi, Stief.
Other (specify): none.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: none.

Funding/Support and role of the sponsor: none.

References


Capitanio U, Jeldres C, Shariat SF, Karakiewicz P. Clinicians are most familiar with nomograms and rate their clinical usefulness highest, look-up tables are second best. Eur Urol 2008;54:958–9.


[57] Pickles T, Ruether JD, Weir L, Carlson L, Jakulj F. Psychosocial barriers to active surveillance for the management of early prostate cancer and a strategy for increased acceptance. BJU Int 2007;100:544–51.


[77] Schroder FH, Bangma CH. Prospective validation of active surveillance; a reasonable management alternative for prostate cancer diagnosed in the prostate specific antigen era. J Urol 2008;180:1336–9, discussion 1340–1.

An increasing number of comparatively young men are diagnosed today with prostate cancer in an apparently early stage. Most studies that have examined the natural course of early stage prostate cancer have come to the same conclusion: The course of the disease is fairly indolent for the first 15 yr, but after that, a considerable increase in prostate cancer mortality is seen [1]. This pattern has been seen as a reason for men with a very long life expectancy to undergo immediate curative therapy, even when diagnosed with early stage prostate cancer. Recently, the need for immediate treatment of all young men has been challenged, and the concept of active monitoring has gained popularity as a treatment policy. The idea is that men who are otherwise considered to be good candidates for treatment with curative intent (good health, long life expectancy) are handled with close observation and are offered potentially curative therapy first when signs of disease progression occur. Bastian and coworkers [2] present an extensive and well-written review of the current literature dealing with active monitoring.

From a clinical perspective, a few reflections might be worth considering. The first is that the available data are based on low-quality evidence (case series with selected patients and often a mix of active monitoring and watchful waiting) and the follow-up periods are generally short. This means that young men who consider active monitoring as a treatment option need to be informed about the fact that long-term results are not available.

The second consideration is that most of the insecurity involved is related to the fact that the available histopathologic information from one set of biopsies is somewhat unreliable. Several studies have shown that upgrading is common, even after 8–12 core biopsies [3]. One might raise the question of whether these young patients should be offered an immediate rebiopsy prior to embarking on the active monitoring program. Such a policy should reduce the uncertainties related to the true tumor burden or grade.

The third consideration and the last thing to remember is that dynamic prostate-specific antigen (PSA) changes (ie, PSA doubling time) are unable to predict that a patient will be at high risk. A short doubling time indicates that the patient already is at high risk for progression (even after therapy); that is, the information that comes from PSA changes comes late in certain cases [4].

References


DOI: 10.1016/j.eururo.2009.02.029
DOI of original article: 10.1016/j.eururo.2009.02.028
Clearly, testing for PSA has driven the rise in incident cases, but repeated annual PSA testing as practiced in North America also has had a more subtle impact. Repeated PSA testing has selectively increased the number of men with minimal-volume, low-grade disease. Consequently, estimates suggest that as much as half of older men who have been repeatedly screened for PSA are diagnosed with clinically insignificant disease [2]. Many urologists have responded by exploring whether a subset of these patients might safely be spared treatment interventions.

The article by Bastian et al in this issue of *European Urology* reviews the global efforts to address this public health problem [3]. The concept of active surveillance for appropriately selected patients is gaining credibility. Bastian et al summarize the literature supporting the selection criteria for active surveillance protocols and the outcomes of case series published by several centers. They conclude that active surveillance is a reasonable alternative for properly selected men who present with low-volume, low-risk disease. Standardization of follow-up protocols is still evolving, but already there is general consensus among many academic urologists. Until data are available from randomized trials, urologists should consider offering this option to appropriate selected patients and tracking their outcomes so that information can be shared with the larger urologic community.

**References**


DOI: 10.1016/j.eururo.2009.02.030

DOI of original article: 10.1016/j.eururo.2009.02.028